Clinical Investigation

Associations With Eicosapentaenoic Acid to Arachidonic Acid Ratio and Mortality in Hospitalized Heart Failure Patients

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ABSTRACT

Background: Intake of n-3 polyunsaturated fatty acids (n-3 PUFAs) lowers the risk of atherosclerotic cardiovascular events, particularly ischemic heart disease. In addition, the ratio of eicosapentaenoic acid (EPA; n-3 PUFA) to arachidonic acid (AA; n-6 PUFA) has recently been recognized as a risk marker of cardiovascular disease. In contrast, the prognostic impact of the EPA/AA ratio on patients with heart failure (HF) remains unclear.

Methods and Results: A total of 577 consecutive patients admitted for HF were divided into 2 groups based on median of the EPA/AA ratio: low EPA/AA (EPA/AA <0.32 mg/dl, n = 291) and high EPA/AA (EPA/AA ≥0.32, n = 286) groups. We compared laboratory data and echocardiographic findings and followed cardiac mortality. Although body mass index, blood pressure, B-type natriuretic peptide, hemoglobin, estimated glomerular filtration rate, total protein, albumin, sodium, C-reactive protein, and left ventricular ejection fraction did not differ between the 2 groups, cardiac mortality was significantly higher in the low EPA/AA group than in the high EPA/AA group (12.7 vs 5.9%, log-rank $P = .004$). Multivariate Cox proportional hazard analysis revealed that the EPA/AA ratio was an independent predictor of cardiac mortality (hazard ratio 0.677, 95% confidence interval 0.453–0.983, $P = .041$) in patients with HF.

Conclusion: The EPA/AA ratio was an independent predictor of cardiac mortality in patients with HF; therefore, the prognosis of patients with HF may be improved by taking appropriate management to control the EPA/AA balance. (*J Cardiac Fail 2016;22:962–969*)

Key Words: Heart failure, n-3 polyunsaturated fatty acids, eicosapentaenoic acid to docosahexaenoic acid ratio, prognosis.

Heart failure (HF) remains one of the major causes of cardiovascular morbidity and mortality, despite therapeutic advances in its treatment. The cardiovascular protective effects of seafood consumption and long-chain n-3 polyunsaturated fatty acid (n-3 PUFA) intake(eg, plaque stabilization, antiarrhythmic and hemodynamic effects) have been reported.[1–6] The balance between dietary n-3 and n-6 fatty acids, especially a low serum ratio of eicosapentaenoic acid (EPA; n-3 PUFA) to arachidonic acid (AA; n-6 PUFA) may be strongly associated with increased risk of cardiovascular disease (CVD).[1,7] Although AA increases inflammation, platelet aggregation, and vasoconstriction through cyclooxygenase and lipoxygenase, EPA impairs inflammatory eicosanoid derived from AA, platelet aggregation, and vasodilatation. EPA competes or cooperates with AA, and thus the balance of EPA and AA may be important.[1] In addition, the EPA/AA ratio has

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a linear relationship with the ratio of prostaglandin I_3 and prostaglandin I_2 to thromboxane A_2.[1] Therefore, the EPA/AA ratio has recently been recognized as a risk marker of CVD including myocardial infarction, sudden cardiac death, stroke, and thromboembolism in various populations.[1,8–11] However, the association between circulating levels of EPA/AA ratio and cardiac mortality in patients with HF still remains unclear. In addition, such an association may vary depending upon several clinical backgrounds, such as age, gender, HF etiology, comorbidities, and treatments.[10,12–16] Furthermore, n-3 PUFA also attracts attention as a therapeutic target[1,10] to reduce the residual risk of CVD after low-density cholesterol-lowering therapy with statins, which is common in the management of CVD and/or HF.[17,18] In the Japan EPA Lipid Intervention Study (JELIS) study, the administration of EPA and statins in dyslipidemia patients resulted in a significant reduction in the risk of CVD events when the EPA/AA ratio was >0.75 (hazard ratio [HR] 0.83, $P = .031$).[19]

Thus, the aim of the present study was to investigate the associations between the EPA/AA ratio and cardiac mortality in patients with HF, with a focus on patients' clinical backgrounds (especially in HF patients with or without statins).

Methods

Subjects and Study Protocol

This was a prospective observational study that enrolled consecutive symptomatic HF patients who were hospitalized to treat decompensated HF at Fukushima Medical University between 2009 and 2013. The diagnosis of decompensated HF was defined by several cardiologists based on the Framingham criteria.[20] Patients with acute coronary syndrome, on dialysis, or undergoing n-3 PUFA treatment were excluded. Patients who were selected for this study were divided into 2 groups based on the median value of the EPA/AA ratio: those with high EPA/AA (EPA/AA ≥ 0.32, n = 286) and those with low EPA/AA (EPA/AA < 0.32, n = 291). A fasting blood sample was obtained from each patient within 24 hours of admission, and the serum levels of fatty acids were blindly measured at SRL Co., Ltd. (Tokyo, Japan) using a gas chromatrophy-flame ionization detector system (6890N; Agilent Technologies, Tokyo, Japan).[21] We performed several examinations on admission, such as general laboratory tests and echocardiography, and compared the parameters between the 2 groups. Comorbidities were also defined by several attending physicians. Hypertension was defined as the recent use of antihypertensive drugs, systolic blood pressure >140 mmHg, and/or diastolic blood pressure >90 mmHg. Diabetes was defined as the recent use of insulin or antidiabetic drugs, a fasting blood glucose value >126 mg/dl, and/or a hemoglobin A1c value >6.5%. Dyslipidemia was defined as the recent use of cholesterol-lowering drugs, a triglyceride value >150 mg/dl, a low-density lipoprotein (LDL) cholesterol value >140 mg/dl, and/or a high-density lipoprotein cholesterol value <40 mg/dl. Chronic kidney disease was defined as an estimated glomerular filtration rate <60 ml/min/1.73 m^2.[22] Anemia was defined as a hemoglobin level <12.0 g/dl in females and <13.0 g/dl in males.[23] Reduced left ventricular ejection fraction (LVEF) was defined as less than 50%. The patients were followed up until March 2015 for cardiac mortality, which was the primary outcome of our study. Cardiac death was confirmed by independent experienced cardiologists as death either from worsened HF in accordance with the Framingham criteria,[20] ventricular fibrillation documented by electrocardiograph or implantable devices, or acute coronary syndrome. This follow-up was performed blindly to the analyses of this study. Status and dates of death were obtained from the patients' medical records or their referring cardiologists. Survival time was defined as from the date of hospitalization until the date of death or last follow-up. We could follow-up on all patients. Written informed consent was obtained from all study subjects. The study protocol was approved by the ethical committee of Fukushima Medical University. The investigation conforms with the principles outlined in the Declaration of Helsinki. Reporting of the study conforms to Strengthening the Reporting of Observational Studies in Epidemiology along with references to Strengthening the Reporting of Observational Studies in Epidemiology and the broader Enhancing the Quality and Transparency of Health Research guidelines.[24]

Echocardiography

Echocardiography was performed blindly by an experienced echocardiographer using standard techniques. The echocardiographic parameters we investigated included interventricular septum thickness, left ventricular dimension, posterior wall thickness, LVEF, left atrial volume, the ratio of early transmitral flow velocity to mitral annular velocity, inferior vena cava diameter, peak systolic pulmonary artery pressure, and right ventricular fractional area change.[25] LVEF was calculated using a modification of Simpson's method. Early transmitral flow velocity to mitral annular velocity was calculated by transmitral Doppler flow and tissue Doppler imaging. Tissue Doppler imaging was obtained from the average of lateral and septal annulus velocities. Systolic pulmonary artery pressure was calculated by adding the right atrial pressure (estimated by the diameter and collapsibility of the inferior vena cava) to the systolic trans tricuspid pressure gradient.[25] The right ventricular fractional area change, defined as (end diastolic area − end systolic area)/end diastolic area × 100, is a measure of right ventricular systolic function.[25] All recordings were performed on ultrasound systems (ACUSON Sequoia, Siemens Medical Solutions USA, Inc., Mountain View, CA).

Statistical Analysis

Normally distributed data are presented as mean ± standard deviation, and non-normally distributed data are presented as the median (inter-quartile range). Categorical variables are expressed as numbers and percentages. The chi-square test was used for comparisons of categorical variables. Data of the 2 groups were compared using the independent Student *t* test for normally distributed data and the Mann-Whitney *U* test for nonnormally distributed data. The Kaplan-Meier method was used for presenting cardiac mortality; the log-rank test

was used for initial comparisons. Univariate and multivariate Cox proportional hazard analyses were used to analyze predictors of cardiac mortality adjusting for clinical variables that were different between the 2 groups: age, New York Heart Association (NYHA) class, glomerular filtration rate, high-density lipoprotein, and triglyceride. The proportional hazard assumption for the Cox model was checked by examining log-minus-log–transformed Kaplan-Meier estimates of the survival curves for the 2 groups plotted against time to follow-up. These curves help in identifying nonproportionality patterns in hazard function such as convergence (difference in risk between the 2 groups decreases with time), divergence, or crossing of the curves. In addition, the Schoenfeld test for the violation of proportional hazards, which assesses the correlation between scaled residuals and time, was also conducted. To assess potential heterogeneity of associations between circulating levels of EPA/AA ratio and cardiac mortality, we also conducted subgroup analyses. Interactions between EPA/AA ratio and clinically relevant variables that are known to affect the risk of cardiac mortality in patients with HF (age >65 years of age, male gender, NYHA functional class III or IV, reduced LVEF, ischemic etiology, diabetes, atrial fibrillation, chronic kidney disease, anemia, and use of statins) were estimated by a Cox proportional hazard regression model and are shown in a Forest plot. $P < .05$ was considered statistically significant for all comparisons. These analyses were performed using a statistical software package (SPSS, version 21.0, IBM, Armonk, NY).

Results

The clinical features of the study subjects are summarized in Table 1. The low EPA/AA group patients were of a lower age and had a higher prevalence of NYHA class III or IV than the high EPA/AA group. In contrast, blood pressure, heart rate, presence of reduced LVEF, etiology, comorbidity, and medications did not differ between the 2 groups. Comparisons of the laboratory and echocardiographic data between the 2 groups are shown in Table 2. The low EPA/AA group had lower EPA, docosahexaenoic acid, and high-density lipoprotein as well as higher levels of arachidonic acid, dihomo-γ-linoleic acid and triglyceride. In contrast, hemoglobin, B natriuretic peptide, C-reactive protein, total protein, albumin, sodium, glucose, hemoglobin A1c, LDL cholesterol, oxidative LDL cholesterol, and echocardiographic parameters did not differ between the 2 groups.

During the follow-up period (mean 710 days), there were 54 cardiac deaths, including 39 from worsening HF, 10 from ventricular fibrillation, and 5 from acute coronary syndrome (37 and 17 in the low EPA/AA group and high EPA/AA group, respectively). As shown in Fig. 1, cardiac mortality was significantly higher in the low EPA/AA group than in the high EPA/AA group ($P = .004$). A Cox proportional hazard model was used to examine the prognostic value of the low EPA/AA ratio in patients with HF (Table 3). We confirmed that the Cox models supported the assumption of proportional hazards. In the multivariate analysis after adjusting for

Table 1. Comparisons of Clinical Features Between High-EPA/AA and Low-EPA/AA Groups (N = 577)

	High-EPA/AA (≥0.32, n = 286)	Low-EPA/AA (<0.32, n = 291)	*P* Value
Age (y)	70.2 ± 11.4	64.2 ± 15.7	<.001
Male (n, %)	186 (65.0)	186 (63.9)	.779
Body mass index (kg/cm^2)	22.9 ± 3.7	23.1 ± 3.9	.589
Systolic blood pressure (mmHg)	127.2 ± 32.8	126.4 ± 31.9	.790
Diastolic blood pressure (mmHg)	70.8 ± 19.7	72.7 ± 22.1	.263
Heart rate (beats/min)	79.3 ± 27.4	81.7 ± 24.1	.266
NYHA class III or IV (n, %)	44 (15.4)	64 (22.0)	.042
Reduced EF (n, %)	158 (55.2)	171 (58.8)	.393
Etiology			.433
Ischemic etiology (n, %)	72 (25.2)	80 (27.5)	
Valvular (n, %)	96 (33.6)	79 (27.1)	
Cardiomyopathy (n, %)	80 (28.0)	82 (28.2)	
Others (n, %)	38 (13.3)	50 (17.2)	
Comorbidity			
Hypertension (n, %)	224 (78.3)	221 (75.9)	.497
Diabetes (n, %)	115 (40.2)	118 (40.5)	.934
Dyslipidemia (n, %)	231 (80.8)	242 (83.2)	.455
Atrial fibrillation (n, %)	116 (40.6)	106 (36.4)	.308
Chronic kidney disease (n, %)	177 (61.9)	171 (58.8)	.443
Anemia (*n*, %)	162 (56.6)	167 (57.4)	.857
Medications			
RAS inhibitors (n, %)	226 (79.0)	224 (77.0)	.553
β-blockers (n, %)	233 (81.5)	230 (79.0)	.463
Diuretics (n, %)	200 (69.9)	204 (70.1)	.964
Inotropics (n, %)	37 (12.9)	43 (14.8)	.523
Statins (n, %)	118 (41.3)	116 (39.9)	.733
Antidiabetic drugs (n, %)	69 (24.1)	68 (23.4)	.831

AA, arachidonic acid; EPA, eicosapentaenoic acid; NYHA, New York Heart Association; RAS, renin-angiotensin-aldosterone system.

Table 2. Laboratory and Echocardiographic Data

	High-EPA/AA (n = 286)	Low-EPA/AA (n = 291)	*P* Value
Laboratory data			
EPA/AA ratio	0.55 ± 0.23	0.20 ± 0.07	<.001
Eicosapentaenoic acid (mg/dl)	86.8 ± 38.5	33.9 ± 14.4	<.001
Arachidonic acid (mg/dl)	156.5 ± 42.4	174.0 ± 60.5	<.001
Dihomo-γ-linolenic acid (mg/dl)	29.5 ± 12.7	32.4 ± 14.7	.010
Docosahexaenoic acid (mg/dl)	150.5 ± 50.0	107.0 ± 38.0	<.001
Hemoglobin (g/dl)	12.5 ± 2.1	12.7 ± 2.4	.507
BNP (pg/ml)*	337.0 (497)	317.4 (532)	.286
Estimated GFR (ml/min/1.73 m^2)	53.3 ± 22.3	57.4 ± 25.9	.077
C-reactive protein (mg/dl)*	0.17 (1)	0.25 (1)	.127
Total protein (g/dl)	7.0 ± 0.7	6.9 ± 0.9	.178
Albumin (g/dl)	3.7 ± 0.6	3.7 ± 0.6	.089
Sodium (mEq/l)	138.6 ± 3.6	139.0 ± 3.4	.201
Glucose (g/dl)	125.6 ± 54.3	126.1 ± 56.5	.910
Hemoglobin A1c (%)	5.8 ± 1.0	5.8 ± 1.1	.801
Total cholesterol (mg/dl)	182.1 ± 40.1	176.0 ± 43.6	.169
HDL cholesterol (mg/dl)	53.8 ± 23.4	47.7 ± 19.4	.009
LDL cholesterol (mg/dl)	103.0 ± 35.0	104.9 ± 37.9	.588
Triglyceride (mg/dl)	113.8 ± 63.3	129.8 ± 94.1	.044
Oxidative LDL (mg/dl)	109.0 ± 38.1	111.1 ± 50.0	.667
Echocardiographic data			
Interventricular septum thickness (mm)	11.5 ± 3.2	11.0 ± 2.6	.219
LV end-diastolic dimension (mm)	53.1 ± 10.6	53.8 ± 11.1	.447
LV end-systolic dimension (mm)	39.2 ± 13.1	40.8 ± 13.5	.163
Posterior wall thickness (mm)	11.2 ± 2.6	11.1 ± 2.6	.488
LV ejection fraction (%)	48.2 ± 15.9	46.7 ± 17.0	.327
Left atrial volume (ml)	90.7 ± 64.4	85.5 ± 54.2	.371
Mitral valve E/E′	15.5 ± 7.3	16.5 ± 9.9	.241
Inferior vena cava diameter (mm)	15.0 ± 4.9	15.4 ± 5.3	.383
SPAP (mmHg)	31.0 ± 16.1	32.0 ± 17.3	.546
RV-FAC (%)	42.7 ± 16.6	41.0 ± 13.9	.359

BNP, B-type natriuretic peptide; EPA/AA ratio, eicosapentaenoic acid to arachidonic acid ratio; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LV, left ventricular; mitral valve E/E′, ratio of the peak transmitral velocity during early diastole to the peak mitral valve annular velocity during early diastole; RV-FAC, right ventricular fractional area change; SPAP, systolic pulmonary artery pressure.

*Data are presented as median (interquartile range).

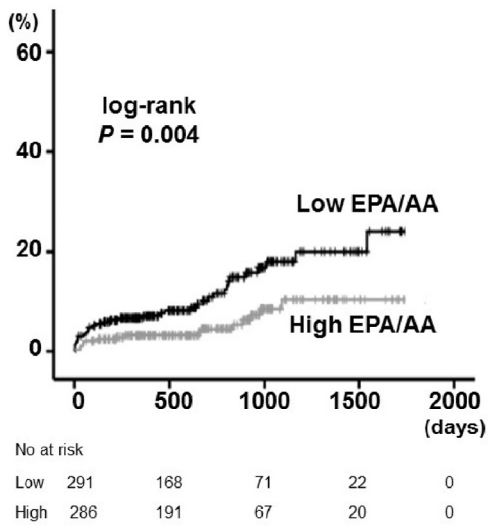

Fig. 1. Comparison of cardiac mortality between the low and high EPA/AA groups. Kaplan-Meier analysis for cardiac mortality in patients with HF (n = 577). Cardiac mortality was significantly higher in the low EPA/AA group than in the high EPA/AA group (*P* = .004). AA, arachidonic acid; EPA, eicosapentaenoic acid.

clinical variables including age, NYHA class, glomerular filtration rate, high-density lipoprotein, and triglyceride (Table 3), EPA/AA ratio (as a continuous variable), and low-EPA/AA group (as a categorical variable, vs high-EPA/AA group) were independent predictors of cardiac mortality in patients with HF (EPA/AA ratio, HR 0.677, 95% confidence interval [CI] 0.453–0.983, *P* = .041; low EPA/AA group, HR 2.468, 95% CI 1.097–5.549, *P* = .029). Then, we focused on the presence of ischemic etiology. Irrespective of ischemic or nonischemic etiology (Fig. 2), cardiac mortality was significantly higher in the low EPA/AA group than in the high EPA/AA group. In addition, we focused on the presence of statin therapy (Fig. 3), cardiac mortality was significantly higher in the low EPA/AA group than in the high EPA/AA group in patients with HF taking statins (*P* = .003), and not in patients with HF not taking statins (*P* = .193). Furthermore, to assess potential heterogeneity of impact of low EPA/AA ratio on cardiac mortality, we conducted subgroup analyses and examined interaction terms (Fig. 4). There were no interactions except for a significant interaction with statins use (*P* = .042) in associations of low EPA/AA and cardiac mortality between subgroups.

Table 3. Cox Proportional Hazard Model of Cardiac Death in HF: Impact of EPA/AA

Event			
Cardiac death (N = 54/577)	HR	95% CI	*P* Value
EPA/AA ratio (+1 SD increase) unadjusted	0.660	0.462–0.943	.023
EPA/AA ratio (+1 SD increase) adjusted model*	0.677	0.453–0.983	.041
Low EPA/AA (vs high EPA/AA) unadjusted	2.262	1.273–4.020	.005
Low EPA/AA (vs high EPA/AA) adjusted model*	2.468	1.097–5.549	.029

HR, hazard ratio; SD, standard deviation. Other abbreviations as in Table 2.
*Adjusted model: adjusted for age, New York Heart Association class, glomerular filtration rate, high-density lipoprotein, and triglyceride.

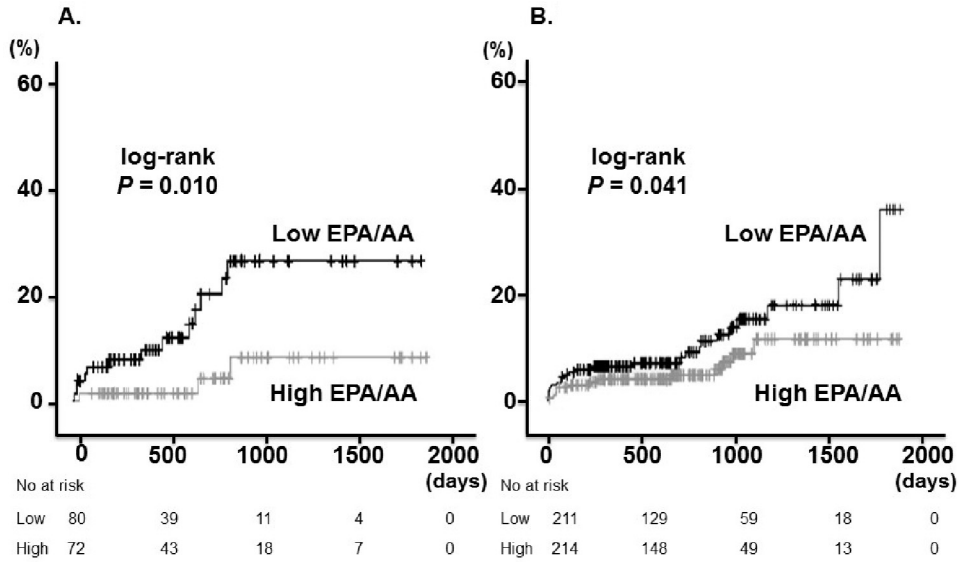

Fig. 2. Cardiac mortality with or without ischemic etiology. Kaplan-Meier analysis for cardiac mortality (A) with ischemic etiology (n = 152) and (B) without ischemic etiology (n = 425). Cardiac mortality was significantly higher in the low EPA/AA group than in the high EPA/AA groups irrespective of ischemic or nonischemic etiologies. Abbreviations as in Fig. 1.

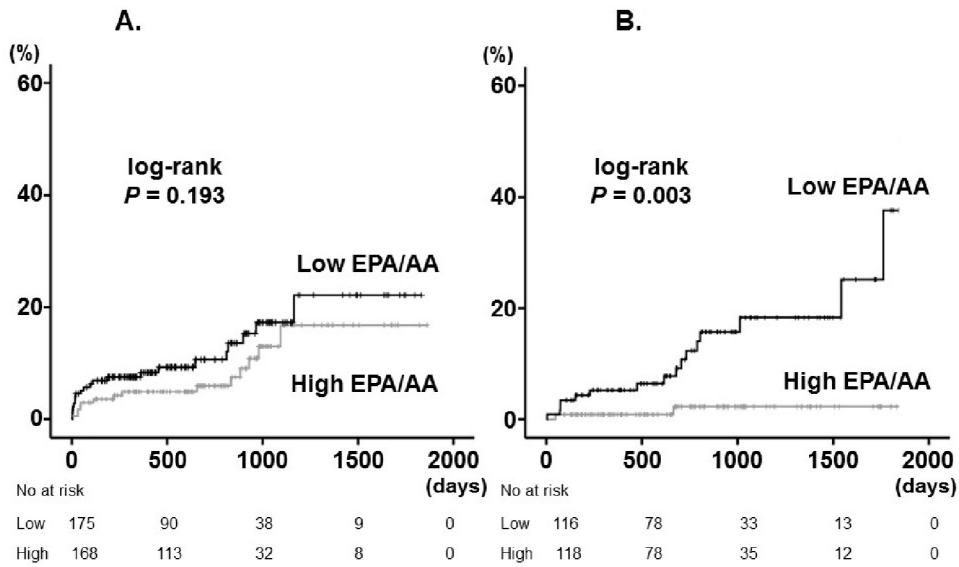

Fig. 3. Cardiac mortality with or without statins. Kaplan-Meier analysis for cardiac mortality (A) without statins (n = 343) and (B) with statins (n = 234). Cardiac mortality was significantly higher in the low EPA/AA group than in the high EPA/AA group in HF patients with statins (*P* = .003), but not in HF patients without statins (*P* = .193). Abbreviations as in Fig. 1.

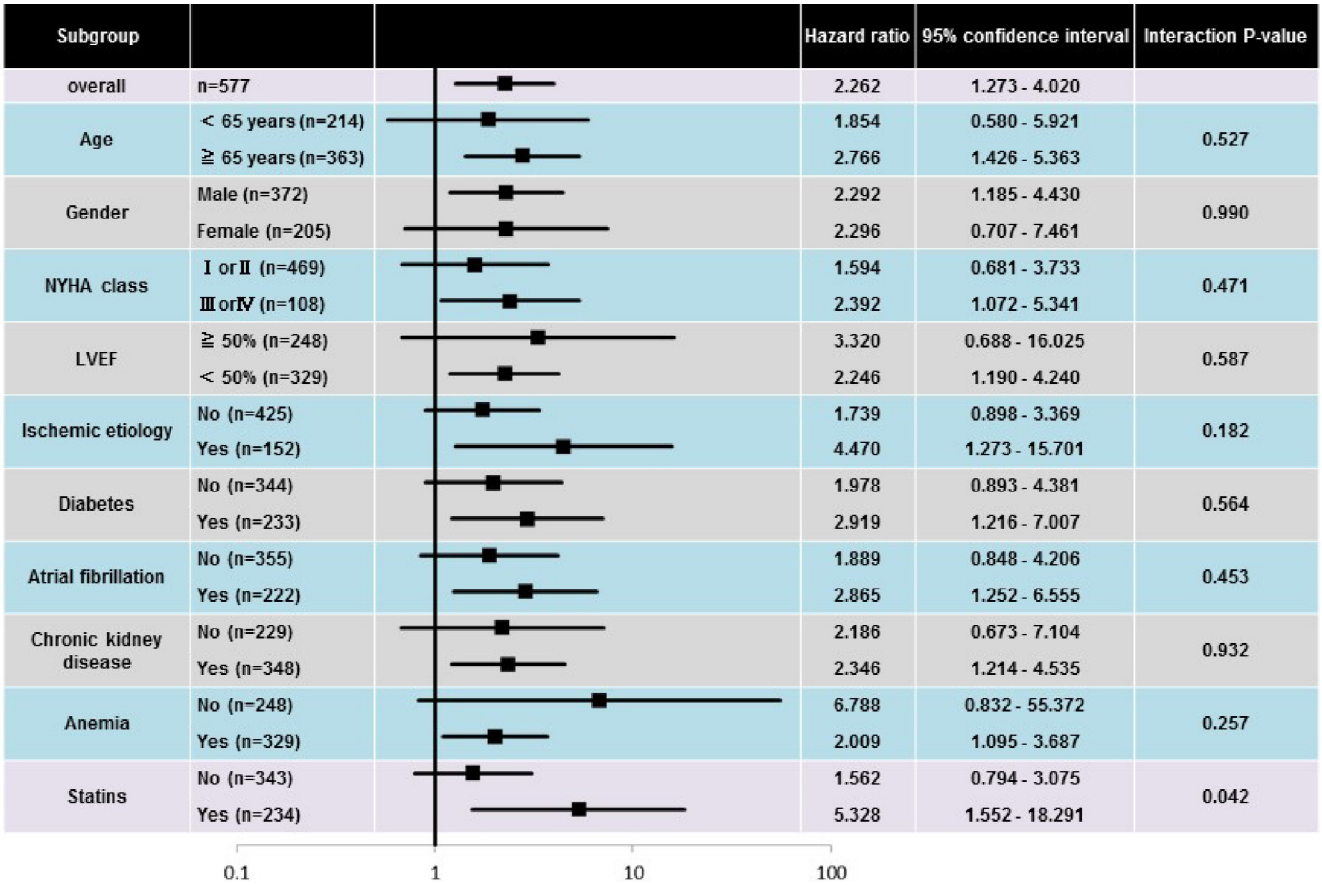

Fig. 4. Forrest plot with subgroup analyses for cardiac mortality. There were no interactions, except for a significant interaction with statins use ($P = .042$), in associations between low EPA/AA and cardiac mortality between subgroups; hazard ratio of 5.328 ($P = .008$) with statin use and hazard ratio of 1.562 ($P = .196$) without statin use. LVEF, left ventricular ejection fraction; NYHA, New York Heart Association. Other abbreviations as in Fig. 1.

Discussion

To the best of our knowledge, the present study is the first to show that patients with HF with a low circulating EPA/AA ratio exhibited higher cardiac mortality. This impact was found to be more distinct when patients with HF took statins.

The circulating level of n-3 PUFA is inversely associated with HF incidence in those of the American general population aged >65 years without prevalent CVD (HR 0.51, $P = .003$).[12] A Japanese epidemiological study showed an inverse association between n-3 PUFA intake and cardiovascular mortality, especially HF.[26]

Multiple physiological effects of n-3 PUFA in multiple tissues, including the heart, liver, vasculature, and circulating cells, have been reported.[3] The n-3 PUFA can improve mitochondrial function and adenosine triphosphate generation. This can reduce blood pressure, heart rate, cardiac remodeling,[26–28] cardiac fibrosis, inflammation, atherosclerotic plaque formation, platelet aggregation and thrombotic factors, arrhythmic tendencies, and sudden death. It can also improve cardiac systolic and diastolic function, myocardial efficiency, endothelial function, blood lipid concentrations, and autonomic function, and increase stroke volume and oxygen consumption at peak exercise.[2–4] The molecular mechanisms include effects on cellular function including improved membrane function, improved ion channel function, improved nuclear receptor function and transcription factors, and increased nitric oxide.[2,3] In the present study, we could not explain why blood pressure, heart rate, C-reactive protein, and echocardiographic parameters were not different between the 2 groups, or why the low EPA/AA group had more cardiac deaths. The association between n-3 PUFA and arrhythmia may play an important role.[2–4,29,30]

Supplementation of n-3 PUFA in patients with CVD have been reported.[5,6,19,31–35] In a Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione trial from Italy, a 30% reduction in CVD mortality and a 45% reduction in sudden cardiac death were observed in patients who received n-3 PUFA (1.0 g/d) after myocardial infarction.[6,31] In JELIS, patients with dyslipidemia who received both statin and n-3 PUFA (1.8 g/d) had a 19% reduction in major coronary events, but no significant sudden cardiac death reduction was observed.[19] In the GISSI-HF trial, before n-3 PUFA supplementation, circulating n-3 PUFA levels in patients with HF were inversely related to C-reactive protein, pentraxin-3, adiponectin, natriuretic peptide, and troponin levels.[32,33] EPA supplementation has recently been reported to improve LVEF with an increased EPA/AA ratio and reduced inflammatory

cytokines.[21] On the contrary, recent meta-analysis revealed that there was insufficient evidence of a secondary preventive effect of n-3 PUFA supplements against cardiovascular events in patients with CVD.[34] Several confounders including dose of n-3 PUFA, underlying CVD and comorbidities, race, gender, and other factors may affect the impact of n-3 PUFA on CVD outcomes. The potential effects of n-3 PUFA supplementation on the prognosis of HF are controversial and require further investigation.[3,4]

Study Limitations

The present study has several limitations. First, the present study, which was conducted as a prospective observational study in a single institution with homogenous racial mix and a relatively small number of subjects, might be insufficient to accurately estimate the association between EPA/AA ratio and mortality in patients with HF. However, diagnosis of cardiac death was accurately made by our experienced cardiologists. Although we analyzed using multivariate Cox proportional hazard regression analyses and subgroup analyses under consideration of multiple confounding factors, the effects of the differences in clinical backgrounds between the 2 groups might not be completely adjusted; thus, the present results should be viewed as preliminary and potentially limiting the generalizability of the findings. Further studies with a larger population are needed. Second, we did not measure and consider any changes in the EPA/AA ratio, and only the baseline EPA/AA ratio at admission was used for the analyses. Third, our study did not elucidate whether an increased EPA/AA ratio has a causal role in the adverse outcome, nor did it clarify the mechanisms underlying the association. Our data suggest that a lowered EPA/AA ratio is a potential biomarker that may be helpful in the risk stratification of patients with HF. Future studies to determine the causal relationship and the impact of an increased EPA/AA ratio and develop treatment strategies in reducing mortality in patients with HF are required.

Conclusions and Perspectives

The EPA/AA ratio was an independent predictor of cardiac mortality in patients with HF. This effect was found to be more distinct when patients with HF took statins. Although it is not well-known whether EPA supplementation improves prognosis in patients with HF, taking appropriate management to control the EPA/AA balance may reduce the residual risk of patients with HF.

Disclosures

None.

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