Original Article

Relationship between Coronary Artery Disease and Non-HDL-C, and Effect of Highly Purified EPA on the Risk of Coronary Artery Disease in Hypercholesterolemic Patients Treated with Statins: Sub-Analysis of the Japan EPA Lipid Intervention Study (JELIS)

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***Aim*: The present study examined the importance of reducing non-high-density lipoprotein cholesterol (non-HDL-C) for the primary prevention of the occurrence of coronary artery disease (CAD) in the JELIS, and the effects of EPA.**

***Methods*: The patients were distributed into 4 subgroups using the lipid management goal for LDL-C recommended by the Japan Atherosclerosis Society guideline (2007) and the goal for non-HDL-C defined as 30 mg/dL higher than LDL-C: A) achieved both goals; B) achieved the LDL-C but not non-HDL-C goal; C) achieved the non-HDL-C but not LDL-C goal; and D) did not attain either goal. The incidences of CAD in the 4 subgroups were compared, and the effects of eicosapentaenoic acid (EPA) on the risk of CAD in these subgroups were examined.**

***Results*: In the non-EPA group, the incidence of CAD in patients who did not achieve the goals for LDL-C or non-HDL-C was higher than in patients who achieved those goals. Patients in subgroups B, C, and D were at higher risk for CAD than those in subgroup A (B, HR 2.31; C, HR 1.90; D, HR 2.47). EPA reduced the risk of CAD by 38% in subgroups B, C, and D ($p = 0.007$).**

***Conclusion*: We reconfirmed non-HDL-C as a predictor of the risk for CAD and a residual risk marker of CAD after LDL-C-lowering therapy. EPA was useful to reduce the occurrence of CAD in patients who did not achieve the goals for LDL-C and/or non-HDL-C.**

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Key words; Eicosapentaenoic acid, Non HDL-C, Coronary artery disease, Residual risk

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Introduction

Coronary artery disease (CAD) is one of the major causes of death in developed countries. This is a disease based on atherosclerosis whose onset and progression are closely related to serum lipids. Low density lipoprotein cholesterol (LDL-C) is considered a

very important risk factor for CAD, and lowering of LDL-C has been adopted as a treatment goal[1, 2]. The LDL-C goals for the primary prevention group in categories I (Low risk), II (Intermediate risk), and III (High risk), and for the secondary prevention group are less than 160, 140, 120 and 100 mg/dL, respectively, by the Japan Atherosclerosis Society (JAS) established in 2007[3].

Although the results of many randomized controlled trials (RCTs) using statins have shown the usefulness of LDL-C-lowering therapy, the extent of CAD suppression did not exceed 30%[4-6]; therefore, the residual risk of CAD has become a problem. Recently, non-high density lipoprotein cholesterol (non-HDL-C) has begun to attract attention as a new predictor of CAD risk[2, 7-10]. Tanabe *et al*. reported the results of the Japan Arteriosclerosis Longitudinal Study (JALS), which stated that the risk of acute myocardial infarction is more reliably predicted by serum non-HDL-C than by serum total cholesterol (TC)[9]. Robinson *et al*. found that the percent of non-HDL-C lowering correlates with coronary heart disease reduction[10]. Furthermore, Kastelein at el. reported that on-treatment levels of non-HDL-C and apolipoprotein B are more closely associated with cardiovascular outcome than with LDL-C levels in patients receiving statin therapy[11]. Non-HDL-C levels reflect the amount of remnant lipoproteins and small-dense LDL, which also are atherogenic. Since these atherogenic lipoproteins are known to increase in patients with hypertriglyceridemia or low levels of HDL-C, the levels of non-HDL-C may reflect an abnormal lipid metabolism associated with metabolic syndrome, obesity, and insulin resistance.

The Adult Treatment Panel III (ATP III) recommends that the goals for non-HDL-C in the high, intermediate, and low risk groups should be less than 130, 160, and 190 mg/dL, respectively; these values are 30 mg/dL higher than the recommended level of LDL-C[12]. Based on clinical data, Shimano *et al*. confirmed the same management goals for non-HDL-C[13]; however, there is no evidence that the goals for non-HDL-C (LDL-C plus 30 mg/dL) are useful for reducing CAD in Japanese patients with dyslipidemia.

On the other hand, an epidemiological study of Innuits in Greenland[14] and analyses of the fatty acid composition in their diet[15] and blood[16] showed a long time ago that n-3 polyunsaturated fatty acids (PUFAs) contained in fish oil suppressed the development of CAD. Many subsequent studies including epidemiological studies, clinical studies, and RCTs have provided evidence of the suppression of CAD by n-3 PUFAs[17-22].

In the Japan EPA Lipid Intervention Study (JELIS), a large-scale RCT of highly purified eicosapentaenoic acid (EPA), we demonstrated that EPA reduced the occurrence of major coronary events (MCE) independent of LDL-C reduction[23]. We also reported that patients with abnormal serum triglyceride (TG) and HDL-C levels (TG ≥150 mg/dL; HDL-C <40 mg/dL) had a significantly higher CAD risk than those with normal serum TG and HDL-C levels, and intervention with EPA markedly reduced the risk of CAD in this high-risk population in subanalysis of primary prevention cases from the JELIS[24]. Sugimoto *et al*. reported that non-HDL-C had a positive correlation with TG concentration[25]. The present study examined the importance of non-HDL-C for prevention of the occurrence of CAD and the effects of EPA.

Methods

Study Design and Patients

Details of the design of JELIS have been reported in a previous paper[26]. Briefly, patients with a serum TC level ≥250 mg/dL (men: 40-75 years; women: postmenopausal-75 years) were followed for up to 5 years (mean: 4.6 years) using a prospective, randomized, open-label, blinded-endpoint evaluation (PROBE) method. A total of 18,645 patients,, including 3,664 with a history of CAD were registered and randomly assigned to either an EPA with statin (EPA group; $n=9,326$) or a statin-alone (non-EPA group; $n=9,319$) group using a central registration system.

The study population was randomly assigned to receive EPA or not after a 4- to 8-week washout period of antihyperlipidemic drugs. In the EPA group, we administered a daily dose of 1800 mg EPA as 6 capsules, each containing 300 mg of highly purified (>98%) EPA ethylester. The primary endpoint of JELIS was the cumulative incidence of MCE, including sudden cardiac death, fatal or nonfatal myocardial infarction, unstable angina pectoris with documented myocardial ischemia, and angioplasty/stenting or coronary artery bypass grafting. Clinical endpoints were reviewed by expert cardiologists belonging to the Event Evaluation Committee and without knowledge of treatment allocation. Local physicians monitored compliance with dietary instructions and the use of medications at each hospital visit. Patients (non-EPA group: $n=5,806$, EPA group: $n=5,863$) with the fasting serum lipid determined at one year and without a history of CAD were the subjects of this report (**Fig. 1**).

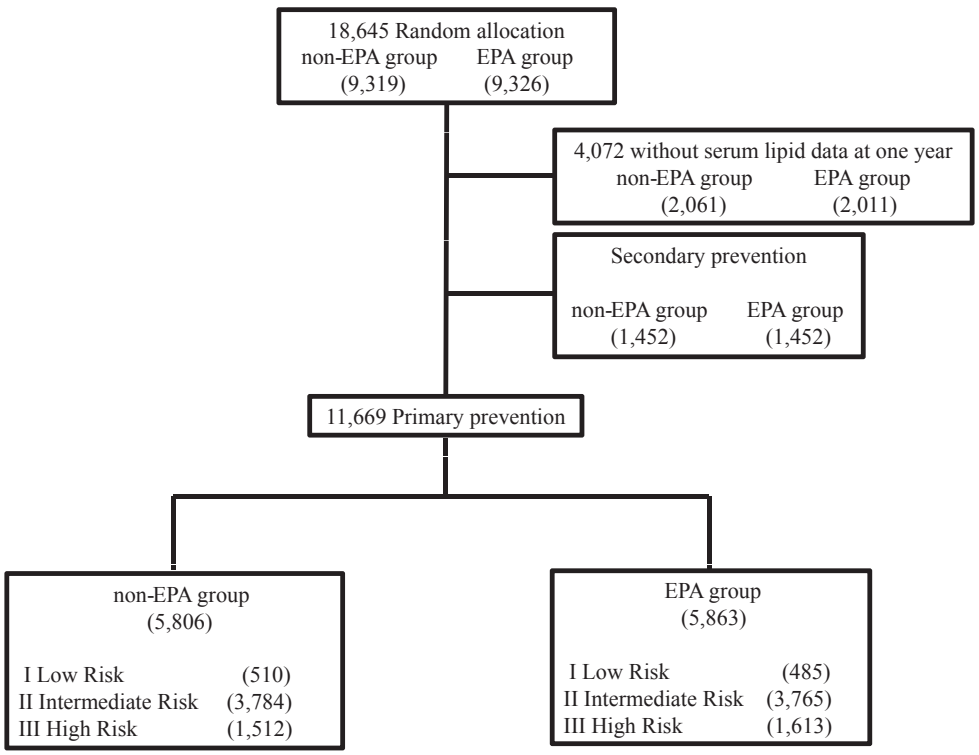

Fig. 1. Randomization and analysis set.

Categorization to Prevent CAD in Reference to the JAS Guideline (2007)[3)]

Patients in the primary prevention group were categorized as low risk, intermediate risk or high risk depending on the number of CAD risk factors. Gender, aging, hypertension, impaired glucose metabolism (IGM) [including diabetes mellitus (DM)], smoking, and low HDL-C (<40 mg/dL) were defined as risk factors.

Patients with DM, a history of stroke, or with arteriosclerosis obliterans (ASO) were classified as category Ⅲ. The patients were divided into Categories Ⅰ, Ⅱ, and Ⅲ according to the JAS Guideline (2007)[3)] and randomization of the study population is shown in **Fig. 1**.

Lipid Management Goal Levels for LDL-C According to the JAS Guideline (2007)

The serum LDL-C concentration was calculated using the Friedewald formula. The goal levels for LDL-C in categories Ⅰ, Ⅱ, and Ⅲ in the primary prevention group were <160 mg/dL, <140 mg/dL, and 120 mg/dL, respectively[3)].

Lipid Management Goal levels for Non-HDL-C

The goal level for non-HDL-C was 30 mg/dL higher than that of LDL-C according to the ATP Ⅲ recommendation[12)].

All subjects were distributed into the four subgroups below, based on their serum LDL-C and non HDL-C levels. We examined the incidence of CAD in these four subgroups and the effects of EPA on CAD during the follow-up period.

Subgroup A: The patients achieved the goals for both LDL-C and non-HDL-C

Subgroup B: The patients achieved the goals for LDL-C but not for non-HDL-C

Subgroup C: The patients did not achieve the goals for LDL-C but achieved those for non-HDL-C

Subgroup D: The patients did not achieve the goals for LDL-C and non-HDL-C

We investigated the incidence of CAD during the follow-up period in patients who achieved and those who did not achieve the goals for LDL-C and/or non-HDL-C after treatment for one year.

Statistical Analysis

All analyses were for intention-to-treat with the level of significance set at $p<0.05$ (2-sided). The Wilcoxon two-sample test was used to compare continuous variables. The chi-square test was used to compare class variables. The Kaplan-Meier method, log-rank

Table 1. Proportion of patients with risk factors for coronary artery disease between those who did and did not achieve the goals for LDL-C or non-HDL-C

(A) LDL-C

Goals for LDL-C	non-EPA					EPA				
	Achieved % total $n=2,853$		Did not achieve % total $n=2,953$		p value	Achieved % total $n=2,975$		Did not achieve % total $n=2,888$		p value
Age (male ≥ 45 years, female ≥ 55 years)	2,273	79.7%	2,522	85.4%	< 0.001	2,431	81.7%	2,450	84.8%	0.001
Hypertension	939	32.9%	1,013	34.3%	0.26	1,039	34.9%	981	34.0%	0.44
IGM (including DM)	442	15.5%	847	28.7%	< 0.001	477	16.0%	868	30.1%	< 0.001
DM	251	8.8%	597	20.2%	< 0.001	279	9.4%	591	20.5%	< 0.001
Smoking	372	13.0%	531	18.0%	< 0.001	405	13.6%	538	18.6%	< 0.001
Low HDL-C (< 40 mg/dL)	155	5.4%	224	7.6%	< 0.001	156	5.2%	264	9.1%	< 0.001
Stroke	93	3.3%	167	5.7%	< 0.001	122	4.1%	191	6.6%	< 0.001
ASO	11	0.4%	15	0.5%	0.48	9	0.3%	23	0.8%	0.009

(B) non-HDL-C

Goals for non-HDL-C	non-EPA					EPA				
	Achieved % total $n=2,841$		Did not achieve % total $n=2,965$		p value	Achieved % total $n=3,067$		Did not achieve % total $n=2,796$		p value
Age (male ≥ 45 years, female ≥ 55 years)	2,285	80.4%	2,510	84.7%	< 0.001	2,516	82.0%	2,365	84.6%	0.009
Hypertension	934	32.9%	1,018	34.3%	0.24	1,048	34.2%	972	34.8%	0.63
IGM (including DM)	436	15.3%	853	28.8%	< 0.001	489	15.9%	856	30.6%	< 0.001
DM	260	9.2%	588	19.8%	< 0.001	292	9.5%	578	20.7%	< 0.001
Smoking	315	11.1%	588	19.8%	< 0.001	380	12.4%	563	20.1%	< 0.001
Low HDL-C (< 40 mg/dL)	92	3.2%	287	9.7%	< 0.001	103	3.4%	317	11.3%	< 0.001
Stroke	94	3.3%	166	5.6%	< 0.001	136	4.4%	177	6.3%	0.001
ASO	13	0.5%	13	0.4%	0.91	10	0.3%	22	0.8%	0.02

IGM, impaired glucose metabolism; DM, diabetes mellitus; HDL-C, high density lipoprotein cholesterol; ASO, arteriosclerosis obliterans.

test, and Cox proportional hazard model were used for the analysis of survival. All analyses were conducted using version 5.0.1a of the JMP statistical software program (SAS Institute, Inc., Cary, NC).

Results

At baseline, the numbers of patients with aging, hypertension, IGM (including DM), DM, smoking, low HDL-C, stroke, and ASO were 4,795 (82.6%), 1,952 (33.6%), 1,289 (22.2%), 848 (14.6%), 903 (15.6%), 379 (6.5%), 260 (4.5%), and 26 (0.4%) in the non-EPA group ($n=5,806$), respectively, and 4,881 (83.3%), 2,020 (34.5%), 1,345 (22.9%), 870 (14.8%), 943 (16.1%), 420 (7.2%), 313 (5.3%), and 32 (0.5%) in the EPA group ($n=5,863$), respectively. Only the proportion of stroke was significantly different between the two groups ($p=0.03$).

Table 1 shows the proportion of patients with risk factors for CAD with reference to the JAS Guideline (2007)[3] between achieved and not achieved goals for LDL-C or non-HDL-C. The proportion of patients who achieved the goals for both LDL-C and non-HDL-C in patients with aging, IGM, DM, smoking, low HDL-C, or stroke was significantly lower than those who did not achieve the goals in both groups, and in patients with ASO, the proportion was significantly lower only in the EPA group.

The distribution of patients in the non-EPA group by risk category was 8.8% ($n=510$) in category Ⅰ, 65.2% ($n=3,784$) in category Ⅱ, and 26.0% ($n=1,512$) in category Ⅲ. In the EPA group, 8.3% ($n=485$) of patients were in category Ⅰ, 64.2% ($n=3,765$) were in category Ⅱ, and 27.5% ($n=1,613$) were in category Ⅲ (**Fig. 1**). The proportion of patients who achieved the goals for LDL-C in the non-EPA and EPA groups was 49.1% (2,853/5,806) and 50.7% (2,975/5,863), respectively ($p=0.08$). The proportion of patients who achieved the goals for non-HDL-C in the non-EPA and EPA groups was 48.9%

Table 2. Incidence of CAD compared between patients who did and did not achieve goals for LDL-C

(A) non-EPA

Goals for LDL-C	Incidence of CAD (Events/n, %)				HR	(95%CI)	*p* value
	Achieved		Did not achieve				
Total	36/2,853	1.3%	74/2,953	2.5%	2.02	(1.36-3.03)	<0.001
Ⅰ Low Risk	3/356	0.8%	1/154	0.6%			
Ⅱ Intermediate Risk	15/2,017	0.7%	32/1,767	1.8%			
Ⅲ High Risk	18/480	3.8%	41/1,032	4.0%			

(B) EPA

Goals for LDL-C	Incidence of CAD (Events/n, %)				HR	(95%CI)	*p* value
	Achieved		Did not achieve				
Total	43/2,975	1.4%	44/2,888	1.5%	1.06	(0.70-1.62)	0.78
Ⅰ Low Risk	3/339	0.9%	0/146	0.0%			
Ⅱ Intermediate Risk	23/2,093	1.1%	22/1,672	1.3%			
Ⅲ High Risk	17/543	3.1%	22/1,070	2.1%			

CAD, coronary artery disease; HR, hazard ratio; 95%CI, 95% confidence interval.

Table 3. Incidence of CAD compared between patients who achieved and did not achieve the goals for non-HDL-C

(A) non-EPA

Goals for non HDL-C	Incidence of CAD (Events/n, %)				HR	(95%CI)	*p* value
	Achieved		Did not achieve				
Total	34/2,841	1.2%	76/2,965	2.6%	2.18	(1.46-3.30)	<0.001
Ⅰ Low Risk	2/344	0.6%	2/166	1.2%			
Ⅱ Intermediate Risk	17/2,036	0.8%	30/1,748	1.7%			
Ⅲ High Risk	15/461	3.3%	44/1,051	4.2%			

(B) EPA

Goals for non HDL-C	Incidence of CAD (Events/n, %)				HR	(95%CI)	*p* value
	Achieved		Did not achieve				
Total	41/3,067	1.3%	46/2,796	1.6%	1.24	(0.81-1.89)	0.32
Ⅰ Low Risk	3/351	0.9%	0/134	0.0%			
Ⅱ Intermediate Risk	22/2,169	1.0%	23/1,596	1.4%			
Ⅲ High Risk	16/547	2.9%	23/1,066	2.2%			

CAD, coronary artery disease; HR, hazard ratio; 95%CI, 95% confidence interval

(2,841/5,806) and 52.3% (3,067/5,863), respectively ($p<0.001$).

In the non-EPA group, the incidence of CAD in patients who did not achieve the goals for LDL-C was significantly higher than in patients who achieved the goals [hazard ratio (HR), 2.02; 95% confidence interval (CI), 1.36-3.03; $p<0.001$] (**Table 2A**). On the other hand, it was not higher in the EPA group (HR, 1.06; 95%CI, 0.70-1.62; $p=0.78$) (**Table 2B**). In the non-EPA group, the incidence of CAD in patients who did not achieve the goals for non-HDL-C was significantly higher than in patients who achieved those goals (HR, 2.18; 95%CI, 1.46-3.30; $p<0.001$) (**Table 3A**). On the other hand, it was not higher in the EPA group (HR, 1.24; 95%CI, 0.81-1.89; $p=0.32$) (**Table 3B**).

Table 4 shows the relationships between serum lipid levels and the incidence of CAD in the non-EPA

Table 4. Hazard ratio of the risk of CAD for 1SD increased serum lipids in the first year in the non-EPA group

	1SD change	HR	95% confidence interval	*p* value
TC	35 mg/dL	1.01	(0.82-1.24)	0.91
LDL-C	35 mg/dL	1.19	(1.00-1.42)	0.05
ln TG	0.5 ln(mg/dL)	1.08	(0.88-1.32)	0.46
HDL-C	17 mg/dL	0.60	(0.47-0.76)	<0.001
non-HDL-C	37 mg/dL	1.35	(1.11-1.66)	0.003

CAD, coronary artery disease; HR, hazard ratio; SD, standard deviation; ln TG, logarithm of TG
The given hazard ratio was for a 1SD change adjusted for gender, age, hypertension, diabetes mellitus, and smoking.

Table 5. Patients' background

	A subgroup		B subgroup			C subgroup			D subgroup		
	LDL-C Achieved	non-HDL-C Achieved	LDL-C Achieved	non-HDL-C Did not achieve	*p* value	LDL-C Did not achieve	non-HDL-C Achieved	*p* value	LDL-C Did not achieve	non-HDL-C Did not achieve	*p* value
	(*n*=5,077)		(*n*=751)			(*n*=831)			(*n*=5,010)		
Male	1,104	21.7%	294	39.1%	<0.001	163	19.6%	0.16	1,516	30.3%	<0.001
Age	60.9±8.4		59.2±8.8		<0.001	61.5±7.6		0.14	60.2±8.3		<0.001
BMI (kg/m^2)	23.6±3.2		24.9±3.2		<0.001	23.5±3.1		0.47	24.4±3.2		<0.001
Smoking	595	11.7%	182	24.2%	<0.001	100	12.0%	0.80	969	19.3%	<0.001
Drinker	986	19.4%	243	32.4%	<0.001	155	18.7%	0.60	1,332	26.6%	<0.001
Clinical history											
Diabetes	422	8.3%	108	14.4%	<0.001	130	15.6%	<0.001	1,058	21.1%	<0.001
Hypertension	1,722	33.9%	256	34.1%	0.93	260	31.3%	0.13	1,734	34.6%	0.46
IGM	734	14.5%	185	24.6%	<0.001	191	23.0%	<0.001	1,524	30.4%	<0.001
Blood pressure											
Systolic (mmHg)	134.8±18.0		136.5±17.8		0.02	134.5±18.4		0.97	136.3±18.4		<0.001
Diastolic (mmHg)	79.3±10.8		80.8±10.8		0.003	78.7±11.2		0.12	80.0±10.9		0.02
Lipid profile											
Total cholesterol (mg/dL)	270.0±19.5		273.4±23.5		0.002	273.2±20.8		<0.001	281.9±28.9		<0.001
LDL cholesterol (mg/dL)	174.6±24.9		171.4±28.0		<0.001	183.9±23.4		<0.001	191.4±31.7		<0.001
HDL cholesterol (mg/dL)	64.4±18.9		51.5±13.2		<0.001	64.2±15.8		0.34	55.2±14.8		<0.001
non HDL cholesterol (mg/dL)	205.7±26.2		222.3±25.7		<0.001	208.8±23.6		0.007	226.7±31.9		<0.001
Triglycerides (mg/dL)	164.2±113.9		289.7±178.4		<0.001	124.4±56.6		<0.001	182.8±107.7		<0.001
Fatty acid profile											
C20:5 (mol%)	2.90±1.58		2.41±1.30		<0.001	3.02±1.62		0.04	2.85±1.55		0.11
C18:1/C18:0 ratio	2.83±0.56		3.28±0.61		<0.001	2.72±0.45		<0.001	3.01±0.58		<0.001
C16:1/C16:0 ratio	0.118±0.035		0.128±0.038		<0.001	0.114±0.033		0.002	0.122±0.036		<0.001

Data are reported as a percentage or the mean ± standard deviation. BMI, body mass index; IGM, impaired glucose metabolism; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; C20:5, eicosapentaenoic acid; C18:1, oleic acid; C18:0, stearic acid; C16:1, palmitoleic acid; C16:0, palmitic acid.
p value vs. A subgroup.

group. Non-HDL-C was more strongly positively associated with the incidence of CAD than LDL-C (HR, 1.35; 95%CI, 1.11-1.66; $p=0.003$ and HR, 1.19; 95%CI, 1.00-1.42; $p=0.05$, respectively). HDL-C level showed a negative correlation with CAD, but serum TC and the logarithm of the TG level did not.

Table 5 shows the baseline characteristics of

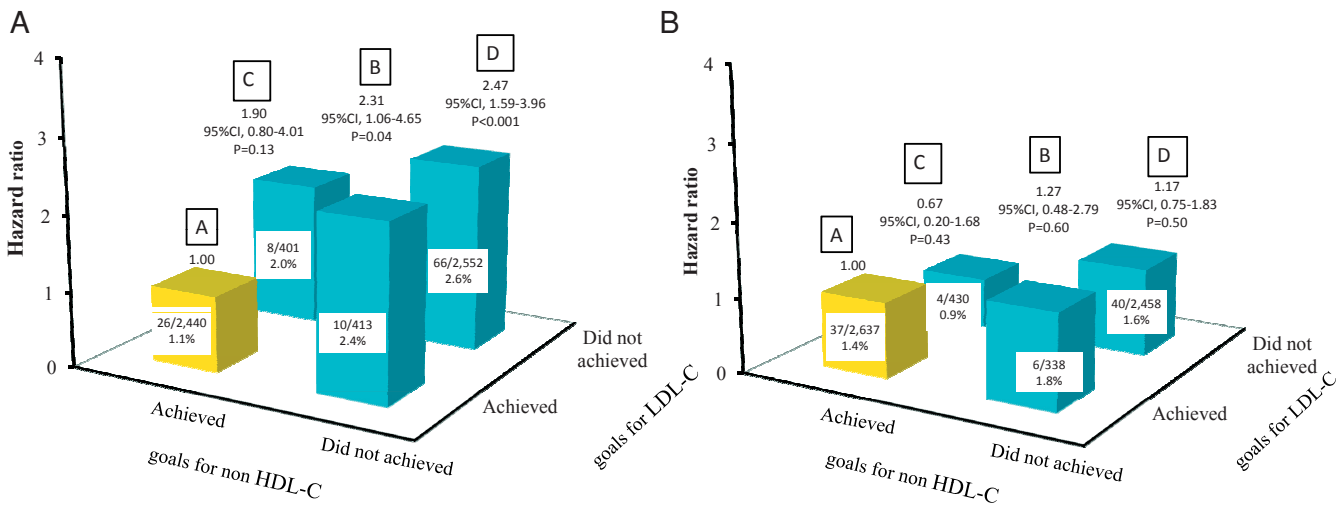

Fig. 2. Relationships between the risk of CAD and the goals for LDL-C and non-HDL-C.

(A) Non-EPA group; (B) EPA group

CAD, coronary artery disease; LDL-C, low density lipoprotein cholesterol; non-HDL-C, non-high density lipoprotein cholesterol; 95%CI, 95% confidence interval; A, achievement of goals in LDL-C and non-HDL-C groups; B, achievement of goals in LDL-C group and failure to achieve goals in the non-HDL-C group; C, failure to achieve goals in the LDL-C group and achievement of goals in the non-HDL-C group; D, failure to achieve goals in the LDL-C and non-HDL-C groups. Incidences of CAD in each selfgroups were shown in each box (events, %).

patients in the 4 subgroups. In subgroups B, C, and D, the prevalence of DM, IGM, TC, and non-HDL-C at baseline was significantly higher than in subgroup A. On the other hand, in subgroups B and D who did not achieve the goals for non-HDL-C, the proportion of men, smoking and drinking, the mean body mass index (BMI), systolic and diastolic blood pressure, TG, oleic acid (C18:1)/stearic acid (C18:0) ratio and palmitoleic acid (C16:1)/palmitic acid (C16:0) ratio at baseline were significantly higher and HDL-C at baseline was significantly lower than in subgroup A (**Table 8**).

In the non-EPA group, HRs for CAD in subgroups B and D (B subgroup, HR, 2.31; 95%CI, 1.06-4.65; $p=0.04$; D subgroup, HR, 2.47; 95%CI, 1.59-3.96; $p<0.001$) were significantly higher than in subgroup A. The HR in subgroup C was not higher than in subgroup A (C subgroup, HR, 1.90; 95%CI, 0.80-4.01; $p=0.13$) (**Fig. 2A**). In the EPA group, the HRs for CAD in patients with B, C and D subgroups were not higher than in subgroup A (B subgroup, HR, 1.27; 95%CI, 0.48-2.79; $p=0.60$; C subgroup, HR, 0.67; 95%CI, 0.20-1.68; $p=0.43$; D subgroup, HR, 1.17; 95%CI, 0.75-1.83; $p=0.50$) (**Fig. 2B**).

In patients who did not achieve the goals for LDL-C and/or non-HDL-C (subgroups B, C, and D), EPA treatment significantly suppressed the risk of CAD by 38% (HR, 0.62; 95%CI, 0.43-0.88; $p=0.007$) (**Fig. 3**).

Other than MCE, the incidence of stroke was 1.8% (61/3,366) in the non-EPA group and 1.5% (50/3,226) in the EPA group, and the all-cause mortality was 1.9% (63/3,366) in the non-EPA group and 2.0% (66/3,226) in the EPA group in patients who did not achieve the goals for LDL-C and/or non-HDL-C. There were no differences between the two treatment groups. The occurrence rate of gastrointestinal disturbance and skin abnormality in the EPA group was significantly higher than in the non-EPA group.

Discussion

In the present sub-analysis, we found that patients in the non-EPA group who did not achieve the goals for LDL-C recommended by the JAS Guideline (2007)[3] were at a significantly higher risk of developing CAD than those who achieve them. These results suggested that the goals for LDL-C were useful to reduce the risk of CAD in Japanese patients with dyslipidemia.

It is well known that hypertriglyceridemia is strongly correlated with high levels of non-HDL-C[25] and that non-HDL-C levels reflect remnant lipoprotein and small-dense LDL, which are also atherogenic. The present analysis demonstrated that non-HDL-C levels were positively associated with the risk of CAD, the same as LDL-C levels, and that patients in the

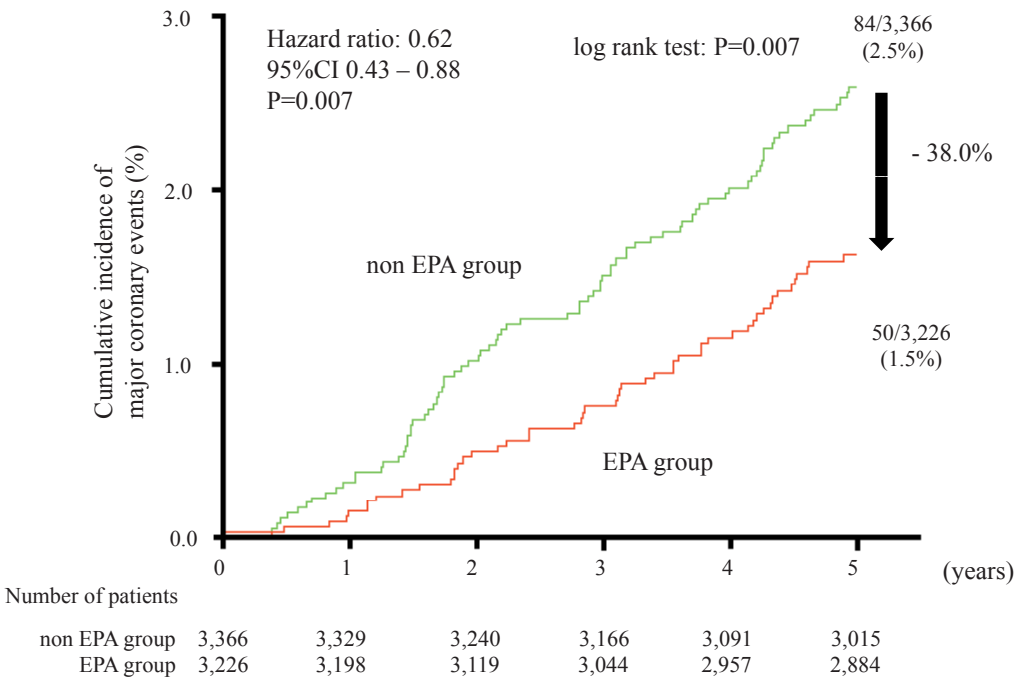

Fig. 3. Effects of EPA on CAD in patients who did not achieve the goals for LDL-C and/or non-HDL-C (B, C, and D subgroups).

CAD: coronary artery disease, LDL-C: low density lipoprotein cholesterol, non-HDL-C: non-high density lipoprotein cholesterol, 95%CI: 95% confidence interval, B: achievement of goals in the LDL-C group and failure to achieve goals in the non-HDL-C group, C: failure to achieve goals in the LDL-C group and achievement of goals in the non-HDL-C group, D: failure to achieve goals in the LDL-C group and non-HDL-C group.

non-EPA group who could not achieve the goals for non-HDL-C had a significantly higher risk of developing CAD than those who could achieve them. It might be that patients who did not achieve the lipid management goals comprised a higher proportion of the risk of CAD than those who did achieve the goals (**Table 1**). These findings suggest that non-HDL-C is one of the residual risk factors for CAD after LDL-C-lowering therapy and that the goals for non-HDL-C are useful to reduce the risk of CAD in Japanese patients with dyslipidemia. EPA treatment may be a useful strategy to reduce the risk of CAD in patients undergoing lipid-lowering therapy who do not achieve the goals for LDL-C or non-HDL-C.

The present analysis shows that patients in subgroups B, C and D of the non-EPA group were at a higher risk of developing CAD than the patients in subgroup A; however, this was not the case in the EPA group.

In subgroups B and D, the number of patients who did not achieve the goals for non-HDL-C, the proportion of patients with IGM, DM, high BMI, hypertension, and high levels of non-HDL-C and TG at baseline were significantly higher than in subgroup A, and the number of patients with a high level of HDL-C was significantly lower. Thus, these subgroups seemed to include patients with metabolic syndrome. It seems that the goals for LDL-C and non-HDL-C can serve to reduce the risk for CAD associated with metabolic syndrome. We have already reported that EPA treatment markedly reduced the risk for CAD by 53% in patients with high TG and low HDL-C, who had many features of metabolic syndrome[24], similarly to patients in subgroups B and D.

Although EPA mildly reduced the level of non-HDL-C in this study, the proportion of patients who achieve the goal levels for non-HDL-C in the EPA group was significantly higher than in the non-EPA group ($p < 0.001$). Furthermore, even in patients who did not achieve the goals for LDL-C and/or non-HDL-C, EPA treatment significantly reduced the risk of CAD. These results suggested that EPA may be a useful basic drug to prevent the risk of CAD in patients with dyslipidemia.

In patients who did not achieve the goals for non-HDL-C (subgroups B and D), the plasma EPA

levels at baseline were significantly lower and C18:1/C18:0 and C16:1/C16:0 ratios were significantly higher than in patients who achieved both goals (subgroup A). These results may reflect the decreased activity of liver stearoyl-CoA desaturase 1 (SCD-1). Suppression of SCD-1 is considered useful therapy against metabolic syndrome[27, 28] and insulin resistance[29, 30]. It is possible that EPA suppressed liver lipogenesis associated with metabolic syndrome. Recently, Sato *et al*. reported that in mice given a high-fat/high-sucrose diet, EPA suppressed sterol regulatory element binding protein-1, fatty acid synthase, and SCD-1 in the liver[31], indicating that EPA was appropriate for the treatment of metabolic syndrome as it suppressed hepatic lipogenesis and steatosis. Further clinical trials are needed to investigate the relationship between EPA treatment and the development of metabolic syndrome.

In addition, the results may reflect the anti-arteriosclerosis effects of EPA, such as anti- platelet aggregation[32, 33], plaque stabilization[34, 35], anti-inflammation[31, 36-39] nitric oxide production[40, 41], small-dense LDL[38] and remnant-like particle cholesterol[42, 43] -lowering effects.

Conclusion

This analysis indicates that non-HDL-C is a predictor of the risk of CAD and that a high non-HDL-C level is one of the residual risk factors for CAD after LDL-C-lowering therapy. EPA significantly reduced the risk of CAD in patients who did not achieve the goals for LDL-C and/or non-HDL-C. Consequently, EPA may be a useful basic drug to reduce the risk of CAD in patients who resist LDL-C or non-HDL-C lowering.

Limitations

We planned to emulate an evaluation in the real world of medical care, so we did not use a placebo in the non-EPA group, and for ethical reasons we adopted the additional design parameter of treating hypercholesterolemia in all patients with statin administration.

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