

Polyunsaturated Fatty Acid Impact on Clinical Outcomes in Acute Coronary Syndrome Patients With Dyslipidemia: Subanalysis of HIJ-PROPER

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Background—This study aimed to examine the impact of baseline eicosapentaenoic acid (EPA) to arachidonic acid (AA) ratio on clinical outcomes of patients with acute coronary syndrome.

Methods and Results—In the HIJ-PROPER (Heart Institute of Japan Proper Level of Lipid Lowering With Pitavastatin and Ezetimibe in Acute Coronary Syndrome) study, 1734 patients with acute coronary syndrome and dyslipidemia were randomly assigned to pitavastatin+ezetimibe therapy or pitavastatin monotherapy. We divided the patients into 2 groups based on EPA/AA ratio on admission (cutoff 0.34 $\mu\text{g}/\text{mL}$ as median of baseline EPA/AA ratio) and examined their clinical outcomes. The primary end point comprised all-cause death, nonfatal myocardial infarction, nonfatal stroke, unstable angina pectoris, or ischemia-driven revascularization. Percentage reduction of low-density lipoprotein cholesterol and triglyceride from baseline to follow-up was similar regardless of baseline EPA/AA ratio. Despite the mean low-density lipoprotein cholesterol level during follow-up being similar between the low- and high-EPA/AA groups, the mean triglyceride levels during follow-up were significantly higher in the low- than in the high-EPA/AA group. After 3 years of follow-up, the cumulative incidence of the primary end point in patients with low EPA/AA was 27.2% in the pitavastatin+ezetimibe group compared with 36.6% in the pitavastatin-monotherapy group (hazard ratio 0.69; 95% CI, 0.52-0.93; $P=0.015$). However, there was no effect of pitavastatin+ezetimibe therapy on the primary end point in patients with high EPA/AA (hazard ratio 0.92; 95% CI, 0.70-1.20; $P=0.52$).

Conclusions—Among acute coronary syndrome patients who have dyslipidemia and low EPA/AA ratio, adding ezetimibe to statin decreases the risk of cardiovascular events compared with statin monotherapy.

Clinical Trial Registration—URL: <http://www.umin.ac.jp/ctr>. Unique identifier: UMIN000002742 (*J Am Heart Assoc.* 2019;8:e012953. DOI: 10.1161/JAHA.119.012953.)

Key Words: acute coronary syndrome • cholesterol-lowering drugs • eicosapentaenoic acid

Polyunsaturated fatty acids (PUFAs), especially omega-3 and -6 series, are key essential nutrients that play an important role in humans to maintain cell membranes and function. Various omega-3 PUFA trials including randomized controlled studies have been conducted with an expectation of improving the prognosis in patients at a high risk of cardiovascular disease.¹⁻⁴ A recent randomized trial reported

that adding eicosapentaenoic acid (EPA) to statins was beneficial to cardiovascular disease patients who had a residual risk factor.⁵ Further, several studies have reported that the low baseline value for the EPA/arachidonic acid (AA) ratio is related to worse clinical outcomes and plaque vulnerability in coronary artery disease patients.⁶⁻¹¹ We have published the HIJ-PROPER (Heart Institute of Japan Proper

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Accompanying Table S1 and Figure S1 are available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.012953>

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Received April 12, 2019; accepted July 12, 2019.

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Clinical Perspective

What Is New?

- Among patients with acute coronary syndrome who have dyslipidemia with baseline eicosapentaenoic acid/arachidonic acid ratio <0.34, combination therapy with ezetimibe and statin decreased the risk of cardiovascular events compared with statin monotherapy.

What are the Clinical Implications?

- Risk stratification of patients is possible by measuring eicosapentaenoic acid/arachidonic acid ratio on admission.
- Among acute coronary syndrome patients with dyslipidemia and low eicosapentaenoic acid/arachidonic acid ratio, adding ezetimibe to statin for treatment may be recommended.

Level of Lipid Lowering With Pitavastatin and Ezetimibe in Acute Coronary Syndrome) study,¹²⁻¹⁴ which was a randomized controlled trial that tested the efficacy of aggressive lipid-lowering treatment with ezetimibe+pitavastatin and compared it with that of conventional lipid-lowering therapy with pitavastatin in acute coronary syndrome (ACS) patients. The effects of baseline EPA/AA ratio on clinical outcomes in ACS patients have not been thoroughly evaluated. Accordingly, the present study aimed to examine the effect of EPA/AA ratio on clinical outcomes in ACS patients.

Materials and Methods

The data that support the findings of this study are available from the corresponding author according to the ethics committee rules of this study on reasonable request.

This is a subanalysis of the HIJ-PROPER study. In brief, the HIJ-PROPER study was a multicenter, prospective, randomized, open-label, blinded-end point trial with an active-control design comparing 2 lipid-lowering treatment strategies involving 19 Japanese hospitals.¹² Between January 2010 and April 2013, 1734 patients were randomized to an aggressive lipid-lowering therapy group (pitavastatin+ezetimibe group) or a conventional lipid-lowering therapy group (pitavastatin-monotherapy group). In the HIJ-PROPER study, 13 patients were lost to follow-up. As a result, 1721 patients were included in the original study. In the current study, to investigate whether the EPA/AA ratio affects cardiovascular events, patients in whom EPA/AA ratio was measured at baseline were included. Patients were divided into 2 groups based on the EPA/AA ratio during admission (0.34 being the median of EPA/AA ratio at baseline), and clinical outcomes were examined. The primary end point of the current study was the same as that in the original study—a composite of the first occurrence of a

component of the following end points: all-cause death, nonfatal myocardial infarction, nonfatal stroke, unstable angina pectoris, or ischemia-driven revascularization with either percutaneous coronary intervention or coronary artery bypass grafting.

The serum lipid profile including low-density lipoprotein cholesterol (LDL-C), total cholesterol, high-density lipoprotein cholesterol, and triglycerides was assessed at the time of enrollment and at the 3-, 6-, 12-, 24-, and 36-month follow-ups. PUFAs including EPA, AA, docosahexaenoic acid (DHA), and dihomo- γ -linolenic acid were assessed at baseline and at the 3-month follow-up. All laboratory analyses were exclusively performed at SRL Inc, an external laboratory (Hachioji, Tokyo, Japan). LDL-C concentrations were estimated using the Friedewald formula.¹⁵ The composition of serum fatty acids was determined by capillary gas chromatography.

The study was conducted in accordance with the principles of the Declaration of Helsinki. The institutional review board or the relevant ethics committee of each participating medical center approved the protocol, and all patients provided written informed consent for trial enrollment.

Statistical Analyses

Normally distributed data are reported as means \pm SD, non-normally distributed data as medians and interquartile ranges, and categorical data as absolute values and percentages. The comparisons were made using the Welch t test for normally distributed continuous variables or Mann-Whitney U test for nonnormally distributed continuous variables and a Pearson chi-squared test for categorical variables. Time to first occurrence of events was analyzed using the Kaplan-Meier method with a log-rank test and conventional Cox proportional hazards model. Variables were included in the multivariate model if they reached $P<0.10$ after univariate Cox hazard regression analysis and identified independent risk factors for the primary end point in the low-EPA/AA group. A P value of <0.05 was considered to indicate statistical significance unless stated otherwise. All statistical analyses were performed using statistics software JMP Pro 14 (SAS Institute Inc, Cary, NC).

Results

Between January 2010 and April 2013, 1721 patients were analyzed in the HIJ-PROPER study. We limited the present analysis to patients in the HIJ-PROPER study who underwent EPA/AA measurements at baseline. Therefore, a total of 1187 patients were included in this study (Figure 1). Patients excluded from the analysis ($n=534$) were equivalent to those included in the analysis ($n=1187$) with respect to most baseline characteristics. However, patients excluded from the

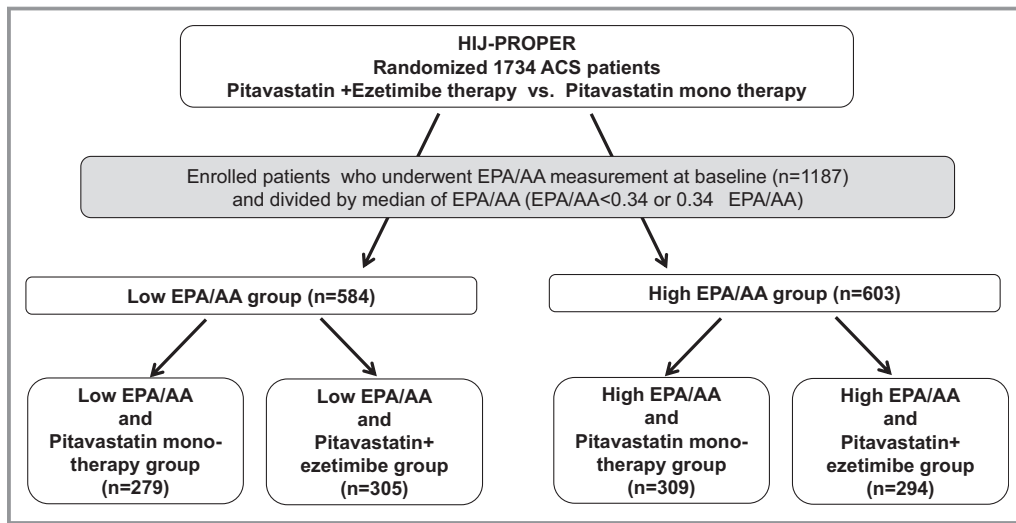


Figure 1. Patient enrollment in this study. AA indicates arachidonic acid; ACS, acute coronary syndrome; EPA, eicosapentaenoic acid.

analysis were more likely to have a higher glomerular filtration rate, frequent use of β -blockers, lower triglyceride levels, and a different distribution of the clinical presentation of ACS (Table S1). Baseline clinical characteristics of the 2 groups (low-EPA/AA group [n=584] with EPA/AA <0.34 $\mu\text{g}/\text{mL}$; high-EPA/AA group [n=603] with EPA/AA \geq 0.34 $\mu\text{g}/\text{mL}$) are shown in Table 1. In comparison with the patients in the high-EPA/AA group, the patients in the low-EPA/AA group had a lower age, higher body mass index, higher glomerular filtration rate, lower rate of hypertension, and higher rate of current smoking. In regard to the clinical presentation of ACS, the low-EPA/AA group showed a significantly higher percentage of ST-elevation myocardial infarction and a lower percentage of unstable angina pectoris than the high-EPA/AA group. The rate of aspirin use was significantly lower in the low-EPA/AA group.

With regard to the lipid profile, compared with patients in the high-EPA/AA group, those in the low-EPA/AA group had significantly higher LDL-C levels, higher triglyceride levels, and lower high-density lipoprotein cholesterol levels.

The percentage reduction of LDL-C, triglycerides, and high-density lipoprotein cholesterol from baseline to follow-up was similar regardless of the baseline EPA/AA ratio (Figure 2). Although the mean LDL-C level during follow-up was similar between the low-EPA/AA group and the high-EPA/AA group (68.8 ± 19.5 versus 67.2 ± 18.7 , $P=0.31$ for the pitavastatin+ezetimibe group; 87.2 ± 18.0 versus 86.2 ± 17.2 , $P=0.53$ for the pitavastatin-mono-therapy group, respectively) (Figure 3A and 3B), the mean triglyceride level during follow-up was significantly higher in the low-EPA/AA group than in the high-EPA/AA group (134.3 ± 67.1 versus 120.0 ± 50.1 , $P=0.004$ for the pitavastatin+ezetimibe group; 159.1 ± 84.1

versus 143.4 ± 77.8 , $P=0.02$ for the pitavastatin-mono-therapy group, respectively) (Figure 3C and 3D).

Kaplan-Meier analysis data for the primary end point in each group are shown in Figure 4. In all, 395 primary events were reported during a median observation period of 3.86 years. After 3 years of follow-up, the cumulative incidence of the primary end point in patients with low EPA/AA was 27.2% in the pitavastatin+ezetimibe group compared with 36.6% in the pitavastatin-mono-therapy group (hazard ratio 0.69; 95% CI, 0.52–0.93; $P=0.015$). The cumulative incidence of the primary end point in patients with high EPA/AA was 33.0% in the pitavastatin+ezetimibe group and 36.6% in the pitavastatin-mono-therapy group (hazard ratio 0.92; 95% CI, 0.70–1.20; $P=0.52$). Table 2 shows the individual components of the primary end point. With regard to the difference in primary end points between groups, the low-EPA/AA group treated with pitavastatin+ezetimibe showed a 37% reduction in the need for ischemia-driven coronary revascularization compared with that treated with pitavastatin mono-therapy. There was no statistically significant difference between the 2 treatment groups among patients with high EPA/AA with regard to each component of the primary end point.

Univariate and multivariate analyses to determine the independent predictors of primary end points in patients with low EPA/AA ratio are shown in Table 3. Univariate analysis showed that higher age ($P=0.03$), lower glomerular filtration rate ($P=0.01$), prevalence of diabetes mellitus ($P=0.05$), history of previous revascularization ($P=0.02$), clinical presentation of non-ST-segment-elevation myocardial infarction ($P=0.03$), use of ezetimibe ($P=0.02$), lower high-density lipoprotein cholesterol level ($P=0.04$), and

Table 1. Baseline Characteristics of the Study Population

	All Patients (n=1187)	Low-EPA/AA Group (n=584)	High-EPA/AA Group (n=603)	P Value
Age, y	65.7±11.7	62.6±12.6	68.7±9.8	<0.0001
Men	902 (76.0%)	455 (77.9%)	447 (74.1%)	0.14
BMI, kg/m ²	24.3±3.5	24.5±3.8	24.0±3.2	0.005
GFR, mL/min per 1.73 m ²	72.2±18.8	73.3±19.5	71.1±17.9	0.04
Statin naive	975 (82.1%)	490 (83.9%)	485 (80.4)	0.13
Hypertension	797 (67.1%)	373 (63.9%)	424 (70.3%)	0.02
Diabetes mellitus	343 (28.9%)	168 (28.8%)	175 (29.0%)	0.95
Current smoker	409 (34.5%)	244 (41.8%)	165 (27.4%)	<0.0001
Previous myocardial infarction	91 (7.7%)	49 (8.4%)	42 (7.0%)	0.38
Previous revascularization	111 (9.4%)	53 (9.1%)	58 (9.6%)	0.77
Previous heart failure	21 (1.8%)	11 (1.9%)	10 (1.7%)	0.83
Type of index event				0.001
STEMI	572 (48.2%)	313 (53.6%)	259 (43.0%)	
Non-STEMI	121 (10.2%)	51 (8.7%)	70 (11.6%)	
Unstable angina pectoris	494 (41.6%)	220 (37.7%)	274 (45.4%)	
Medication				
β-Blocker	111 (9.4%)	53 (9.1%)	58 (9.6%)	0.77
ACEIs/ARBs	352 (29.7%)	162 (27.7%)	190 (31.5%)	0.16
Calcium channel blocker	343 (28.9%)	160 (27.4%)	183 (30.3%)	0.28
Aspirin	207 (17.4%)	87 (14.9%)	120 (19.9%)	0.026
Cholesterol metabolism				
Total cholesterol	210.9±35.3	213.5±37.1	208.3±33.4	0.01
HDL-cholesterol	48.6±12.7	47.4±12.4	49.7±12.9	0.002
LDL-cholesterol	135.2±29.6	137.4±31.1	133.0±27.9	0.01
Triglyceride	133.6±70.6	141.6±71.3	125.9±69.1	0.0001
PUFA				<0.0001
EPA	60.8±32.9	38.5±13.7	82.3±31.7	
DHA	141.0±43.5	122.1±34.1	158.7±44.3	
AA	166.7±44.2	180.6±46.5	153.2±37.3	
DGLA	33.6±12.9	37.7±13.7	29.7±10.7	
EPA/AA ratio	0.39±0.24	0.22±0.07	0.55±0.23	
DHA/AA ratio	0.89±0.38	0.70±0.20	1.07±0.42	

Data are expressed as mean±SD or as number (percentage). AA indicates arachidonic acid; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; BMI, body mass index; DGLA, dihomo- γ -linolenic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PUFA, polyunsaturated fatty acid; STEMI, ST-segment-elevation myocardial infarction.

lower DHA level ($P=0.02$) tended to be associated with the occurrence of the primary end point in patients with low EPA/AA ratios. Multivariate analysis revealed that use of ezetimibe and lower DHA level at baseline were independent predictors of primary end points in patients with low EPA/AA ratios (odds ratio 0.70; 95% CI, 0.52–0.94; $P=0.02$ for use of ezetimibe; odds ratio 0.95; 95% CI, 0.91–0.99; $P=0.04$ for DHA).

Figure 5 shows the percentage change of EPA/AA and DHA/AA ratios from baseline to 3 months after lipid-lowering therapy. Regardless of the EPA/AA ratio at baseline, the percentage change of DHA/AA was similar among patients treated with pitavastatin+ezetimibe and those treated with pitavastatin monotherapy. In contrast, the increase in EPA/AA ratio was significantly higher in the low-EPA/AA group than in the high-EPA/AA group after lipid-lowering therapy (27.9%

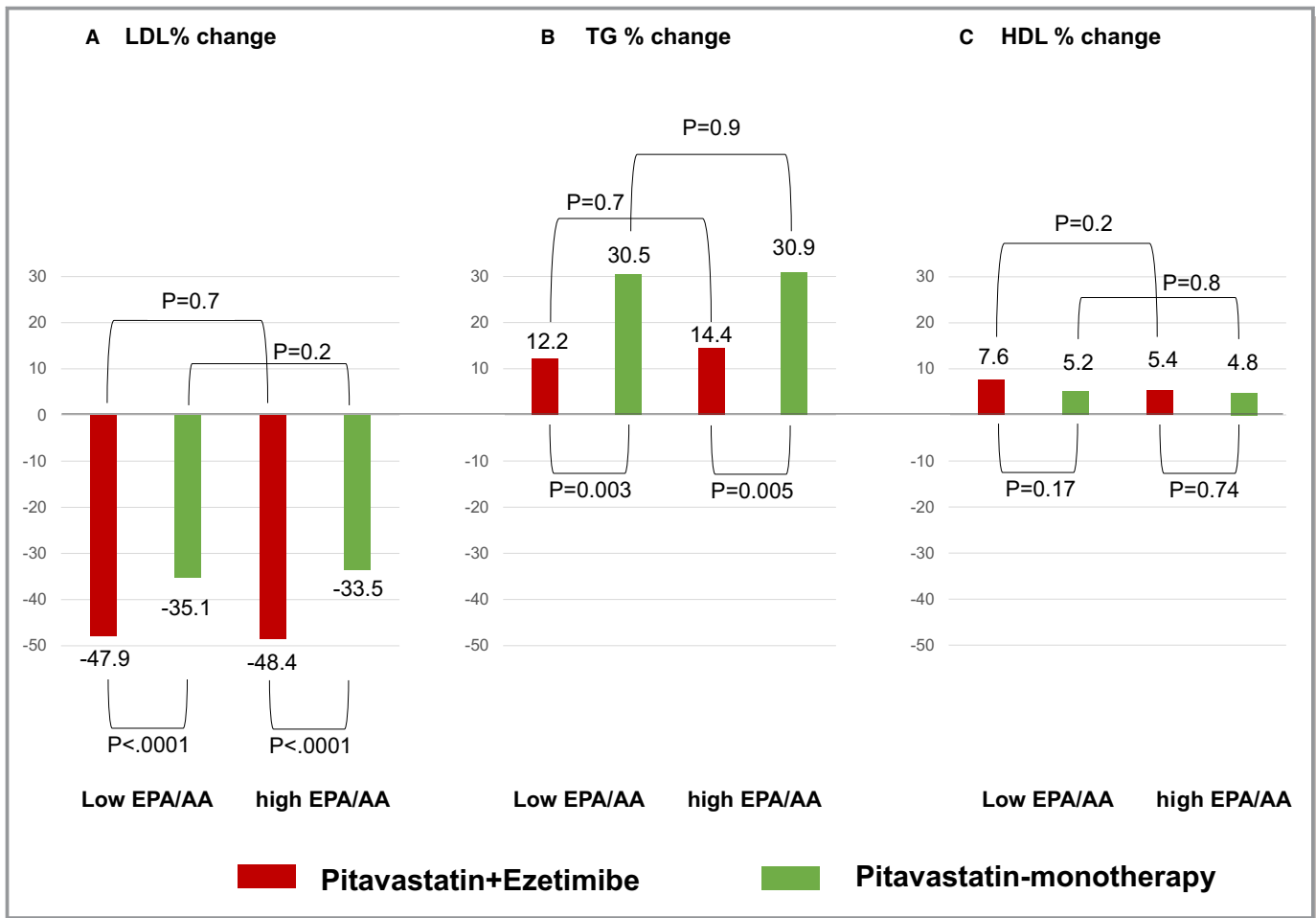


Figure 2. Mean percentage change from baseline to mean of follow-up for LDL-C (A), TG (B), and HDL-C (C). Mean percentage reduction from baseline to follow-up for LDL-C, triglycerides, and HDL-C is similar regardless of baseline EPA/AA ratio. EPA/AA indicates eicosapentaenoic acid/arachidonic acid; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride.

versus -3.4%, $P<0.0001$, for the pitavastatin+ezetimibe group; 50% versus 9.0%, $P<0.0001$, for the pitavastatin-monotherapy group, respectively).

Discussion

The primary findings of this subgroup analysis of HIJ-PROPER were these: among ACS patients who have dyslipidemia with baseline EPA/AA ratio <0.34 (low-EPA/AA group), combination therapy with ezetimibe and statin decreased the risk of cardiovascular events compared with statin monotherapy, and multivariate analysis revealed that the use of ezetimibe and a low DHA level at baseline were independent predictors of cardiovascular events.

In this subanalysis there were several differences in baseline characteristics between the low- and high-EPA/AA groups. No significant difference was observed in primary end points between low- ($n=584$) and high-EPA/AA groups ($n=603$) (Figure S1).

It was noteworthy that the event rates in the high- and low-EPA/AA groups treated with pitavastatin monotherapy were identical; however, the event rate in the low-EPA/AA group treated with pitavastatin+ezetimibe was significantly lower than that in the high-EPA/AA group treated with pitavastatin+ezetimibe.

Although the mean absolute LDL-C level during follow-up was similar between the 2 groups, the mean absolute triglyceride level during follow-up was significantly higher in the low-EPA/AA group than in the high-EPA/AA group. This was because the triglyceride level at baseline in the low-EPA/AA group was significantly higher than that in the high-EPA/AA group. Despite the mean triglyceride level during follow-up being higher, the event rate in the low-EPA/AA group treated with pitavastatin+ezetimibe was significantly lower than that in the high-EPA/AA group treated with pitavastatin+ezetimibe. Therefore, this effect was thought to be independent of LDL-C and triglyceride reduction.

The explanation of this phenomenon might be either of the following: ezetimibe is effective in conditions with a low EPA/

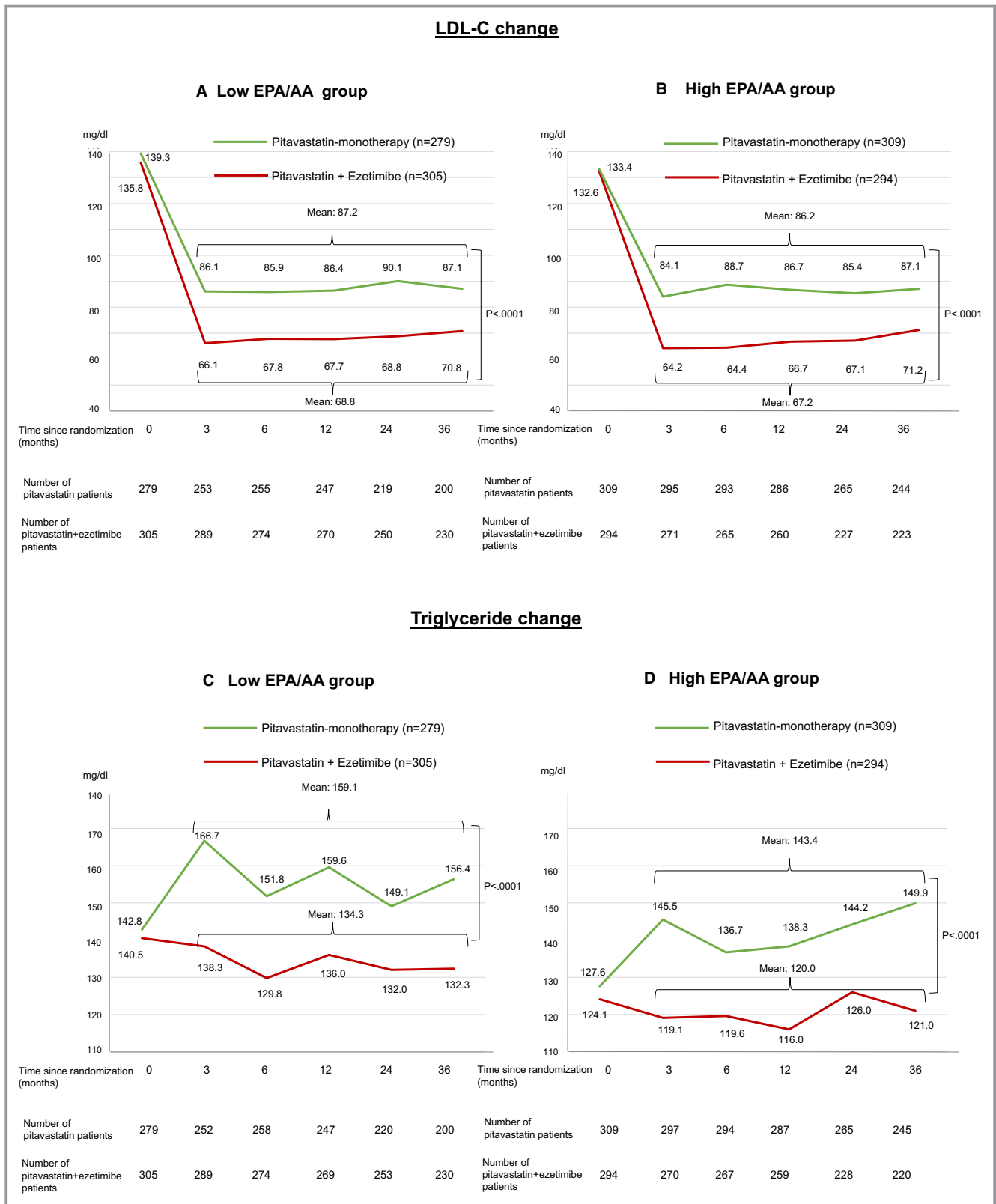


Figure 3. Changes in LDL-C in the low-EPA/AA group (A) and high-EPA/AA group (B) and changes in triglyceride in the low-EPA/AA group (C) and high-EPA/AA group (D). The mean absolute LDL-C level during follow-up is similar between the 2 groups, whereas the mean absolute triglyceride level during follow-up is significantly higher in the low-EPA/AA group than in the high-EPA/AA group because the baseline triglyceride level in the low-EPA/AA group is higher than that in the high-EPA/AA group. EPA/AA indicates eicosapentaenoic acid/arachidonic acid; LDL-C, low-density lipoprotein cholesterol.

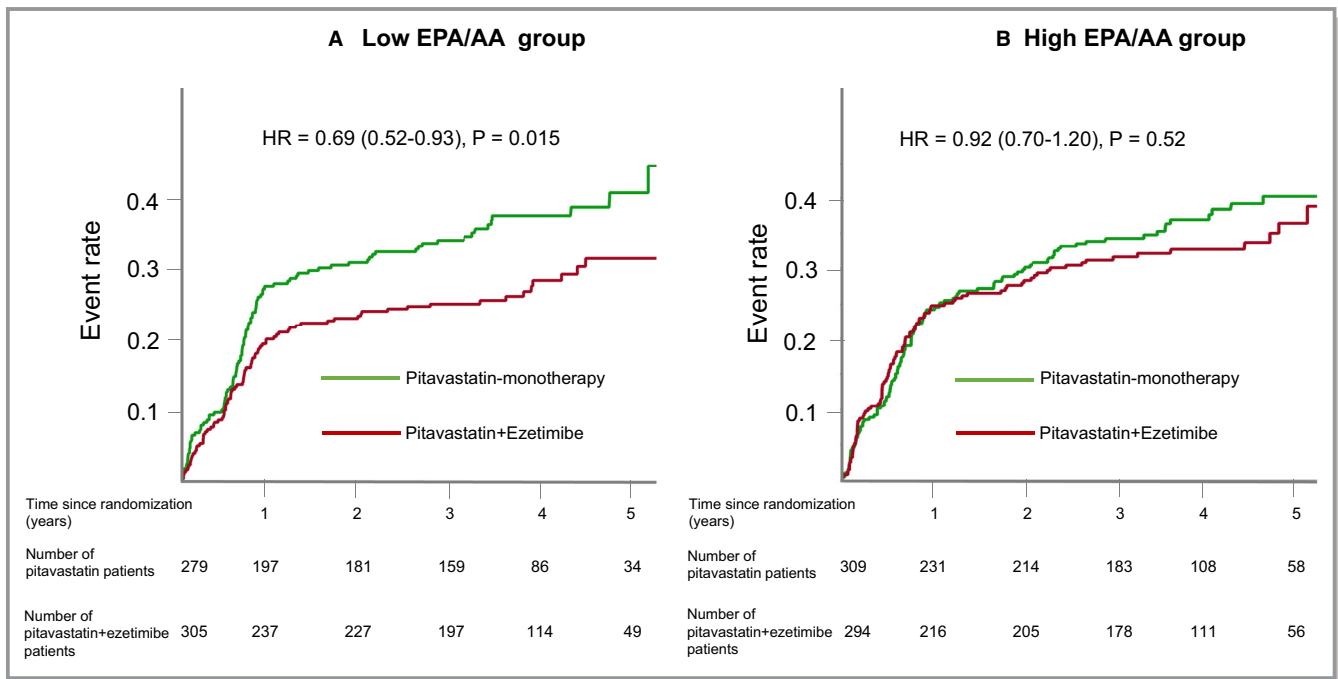


Figure 4. Incidence of primary end point in the low-EPA/AA group (A) and high-EPA/AA group (B). Among ACS patients with a low EPA/AA ratio, pitavastatin+ezetimibe decreases the risk of cardiovascular events compared with pitavastatin monotherapy. ACS indicates acute coronary syndrome; EPA/AA, eicosapentaenoic acid/arachidonic acid; HR, hazard ratio.

AA ratio, or ezetimibe does not work in conditions with a high EPA/AA ratio. There is no clear report on the relationship between ezetimibe efficacy and individual differences. Giugliano et al reported that adding ezetimibe to statin was

beneficial for secondary prevention in non-diabetes mellitus patients with high TIMI (Thrombolysis in Myocardial Infarction) risk scores.¹⁶ In the IMPROVE-IT subanalysis, the investigator suggested that the effect of ezetimibe addition could change

Table 2. Individual Components of the Primary End Point

Low-EPA/AA Group					
	Pitavastatin Monotherapy (n=279)	Pitavastatin+Ezetimibe (n=305)	HR	95% CI	P Value
Primary end point	102 (36.6%)	83 (27.2%)	0.69	0.52 to 0.93	0.015
All-cause death	19 (6.8%)	14 (4.6%)	0.65	0.32 to 1.30	0.22
Nonfatal myocardial infarction	4 (1.4%)	2 (0.7%)	0.43	0.06 to 2.24	0.32
Nonfatal stroke	3 (1.1%)	7 (2.3%)	2.1	0.58 to 9.6	0.27
Unstable angina pectoris	10 (3.6%)	15 (4.9%)	1.35	0.61 to 3.11	0.45
Ischemia-driven coronary revascularization	85 (30.4%)	62 (20.3%)	0.63	0.45 to 0.87	0.005
High-EPA/AA Group					
	Pitavastatin Monotherapy (n=309)	Pitavastatin+Ezetimibe (n=294)	HR	95% CI	P Value
Primary end point	113 (36.6%)	97 (33.0%)	0.92	0.70 to 1.20	0.52
All-cause death	26 (8.4%)	17 (5.8%)	0.71	0.38 to 1.31	0.28
Nonfatal myocardial infarction	5 (1.6%)	3 (1.0%)	0.65	0.13 to 2.66	0.55
Nonfatal stroke	8 (2.6%)	4 (1.4%)	0.54	0.14 to 1.72	0.30
Unstable angina pectoris	7 (2.3%)	8 (2.7%)	1.24	0.44 to 3.54	0.68
Ischemia-driven coronary revascularization	89 (28.8%)	73 (24.8%)	0.87	0.64 to 1.18	0.38

Data are expressed as number (percentage). AA indicates arachidonic acid; EPA, eicosapentaenoic acid; HR, hazard ratio.

Table 3. Independent Predictors Associated With Primary End Point in Low-EPA/AA Group

	Univariate Analysis			Multivariate Analysis		
	Hazard Ratio	95% CI	P Value	Hazard Ratio	95% CI	P Value
Age*	1.01	1.00 to 1.03	0.03	1.01	0.99 to 1.02	0.19
Men	1.35	0.94 to 1.99	0.11			
Body mass index*	0.99	0.95 to 1.03	0.88			
Glomerular filtration rate [†]	0.89	0.83 to 0.96	0.01	0.92	0.85 to 1.01	0.09
Hypertension	1.22	0.90 to 1.67	0.19			
Diabetes mellitus	1.37	1.01 to 1.85	0.05	1.29	0.94 to 1.76	0.11
Current smoker	1.23	0.92 to 1.64	0.16			
Previous myocardial infarction	1.37	0.82 to 2.14	0.21			
Previous revascularization	1.72	1.11 to 2.58	0.02	1.39	0.88 to 2.11	0.15
STEMI	1.16	0.87 to 1.55	0.31			
Non-STEMI	0.52	0.26 to 0.94	0.03	0.59	0.29 to 1.06	0.08
Unstable angina pectoris	1.03	0.76 to 1.38	0.83			
Use of aspirin	1.25	0.84 to 1.81	0.25			
Use of ezetimibe	0.69	0.52 to 0.93	0.02	0.70	0.52 to 0.94	0.02
HDL-C [†]	0.88	0.77 to 0.98	0.04	0.88	0.78 to 1.01	0.053
LDL-C [†]	1.03	0.98 to 1.07	0.25			
Triglyceride [†]	1.01	0.98 to 1.02	0.89			
DHA [†]	0.94	0.90 to 0.99	0.02	0.95	0.91 to 0.99	0.04

AA indicates arachidonic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; STEMI, ST-segment-elevation myocardial infarction.

*Per 1 increase.

[†]Per 10 increase.

depending on the patient's risk factor. Although the mechanism for the improved event rate in the low-EPA/AA group treated with pitavastatin+ezetimibe in this study remains unclear, the differences in the risk factors of patients with coronary artery disease between the low-EPA/AA group and high-EPA/AA group may influence the outcomes of this study.

Most studies have suggested that the EPA/AA ratio remains unchanged or decreases slightly after statin therapy.^{10,17} In addition, Blackwood et al reported that ezetimibe therapy inhibits the absorption of EPA.¹⁸ In our study, compared with the high-EPA/AA group, the low-EPA/AA group showed significant improvement in EPA/AA ratio from baseline to follow-up. Because improvement of EPA/AA ratio was also seen in the low-EPA/AA group treated with pitavastatin monotherapy, we could not speculate that a high EPA/AA ratio was the cause of the better clinical outcome in the low-EPA/AA group treated with pitavastatin+ezetimibe. This change in EPA/AA ratio is interesting, and there might be a hidden key mechanism to clarify why pitavastatin+ezetimibe improved the outcomes in patients with low EPA/AA ratio.

A previous report has shown that DHA levels at baseline correlate with subsequent cardiac events.¹⁹ Similarly, in this study multivariate analysis revealed that lower DHA levels at

baseline were associated with worse clinical outcomes in a subset of ACS patients with dyslipidemia and low EPA/AA ratio. Further, multivariate analysis revealed that the use of ezetimibe was independently associated with better clinical outcomes in ACS patients with a low EPA/AA ratio. Accordingly, this study suggests that risk stratification in ACS patients is possible by measuring the EPA/AA ratio on admission. For ACS patients with dyslipidemia and a low EPA/AA ratio, adding ezetimibe to statin may be recommended. Further prospective studies are needed to validate and understand the current findings.

Limitations

This study has some limitations. First, this study was retrospective and based on the subgroup analysis of a prospective study. Several differences were observed in clinical characteristics between the low-EPA/AA group and the high-EPA/AA group. Thus, the results must be interpreted with caution. Second, measurements of PUFAs were conducted only at baseline and at 3 months. Further, we did not examine the patients' dietary intake, fish consumption, and PUFA supplement intake, including EPA and DHA intake, during the follow-up period. Third, we determined the cutoff

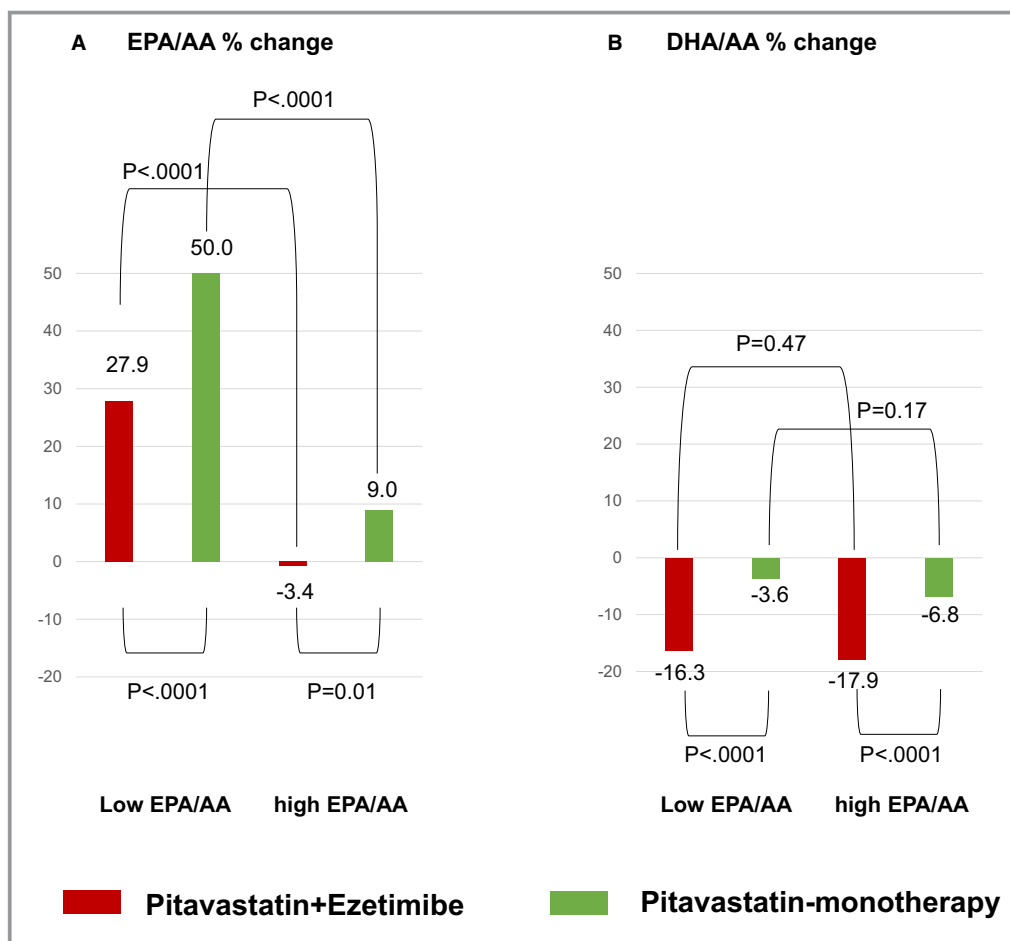


Figure 5. Mean percentage change in EPA/AA (A) and DHA/AA (B) from baseline to 3 months. Regardless of EPA/AA ratio at baseline, the mean percentage change of DHA/AA is similar between patients treated with pitavastatin+ezetimibe and those treated with pitavastatin monotherapy. In contrast, the increase in EPA/AA ratio is significantly higher in the low-EPA/AA group than in high-EPA/AA group after lipid-lowering therapy. DHA/AA indicates docosahexaenoic acid/arachidonic acid; EPA/AA, eicosapentaenoic acid/arachidonic acid.

value for EPA/AA ratio as 0.34 (the median of EPA/AA ratios during admission for the entire study cohort) in the present study. Because currently there is no normal range for EPA/AA in a clinical setting, whether this value of 0.34 is appropriate or not remains to be established. Fourth, although the end point of this study was reviewed by an independent end point committee that was blinded to the study treatment, the fact that ischemia-driven revascularization was the only difference in the low-EPA/AA group treated with pitavastatin+ezetimibe weakens the impact of the study.

Conclusions

Among ACS patients who have dyslipidemia and a low EPA/AA ratio, adding ezetimibe to statin decreases the risk of cardiovascular events compared with statin monotherapy.

Acknowledgments

We thank the HIJ-PROPER participants as well as the staff and investigators of the HIJ-PROPER study for their contributions. We also thank Editage (www.editage.com) for English language editing and publication support.

Author Contributions

Drs Hagiwara, Ogawa, Yamaguchi, and Koyanagi conceptualized and designed the study. Drs Kawada-Watanabe, Arashi, Haruta, Mori, Ishii, Suzuki, Murasaki, and Yamauchi collected data, enrolled patients, and followed up patients. Drs Yamaguchi, Arashi, Kawada-Watanabe, and Haruta analyzed and interpreted the data. Drs Arashi and Yamaguchi drafted and wrote the manuscript. Drs Hagiwara and Ogawa reviewed the manuscript. All authors had full access to all of the data

(including statistical reports and tables) in the study and take responsibility both for the integrity of the data and the accuracy of the data analysis.

Sources of Funding

The trial was funded by the Japan Research Promotion Society for Cardiovascular Diseases.

Disclosures

All members of the HIJ-PROPER study group report having received research support to perform clinical trials from the Japan Research Promotion Society for Cardiovascular Diseases, which is sponsored by Abbott Vascular Japan Co, Ltd, AstraZeneca KK, Bayer Yakuhin, Ltd, Boston Scientific Corporation, Bristol-Myers KK, Daiichi Sankyo Company, Limited, Kowa Pharmaceutical Co, Ltd, Mochida Pharmaceutical Co, Ltd, MSD KK, Nippon Boehringer Ingelheim Co, Ltd, Novartis Pharma KK, Pfizer Japan Inc, Sanofi KK, and Takeda Pharmaceutical Company Ltd. Dr Hagiwara reports that he has received honoraria from Bristol-Myers KK and Nippon Boehringer Ingelheim Co, Ltd and grants from Astellas Pharma Inc, Daiichi Sankyo Company, Limited, Eisai Co, Ltd, Mitsubishi Tanabe Pharma Corporation, Otsuka Pharmaceutical Co, Ltd, Shionogi & Co, Ltd, and Takeda Pharmaceutical Company Ltd. Dr Yamaguchi reports that he belongs to the division (Clinical Research division for Cardiovascular Catheter Intervention) financially maintained by donation from Abbott, Boston Scientific, Medtronic, and Terumo. The HIJ-PROPER Steering Committee had full access to all data in the study and had final responsibility for the decision to submit the article for publication.

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Supplemental Material

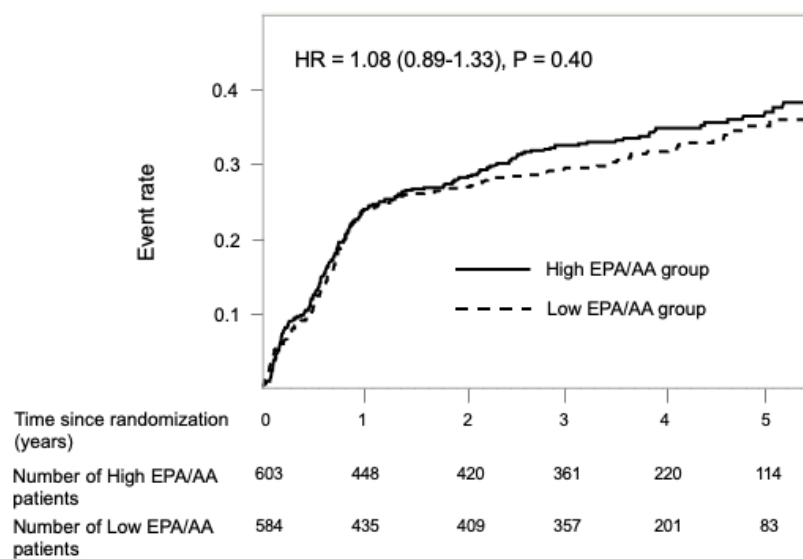
Table S1. Baseline characteristics between included patients and excluded patients.

	Included patients (n = 1187)	Excluded patients (n = 534)	p-value
Age (years)	65.7±11.7	65.4±12.1	0.67
Men	902 (76.0%)	398 (74.5 %)	0.54
BMI (kg/m ²)	24.3±3.5	24.4±3.6	0.49
GFR (mL/min/1.73m ²)	72.2±18.8	75.0±35.3	0.03
Statin naive	975 (82.1 %)	454 (85.0)	0.15
Hypertension	797 (67.1 %)	378 (70.8 %)	0.15
Diabetes mellitus	343 (28.9%)	177 (33.1 %)	0.08
Current smoker	409 (34.5 %)	185 (34.6%)	0.96
Previous myocardial infarction	91 (7.7%)	39 (7.3%)	0.84
Previous revascularization	111 (9.4 %)	44 (8.2 %)	0.52
Previous heart failure	21 (1.8 %)	15 (2.8 %)	0.20
Type of index event			0.0002
STEMI	572 (48.2 %)	308 (57.7 %)	
Non-STEMI	121 (10.2 %)	59 (11.0%)	
Unstable angina pectoris	494 (41.6 %)	167 (31.3 %)	
Medication			
Beta blocker	111 (9.3%)	67 (12.6 %)	0.049
ACEIs/ARBs	352 (29.7 %)	140 (26.2 %)	0.15
Calcium channel blocker	343 (28.9 %)	175 (32.8 %)	0.11
Aspirin	207 (17.4 %)	85 (15.9%)	0.45
Cholesterol metabolism			
Total cholesterol	210.9±35.3	209.4±35.1	0.42
HDL-cholesterol	48.6±12.7	48.9±11.5	0.59
LDL-cholesterol	135.2±29.6	135.2±29.8	0.99
Triglyceride	133.6±70.6	124.5±71.7	0.01

BMI, body mass index; GFR, glomerular filtration rate; STEMI, ST elevation myocardial infarction; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

*Data are expressed as mean ± SD or as number (percentage)

Figure S1. Incidence of primary endpoint between low EPA/AA group (n=584) and high EPA/AA group (n=603).



EPA, eicosapentaenoic acid; AA, arachidonic acid.