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Blood Eicosapentaenoic Acid and Docosahexaenoic Acid as Predictors of All-Cause Mortality in Patients With Acute Myocardial Infarction

— Data From Infarction Prognosis Study (IPS) Registry —

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Background: Although ω-3 polyunsaturated fatty acids are known to have beneficial effects on cardiovascular diseases, their prognostic value has not been studied prospectively in patients with acute myocardial infarction (AMI).

Methods and Results: The plasma levels of phospholipids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (% of total fatty acids), were measured in 508 patients (365 males; mean age, 63 years) with AMI. Clinical and biomarker predictors of all-cause and cardiovascular mortality were identified by stepwise Cox regression model. During a mean follow-up of 16.1 months, 36 (7.1%) patients died. After controlling for confounding variables, age (hazard ratio (HR): 1.09, P<0.001), renal insufficiency (HR: 2.84, P=0.01) and EPA level (HR: 0.29, P=0.004) were identified as independent predictors of all cause-mortality. When stratified by gender, age (HR: 1.08, P=0.001) and renal insufficiency (HR: 4.49, P=0.003) were predictors of all-cause-mortality in males, whereas EPA level (HR: 0.18, P=0.009) and angiotensin-converting enzyme inhibitor use (HR: 0.24, P=0.03) were identified as predictive of all-cause-mortality in females.

Conclusions: Lower plasma level of EPA, but not DHA, was an independent predictor for all-cause-mortality in patients with AMI, but this relationship was significant only in female patients. (*Circ J* 2009; **73:** 2250–2257)

Key Words: Death; Docosahexaenoic acid; Eicosapentaenoic acid; Myocardial infarction; ω-3 fatty acids

Several observational studies regarding the effects of ω-3 polyunsaturated fatty acids (PUFA), particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), on coronary artery disease have focused on fish intake and prognosis in healthy individuals.[1–3] The results show a lower risk of mortality and beneficial effects in people who consume ω-3 PUFA more often. The GISSI Prevenzione study also showed the protective effect of EPA+DHA intake on mortality in survivors of myocardial infarction (MI).[4] Interestingly, a recent Japanese study showed that EPA alone added to statin significantly reduced major coronary events in hypercholesterolemic subjects[5] and patients with established coronary artery disease.[6]

The relationship between ω-3 PUFA and the clinical outcome was also evaluated by analyzing fatty acid content and future risk. EPA+DHA, as the percent of total fatty acids in blood or cell membrane, was predictive of sudden cardiac death.[7,8] Those studies were based on case–control analyses of follow-up data in healthy individuals, but the prognostic value of blood ω-3 PUFA has not been determined in the context of acute MI (AMI).[9] Furthermore, the predictive power of EPA and DHA individually has not been reported.

To answer these questions, we measured fatty acids from among the plasma phospholipids that represent dietary intake.[10] Using a prospective design, we evaluated the relationship between the levels of these fatty acids and all-cause and cardiovascular mortality in patients with AMI after adjustment for other confounding variables.

Methods

Study Population

Patients were drawn from the Infarction Prognosis Study registry of AMI as described previously.[11] Briefly, all consecutive patients admitted to Severance Cardiovascular Hospital between May 2005 and February 2008 were prospectively screened for an AMI. Patients ≥18 years of age

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Table 1. Baseline Characteristics of Survivors and Non-Survivors

Characteristics	All patients (n=508)	Survivors (n=472)	Non-survivors (n=36)	P value
Age (years)	63±12	62±12	72±9	<0.001
Female gender, n (%)	143 (28)	129 (27)	14 (39)	0.14
BMI, kg/m^2	24.0±3.6	24.1±3.6	22.2±3.1	0.005
Medical history				
Diabetes mellitus, n (%)	134 (26)	122 (26)	12 (33)	0.33
Hypertension, n (%)	253 (50)	228 (48)	25 (69)	0.02
Current smoker, n (%)	140 (28)	134 (29)	6 (23)	0.20
Renal insufficiency, n (%)	38 (7)	29 (6)	9 (33)	<0.001
Prior MI, n (%)	30 (6)	28 (6)	2 (6)	0.92
Laboratory examination				
FBG, mg/dl	117 (59–539)	117 (59–539)	125 (72–328)	0.20
TC, mg/dl	174±42	176±42	158±36	0.02
TG, mg/dl	98 (20–566)	99 (20–566)	79 (41–256)	0.004
HDL-C, mg/dl	44±11	44±11	47±15	0.19
LDL-C, mg/dl	111±36	112±36	97±33	0.02
hs-CRP, mg/L	6.8 (0.2–301.0)	6.2 (0.2–301.0)	17.0 (0.9–246.0)	0.001
EPA (%)	1.47 (0.10–3.52)	1.49 (0.10–3.52)	1.24 (0.50–2.14)	0.001
DHA (%)	2.44 (0.18–7.58)	2.48 (0.14–7.58)	2.04 (0.18–6.20)	0.14
Characteristics of MI				
STEMI, n (%)	241 (47)	222 (47)	19 (53)	0.61
Time from symptom onset to arrival, h	3.0 (0.3–24.0)	3.0 (0.3–24.0)	6.0 (1.6–24.0)	0.12
Peak CK-MB, IU/L	65 (7–1,503)	65 (7–1,503)	44 (7–738)	0.55
Culprit artery, n (%)				0.97
LAD	265 (52)	247 (52)	18 (50)	
LCX	89 (18)	82 (17)	7 (19)	
RCA	154 (30)	143 (30)	11 (31)	
Diseased arteries, n (%)				0.35
Minimal disease	14 (3)	13 (3)	1 (3)	
1-vessel disease	154 (30)	148 (31)	6 (17)	
2-vessel disease	155 (31)	145 (31)	10 (28)	
3-vessel disease	184 (36)	166 (35)	18 (50)	
LV systolic dysfunction, n (%)	263 (52)	237 (50)	26 (72)	0.01
Mode of treatment, n (%)				0.09
Conservative medical treatment	41 (8)	38 (8)	3 (8)	
Thrombolysis	18 (4)	14 (3)	4 (11)	
PCI	404 (80)	378 (80)	26 (72)	
Coronary artery bypass graft	45 (9)	42 (9)	3 (8)	
Early invasive therapy, n (%)	508 (84)	399 (85)	30 (83)	0.78
Medications				
β-blocker use, n (%)	372 (73)	355 (75)	17 (47)	<0.001
ACEI/ARB use, n (%)	388 (76)	369 (78)	19 (53)	0.001
Statin use, n (%)	405 (80)	378 (80)	27 (75)	0.47

*Log transformed.

BMI, body mass index; Renal insufficiency, serum creatinine ≥2.0 mg/dl; MI, myocardial infarction; FBG, fasting blood glucose; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; hs-CRP, high-sensitivity C-reactive protein; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; CK-MB, creatine kinase myocardial isoform; LV, left ventricle; Early invasive therapy, emergency thrombolysis, percutaneous coronary intervention (PCI) or coronary artery bypass graft; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker.

were eligible for enrollment for up to 24 h after the onset of symptoms. AMI was defined as an elevated creatine kinase myocardial isoform (CK-MB) value greater than twice the upper reference limit, with 1 of the following: (1) typical chest pain lasting >30 min or (2) ECG showing new ST-T change or new left bundle branch block. We obtained informed consent from all subjects, and the institutional review board approved the study protocol.

Patients received oral aspirin, clopidogrel, and 5,000 U of intravenous heparin. The attending physician and interventional cardiologist decided the allocation of reperfusion therapy.

Data Collection and Laboratory Examinations

Clinical and demographic data were obtained from all patients at the time of admission. Diabetes mellitus was defined as clinically determined or treated disease. Hypertensive patients were those with documented blood pressure >140/90 mmHg on 2 or more occasions, or who were already on antihypertensive therapy. Renal insufficiency was defined as serum creatinine levels >2.0 mg/dl. Every patient underwent serial ECG recording and echocardiographic examination. Left ventricular ejection fraction was calculated by the modified Quinones method. Coronary angiograms were analyzed for the number of diseased arteries (ie, epicardial arteries or their major branches with a lesion with diameter stenosis ≥50%).

Serial CK-MB testing was performed at baseline and at 6, 12 and 24 h. Blood samples from each patient were analyzed using a Dade Behring Dimension unit (Dade Behring Inc, Newark, DE, USA) with upper reference limits of 4.2 ng/ml for men and 3.1 ng/ml for women. Blood samples for biochemical assessment, such as fasting blood glucose and lipids, were obtained after a 12-h fast post-admission. From

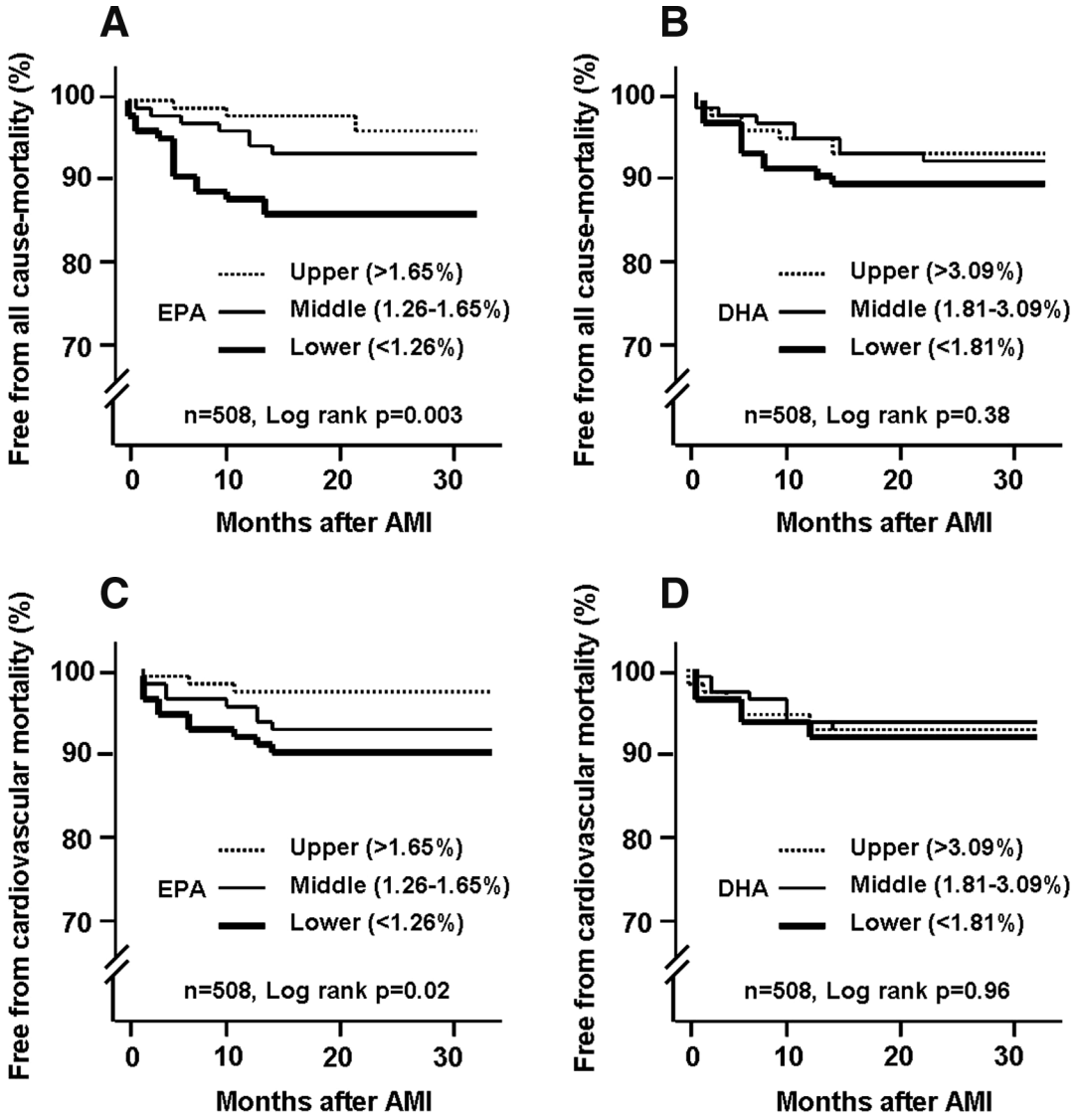

Figure 1. Kaplan-Meier curves showing survival free from all-cause mortality (**A**,**B**) or from cardiovascular mortality (**C**,**D**) by tertiles of the eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) levels. AMI, acute myocardial infarction.

additional blood samples, plasma was isolated within 60 min of acquisition and subsequently stored at −80°C until analysis at a later date. Aliquots of the plasma samples were used to measure the level of the following biomarkers.

Total lipids were extracted by the method of Folch et al[12] and the phospholipid fraction was isolated by thin-layer chromatography with hexane:diethyl ether:acetic acid (80:20:2) development solvent. The phospholipid fraction was then directly transesterified by the method of Lepage and Roy[13] and the methyl esters were separated on a gas chromatograph (model 6890, Agilent Technologies Inc, Palo Alto, CA, USA) equipped with a capillary column (SP-2560; 100 m, Supelco, Bellefonte, PA, USA) as described previously.[14] Peak retention times were identified by comparison with a known standard (37 component FAME mix, Supelco, Bellefonte, PA; GLC37, NuCheck Prep, Elysian, MN, USA) and analyzed with the ChemStation software (Agilent Technologies). The serum phospholipid content of EPA and DHA was expressed as a percentage of the total fatty acids. Serum levels of high-sensitivity C-reactive protein (hs-CRP) were measured with Express^{+} autoanalyzer (Chiron Diagnostics Co, Walpole, MA, USA) using a hs-CRP-Latex (II) X2 kit (Seiken Laboratories Ltd, Tokyo, Japan).

Follow-up

Clinical outcome data were obtained for all patients in the study by telephone contact and medical record review, and in subsequent visits. The primary endpoint was all-cause mortality and the secondary endpoint was cardiovascular mortality. A death was classified as cardiovascular if the cause was related to MI or ischemia, arrhythmia, heart failure or stroke, or if the death was sudden and unexpected. A death was defined as non-cardiovascular if the main underlying process was not related to the cardiovascular system, such as sepsis, hemorrhage, or malignancy.

Statistical Analysis

We compared the baseline characteristics of patients who survived and those who died during follow-up using

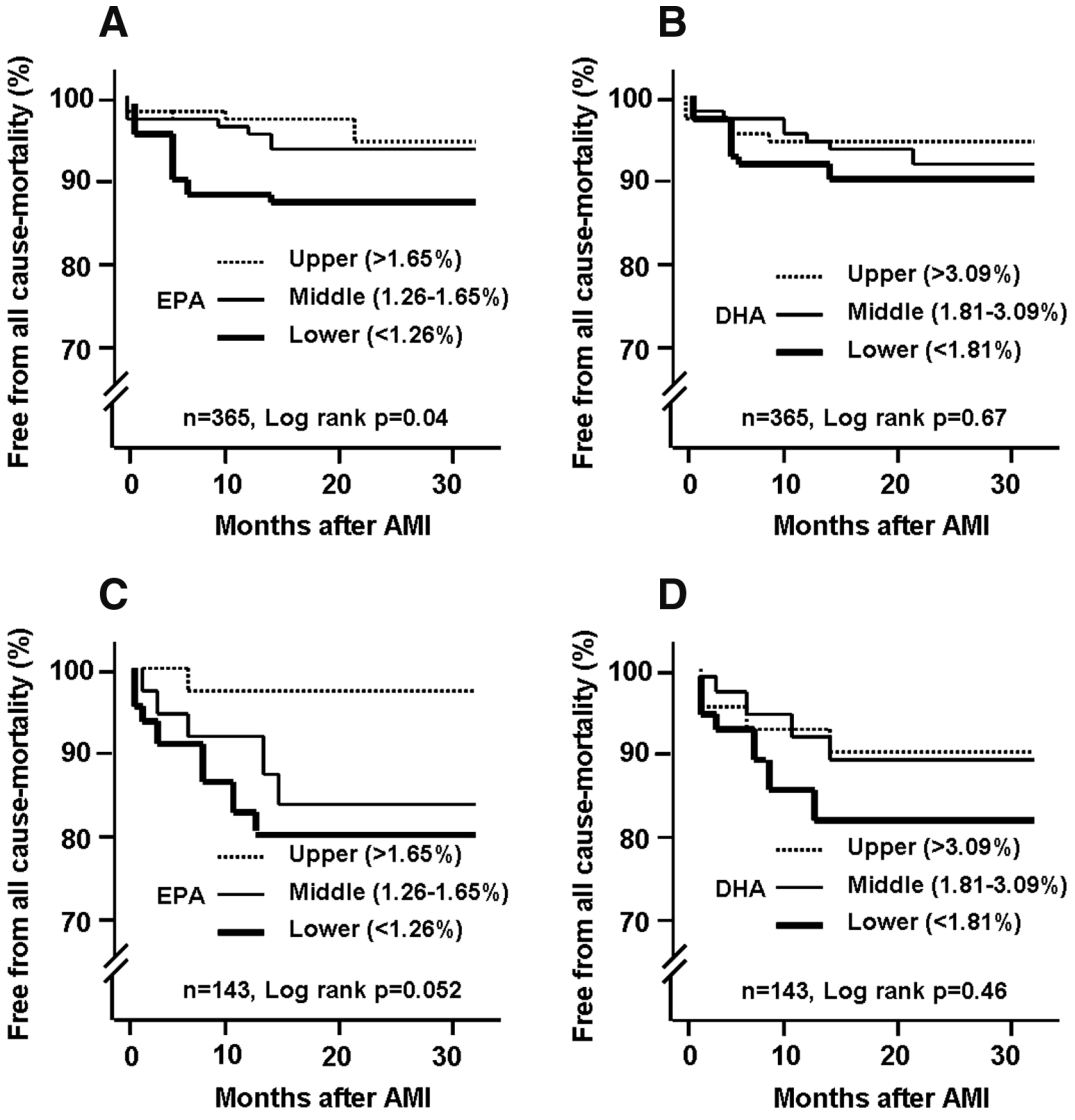

Figure 2. Kaplan-Meier curves showing survival free from all-cause mortality by tertiles of the eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) levels. Survival curves of males (**A**,**B**) and females (**C**,**D**) are shown. AMI, acute myocardial infarction.

Student's t-test and the chi-squared test. Continuous variables with little skewing (age, body mass index, total cholesterol, high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C)) were listed as mean±SD and continuous variables with a skewed distribution (fasting blood glucose, triglyceride, hs-CRP, time from symptoms to admission, peak creatine-kinase (CK)-MB) were listed as median (range). Categorical variables are presented as frequencies and group percentages. Log transformation was applied to fasting blood glucose, triglyceride, hs-CRP, CK-MB, and the period of time from onset of symptoms to admission.

Tertiles of EPA and DHA content were constructed and cumulative survival curves of each tertile established by the Kaplan-Meier method were compared by the log-rank test. The predictors of mortality were identified by univariate Cox regression analysis. Only those univariate predictors with $P<0.05$ were subsequently entered into multivariate Cox proportional hazard analyses by a stepwise method. Hazard ratios (HR) and 95% confidence intervals (CI) were reported. All analyses used 2-tailed tests with a significance level of 0.05. The statistical software package SPSS version 12.0 (SPSS Inc, Chicago, IL, USA) was used for all analyses. To determine the potential difference in prognostic power of EPA and DHA between men and women, predictors of mortality were analyzed by gender.

Results

Baseline Characteristics

We enrolled 508 patients (365 males, 143 females) with a mean age of 63 years (range 27–91 years) and a mean body mass index of 24.0 (±3.6) kg/m^2 (**Table 1**). Levels of both plasma phospholipids, EPA and DHA, had a skewed distribution among the subjects, and the median levels were 1.47% and 2.44%, respectively. Plasma EPA (1.47% vs 1.46% in males and females, respectively) and DHA levels (2.38% vs 2.55% in males and females, respectively) were not significantly different between males and females. In total, 241 patients had ST elevation MI. The median time

Table 2. Predictors of All-Cause and Cardiovascular Mortality by Cox Proportional Hazard Analysis (n=508)

	All-cause mortality				Cardiovascular mortality			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value
Age	1.09 (1.05–1.13)	<0.001	1.09 (1.05–1.14)	<0.001	1.09 (1.05–1.13)	<0.001	1.10 (1.05–1.16)	<0.001
Female gender	1.74 (0.89–3.40)	0.11			1.92 (0.92–4.01)	0.09		
BMI (per kg/m^2)	0.87 (0.79–0.95)	0.001			0.87 (0.79–0.96)	0.006		
Diabetes mellitus	1.38 (0.69–2.76)	0.36			1.69 (0.80–3.57)	0.17		
Hypertension	2.39 (1.18–4.86)	0.02			2.33 (1.06–5.11)	0.04		
Current smoker	0.57 (0.23–1.38)	0.21			0.62 (0.23–1.64)	0.33		
Renal insufficiency	4.71 (2.21–10.01)	<0.001	2.84 (1.24–6.49)	0.01	5.31 (2.35–12.00)	<0.001	6.29 (2.39–16.53)	<0.001
Prior MI	0.99 (0.24–4.11)	0.99			1.23 (0.29–5.19)	0.78		
FBG (per mg/dl)*	2.21 (0.93–5.28)	0.07			2.38 (0.91–6.20)	0.08		
TC (per mg/dl)	0.99 (0.98–1.00)	0.03			0.99 (0.98–1.00)	0.22		
TG (per mg/dl)*	0.39 (0.19–0.79)	0.009			0.38 (0.17–0.84)	0.02		
HDL-C (per mg/dl)	1.02 (0.99–1.05)	0.22			1.02 (0.99–1.05)	0.19		
LDL-C (per mg/dl)	0.99 (0.98–1.00)	0.02			0.99 (0.98–1.00)	0.06		
hs-CRP (per mg/L)*	1.44 (1.16–1.78)	0.001			1.45 (1.14–1.83)	0.002		
EPA (per %)*	0.38 (0.22–0.65)	<0.001	0.29 (0.12–0.67)	0.004	0.41 (0.22–0.76)	0.005		
DHA (per %)*	0.66 (0.42–1.03)	0.07			0.84 (0.49–1.45)	0.84		
Time from symptom onset to arrival (per h)*	1.66 (0.85–3.28)	0.14			1.10 (0.54–2.27)	0.79		
Peak CK-MB (per IU/L)*	0.95 (0.76–1.20)	0.69			1.04 (0.80–1.35)	0.76		
No. of diseased arteries	1.14 (0.94–1.40)	0.19			1.83 (1.05–3.18)	0.03		
LVEF <50%	2.61 (1.21–5.62)	0.01			4.11 (1.55–10.89)	0.005		
Early invasive therapy	0.70 (0.29–1.68)	0.42			0.69 (0.26–1.81)	0.45		
β-blocker use	0.30 (0.16–0.58)	<0.001			0.28 (0.13–0.57)	0.001		
ACEI/ARB use	0.34 (0.17–0.65)	0.001			0.32 (0.16–0.67)	0.002		
Statin use	0.80 (0.38–1.70)	0.56			0.84 (0.36–1.96)	0.69		

*Log transformed.
HR, hazard ratio; CI, confidence interval; EF, ejection fraction. Other abbreviations see in Table 1.

Table 3. Predictors of All-Cause Mortality in Men and Women by Cox Proportional Hazard Analysis

	Men (n=365)				Women (n=143)			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value
Age	1.10 (1.06–1.15)	<0.001	1.08 (1.03–1.13)	0.001	1.06 (0.99–1.13)	0.09		
BMI (per kg/m^2)	0.88 (0.79–0.97)	0.01			0.85 (0.70–1.03)	0.09		
Diabetes mellitus	0.95 (0.35–2.57)	0.92			1.94 (0.68–5.53)	0.22		
Hypertension	2.52 (1.06–6.00)	0.04			1.60 (0.45–5.75)	0.47		
Current smoker	0.70 (0.27–1.81)	0.46			0.05 (0.00–25505)	0.047		
Renal insufficiency	7.35 (2.99–18.04)	<0.001	4.49 (1.64–12.45)	0.003	1.78 (0.40–7.96)	0.45		
Prior MI	1.68 (0.39–7.17)	0.49			0.05 (0.00–961)	0.54		
FBG (per mg/dl)*	1.67 (0.52–5.41)	0.39			2.87 (0.77–10.71)	0.12		
TC (per mg/dl)	0.98 (0.97–0.99)	0.006			1.00 (0.99–1.01)	0.34		
TG (per mg/dl)*	0.28 (0.12–0.68)	0.005			1.00 (0.99–1.01)	0.78		
HDL-C (per mg/dl)	1.02 (0.98–1.06)	0.33			1.01 (0.97–1.06)	0.66		
LDL-C (per mg/dl)	0.98 (0.97–1.00)	0.01			1.00 (0.98–1.01)	0.54		
hs-CRP (per mg/L)*	1.60 (1.21–2.11)	0.001			1.23 (0.89–1.70)	0.21		
EPA (per %)*	0.46 (0.22–0.94)	0.03			0.22 (0.08–0.61)	0.003	0.18 (0.05–0.65)	0.009
DHA (per %)*	0.75 (0.41–1.36)	0.34			0.50 (0.25–0.97)	0.04		
Time from symptom onset to arrival (per h)*	1.73 (0.76–3.98)	0.19			1.51 (0.43–5.30)	0.52		
Peak CK-MB (per IU/L)*	0.87 (0.64–1.18)	0.38			1.11 (0.78–1.58)	0.57		
No. of diseased arteries	1.05 (0.78–1.42)	0.75			1.26 (0.96–1.65)	0.10		
LVEF <50%	1.95 (0.78–4.88)	0.16			4.58 (1.01–20.71)	0.048		
Early invasive therapy	0.58 (0.20–1.72)	0.33			1.03 (0.23–4.67)	0.97		
β-blocker use	0.39 (0.17–0.90)	0.03			0.21 (0.07–0.61)	0.005		
ACEI/ARB use	0.42 (0.18–0.98)	0.045			0.24 (0.08–0.70)	0.008	0.24 (0.07–0.89)	0.03
Statin use	0.65 (0.26–1.67)	0.37			1.21 (0.34–4.32)	0.78		

*Log transformed.
Abbreviations see in Tables 1,2.

from chest pain to admission was 3.0 h; 48% of the patients had reduced left ventricular systolic function (ejection fraction <50%) and 84% of the patients were treated with early invasive therapy (emergency thrombolysis, percutaneous coronary intervention or coronary artery bypass graft).

Compared with patients who were alive, those who died were significantly older, had a lower body mass index, and were more likely to have a history of hypertension. Interestingly, non-survivors showed lower levels of total cholesterol, triglyceride, and LDL-C, but higher hs-CRP levels.

They had lower EPA levels, but their DHA levels did not differ significantly from those of the survivors. The non-survivors suffered more often from left ventricular systolic dysfunction, and had less frequently received prescription for β-blockers or angiotensin-converting enzyme inhibitor (ACEI)/angiotensin-receptor blocker (ARB).

Clinical Outcome and Predictors of Mortality

During 16.1±9.8 months of follow-up, 36 (7.1%) patients died and of these deaths, 29 were identified as cardiovascular and 7 as non-cardiovascular in etiology. Cardiovascular causes of deaths were heart failure in 12, sudden death in 8, arrhythmia in 6, hemorrhagic stroke in 2, and cardiac rupture in 1. Non-cardiovascular causes of deaths were pneumonia in 3, sepsis in 2, and cancer in 2. The number of males and females who died was 22 and 14, respectively, and their incidence were not significantly different (6.0% vs 9.8%, P=0.14). The number of cardiovascular deaths in males and females was 17 and 12, respectively, and the incidence were not different either (4.7% vs 8.3%, P=0.10).

Of the 36 deaths, 11 died during the first month after the enrollment, 14 during the next 5 months, and 11 thereafter. **Figure 1** shows the Kaplan-Meier curves depicting survival free from all-cause or cardiovascular mortality. The survival free from all-cause (P=0.003) and cardiovascular mortality (P=0.02) increased with higher EPA tertiles, but was not significantly related to DHA level. When survival was compared with patients stratified by gender, the relationship of EPA tertile and survival free from all-cause mortality remained in males (P=0.04) and females (P=0.052) (**Figure 2**).

Univariate and multivariate Cox proportional hazard analyses for all-cause and cardiovascular mortality are presented in **Table 2**. Age, body mass index, hypertension, renal insufficiency, total cholesterol, triglyceride, LDL-C, hs-CRP, and EPA were significantly associated with all-cause mortality, whereas DHA was not. Left ventricular systolic dysfunction, β-blocker use, and ACEI/ARB use were also associated with all-cause mortality. After adjustment of the variables derived from univariate analyses, age (P<0.001), renal insufficiency (P=0.01), and EPA (P=0.004) independently predicted all-cause mortality. For cardiovascular mortality, however, only age (P<0.001) and renal insufficiency (P<0.001) remained as independent predictors after controlling for confounding variables.

In the analysis by gender (**Table 3**), EPA (P=0.009) and ACEI/ARB use (P=0.03) predicted all-cause mortality in women (n=143). In men (n=365), however, EPA did not independently predict all-cause mortality.

Discussion

This prospective study of AMI produced several new findings. Independent of clinical and laboratory variables, a low baseline plasma phospholipid EPA level (% of total fatty acids) was related to increased risk of mortality, but this relationship was significant only in women. Although the DHA level showed a marginal association with outcome, it did not independently predict mortality in the multivariate analysis. This study is the first to show, prospectively, the different prognostic value of blood EPA and DHA levels in AMI patients.

As a biomarker, the blood and cellular levels of ω-3 PUFA show a significant negative correlation with the extent of coronary artery disease[15] and the risk for sudden death.[7,8] This has led some investigators to propose using the percentage of EPA+DHA in red blood cell fatty acids as a risk marker for sudden cardiac death.[16] The relationship of ω-3 PUFA with cardiovascular risk was reported to be independent of other traditional risk factors.[17]

Two case–control studies compared the plasma blood and cellular EPA and DHA levels in patients with acute coronary syndrome and healthy people. One of these, with 94 patients and 94 controls, found significantly lower blood EPA (0.33±0.44% in cases, 0.57±0.59% in controls) and DHA (1.34±0.68% in cases, 1.84±0.89% in controls) in the patients.[18] In the other study, this same group measured erythrocyte membrane EPA and DHA in 768 acute coronary syndrome patients and 768 controls. Cases again showed lower values for both EPA (0.46±0.29% in cases, 0.72±0.53% in controls) and DHA (2.93±1.40% in cases, 3.53±1.57% in controls).[19] The authors suggested that low EPA+DHA is associated with a risk for acute coronary syndrome. Their analyses included an adjustment for subjects' lipid profiles, but did not adjust for many other risk factors and markers for coronary artery disease.

In the present study, our subjects with AMI showed a higher median plasma EPA level (1.47%) than those reported for populations in the western hemisphere, except northern Europe.[20] A previous study showed a positive correlation between cellular EPA and DHA with age, and a negative correlation with body mass index.[21] Levels may also differ with ethnicity, even among Asian populations.[22] In addition, there may be higher intakes of this fatty acid in Korea, as reported in comparisons of estimated intake of ω-3 PUFA on a global scale.[23] Hence a number of variables, including differences in subjects' age, body mass index, ethnicity, and food intake, may help to explain why we obtained a higher median plasma value for EPA than previous studies have reported.

In our study, lower EPA content, but not DHA content, was an independent predictor of all-cause mortality. Although the underlying mechanism of this finding is not clear by our results, some plausible mechanisms can be suggested. The better prognostic power can be related to the anti-inflammatory effects of EPA. Both arachidonic acid and EPA are involved in inflammation as sources of lipid mediators, and those formed from EPA are less proinflammatory.[24] In states of inflammation, EPA is released to compete with arachidonic acid for enzymatic metabolism.[25] Although some in-vitro studies have shown DHA to be a more potent antiinflammatory agent than EPA,[26,27] the suppressive effect of EPA on cytokine production was more pronounced in other studies.[28,29] Another important finding in our study is that the relationship between EPA content and cardiovascular mortality was not independent. On the contrary, patient's age and renal insufficiency were independent predictors for cardiovascular mortality. In our data, age and renal insufficiency significantly correlated with EPA content; therefore, EPA content might have lost its prognostic power in the multivariate analysis. Lindberg et al showed that plasma phospholipid ω-3 PUFA content is inversely associated with all-cause mortality in acutely sick elderly patients.[30] Although the prognostic value of DHA content was not assessed, they used the EPA content as a surrogate marker and the main result concords with ours.

The analysis of our data by gender supports a stronger association between plasma EPA and mortality in women than in men. Whether gender modifies the effects of ω-3 PUFA on clinical outcome remains uncertain. Because

most studies have included only male subjects, and of those that included females, few have addressed the relationship between gender and outcome. From the analysis of samples from the Nurses' Health Study, however, Sun et al found an inverse relationship between plasma EPA and risk for future MI among women.[31] A Finnish study found an inverse relationship between fish intake and risk for coronary heart disease among women, but found no significant association among men.[32] Women have higher plasma levels of ω-3 PUFA and synthesize them more efficiently to form α-linolenic acid because of their endocrine factors. In addition, the capacity of sex hormones to modify plasma and tissue ω-3 PUFA content may partly explain the gender difference;[33] however, the significance and magnitude of this difference need further investigation.

Several features distinguish and strengthen our study. First, we adjusted for most traditional risk factors, biomarkers, characteristics of MI, and therapeutic parameters, which may increase the power of our analysis. Second, we evaluated the clinical aspect of plasma EPA and DHA separately. In contrast, most previous studies have treated these fatty acids as a combined parameter. Third, we analyzed the data separately for men and women. Although our data cannot explain the mechanism of the gender difference we found, future studies may now consider it.

We used plasma phospholipid for EPA and DHA content evaluation. Although plasma phospholipids fatty acids content is considered to reflect shorter-term fat intake rather than red blood cell fatty acids, it is known to be highly correlated with red blood cell content.[34] Moreover, phospholipids in plasma are a major contributor in determining the content in blood. We assessed EPA and DHA levels at a single time point in the acute phase of MI. A previous study has shown that fatty acid content in erythrocytes[35] and in blood phospholipids[36] can change after AMI. However, the change in the first several hours is not very large and most of our samples were obtained within this period. Importantly, we selected our subjects from a population most representative of our clinical and research concerns: Koreans with AMI. Hence we cannot generalize our findings directly to other ethnic groups or healthy individuals. Finally, it might be difficult to draw a concrete conclusion from subanalyses of our data because of the limited number of the subjects.

Our study identified low plasma phospholipid EPA, but not DHA, as an independent predictor of all-cause mortality following AMI. The prognostic value of EPA was independent of traditional risk factors, characteristics of MI, biomarkers, and therapeutic variables, and was significant only in female patients. This study is the first to show a difference in the prognostic value of blood EPA and DHA levels in AMI using a prospective design.

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