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ORIGINAL RESEARCH

Plasma Omega-3 Fatty Acids and the Risk of Cardiovascular Events in Patients After an Acute Coronary Syndrome in MERLIN-TIMI 36

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BACKGROUND: Plasma omega-3 polyunsaturated fatty acids (ω3-PUFAs) have been shown to be inversely correlated with the risk of cardiovascular death in primary prevention. The risk relationship in the setting of an acute coronary syndrome is less well established.

METHODS AND RESULTS: Baseline plasma ω3-PUFA composition (α-linolenic acid, eicosapentaenoic acid, docosapentaenoic acid, and docosahexaenoic acid) was assessed through gas chromatography with flame ionization detection in a case-cohort study involving 203 patients with cardiovascular death, 325 with myocardial infarction, 271 with ventricular tachycardia, and 161 with atrial fibrillation, and a random sample of 1612 event-free subjects as controls from MERLIN-TIMI 36 (Metabolic Efficiency With Ranolazine for Less Ischemia in Non–ST–Elevation Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 36), a trial of patients hospitalized with non–ST-segment–elevation-acute coronary syndrome. After inverse-probability-weighted multivariable adjustment including all traditional risk factors, a higher relative proportion of long-chain ω3-PUFAs (eicosapentaenoic acid, docosapentaenoic acid, docosahexaenoic acid) were associated with 18% lower odds of cardiovascular death (adjusted [adj] odds ratio [OR] per 1 SD, 0.82; 95% CI, 0.68–0.98) that was primarily driven by 27% lower odds of sudden cardiac death (adj OR per 1 SD, 0.73; 95% CI, 0.55–0.97). Long-chain ω3-PUFA levels in the top quartile were associated with 51% lower odds of cardiovascular death (adj OR 0.49; 95% CI, 0.27–0.86) and 63% lower odds of sudden cardiac death (adj OR, 0.37; 95% CI, 0.16–0.56). An attenuated relationship was seen for α-linolenic acid and subsequent odds of cardiovascular (adj OR, 0.92; 95% CI, 0.74–1.14) and sudden cardiac death (adj OR, 0.91; 95% CI, 0.67–1.25). No significant relationship was observed between any ω3-PUFAs and the odds of cardiovascular death unrelated to sudden cardiac death, myocardial infarction, atrial fibrillation, or early post-acute coronary syndrome ventricular tachycardia.

CONCLUSIONS: In patients after non–ST-segment–elevation-acute coronary syndrome, plasma long-chain ω3-PUFAs are inversely associated with lower odds of sudden cardiac death, independent of traditional risk factors and lipids.

REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT00099788.

Key Words: acute coronary syndrome ■ omega-3 polyunsaturated fatty acids ■ sudden cardiac death

Omega-3 polyunsaturated fatty acids (ω3-PUFA) are incorporated into cellular membranes where they are believed to modulate cellular signaling, gene expression, and membrane protein function.[1,2] α-linolenic acid (ALA) is obtained through plant-derived dietary intake, whereas the long-chain

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CLINICAL PERSPECTIVE

What Is New?

- In patients with non–ST-segment–elevation–acute coronary syndromes, a higher relative proportion of long-chain omega-3 polyunsaturated fatty acid (ω3-PUFAs) content in plasma is associated with lower odds of cardiovascular and sudden cardiac death, independent of traditional risk factors and lipids.
- Although directional consistency was seen across the ω3 subtypes, the magnitude of the effect appeared to be greatest for the long-chain marine-based ω3-PUFAs including docosahexaenoic acid, docosapentaenoic acid, and eicosapentaenoic acid.

What Are the Clinical Implications?

- These data lend support to the theory that certain types of ω3 supplementation may reduce the risk of adverse cardiovascular outcomes in higher-risk populations.

Nonstandard Abbreviations and Acronyms

ALA	α-linolenic acid
DHA	docosahexaenoic acid
DPA	docosapentaenoic acid
EPA	eicosapentaenoic acid
ω3-PUFA	omega-3 polyunsaturated fatty acid

ω3-PUFAs including eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and docosahexaenoic acid (DHA) are primarily obtained from marine sources. In meta-analyses of randomized controlled trials, ω3-PUFA supplementation has been shown to lower serum triglycerides, lower blood pressure, lower heart rate, and improve endothelial function.[1,2] Based on experimental studies, numerous beneficial roles for ω3-PUFAs have been postulated including a reduction in atherogenesis, collagen deposition, dysrhythmias, inflammation, platelet aggregation and improved plaque stabilization, and vasodilation.[1,2] However, clinical outcome trials of exogenous ω3-PUFA supplementation have yielded mixed results; therefore, the physiological effects as well as the magnitude and dose-response of their effects remain controversial.[3–8]

In the absence of supplementation, ω3-PUFA content has been shown to be inversely correlated with risk of cardiovascular and sudden cardiac death, but less strongly associated with risk of myocardial infarction or stroke.[9,10] As such, it has been hypothesized that ω3-PUFA supplementation could confer beneficial effects following acute coronary syndrome (ACS), when patients are at higher risk of arrhythmic events, due to their favorable effects on membrane stabilization.[11] To that end, in the only large clinical trial of patients with a recent myocardial infarction, ω3-PUFA supplementation reduced the risk of cardiovascular death by 30%, primarily driven by a 45% reduction in the risk of sudden death.[8] However, the trial was open label, and additional studies in this high-risk population with recent ACS have not been performed.

Thus, patients with recent ACS remain a vulnerable population at increased risk for recurrent cardiovascular events and sudden cardiac death, in whom ω3-PUFA could hypothetically be protective. To better understand their physiological effects, we examined the association between ω3-PUFA content and the risk of cardiovascular events, including arrhythmic events, in a large clinical trial population hospitalized with ACS.

METHODS

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. However, we encourage parties interested in collaboration and data sharing to contact the corresponding author directly for further discussions.

Patient Population

The design and the primary results of the MERLIN-TIMI 36 (Metabolic Efficiency With Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 36) trial have been published previously.[12,13] In brief, the MERLIN-TIMI 36 trial was a randomized, controlled, double-blinded trial that compared ranolazine with placebo in 6560 patients hospitalized with a non–ST-segment–elevation ACS within 48 hours of symptoms onset. Patients eligible for enrollment had at least 10 minutes of ischemic symptoms at rest and presented with one of the following additional risk indicators: elevated biomarkers of myonecrosis, ST depression ≥0.1 mV, history of diabetes mellitus, or an intermediate-to-high (≥3) Thrombolysis in Myocardial Infarction (TIMI) Risk Score. Patients were excluded if they had end-stage renal disease requiring dialysis, cardiogenic shock, or a life expectancy of <1 year. The protocol, including the biomarker and Holter substudies, was approved by institutional review boards, and written consent was obtained from all participating patients.

Study Design and Biomarker Testing

At randomization (median 24 hours from symptom onset), a plasma sample was drawn and stored

at –20°C until shipped to the TIMI Clinical Trials Laboratory (Boston, MA), where it was maintained at –80°C or colder. Samples were recorded as fasting or nonfasting by sites.

The present metabolomics array study was designed as a case-cohort study to leverage the control population to examine >1 outcome of interest.[14] The study population included a total of 2407 patients (1167 randomized to ranolazine and 1240 randomized to placebo). Overall, 203 subjects with cardiovascular death (including 86 sudden cardiac deaths), 325 patients with myocardial infarction, 271 with ventricular tachycardia, and 161 with atrial fibrillation events were selected as cases in addition to a random sample of 1612 event-free subjects serving as controls. Plasma samples were collected at randomization, and the composition of fatty acids were assessed through gas chromatography with flame ionization detection in the Nutritional Biomarker Laboratory of the Department of Nutrition at the Harvard T. H. Chan School of Public Health using previously published methodology.[15] Herein, we focus on the baseline plasma ω3-PUFA composition including ALA and the 3 long-chain marine-based ω3-PUFAs, EPA, DPA, and DHA.

End Points

Mode of death and cardiovascular outcomes of interest were adjudicated by an independent and blinded clinical events committee. As part of the study protocol, all patients in the MERLIN-TIMI 36 trial were to wear a Holter monitor (Lifecard CF; DelMar Reynolds/Spacelabs) starting at randomization for a period of 7 days, including after hospital discharge.[12,16] Analysts and cardiologists blinded to treatment assignment and outcomes determined the presence and type of arrhythmia in the TIMI ECG Core Laboratory. As described previously,[17] clinical atrial fibrillation events were identified through adverse-event reporting throughout the duration of study follow-up.

Statistical Analysis

The ω3-PUFA composition including ALA, EPA, DPA, and DHA are expressed as the percentage of the total fatty acid content by weight. The baseline characteristics were compared by quartiles of ω3 fatty acid using the Kruskal-Wallis test for continuous variables and the χ^2 test for categorical variables. Correlations between ω3 fatty acid subtypes were examined using Spearman correlation coefficients.

ω3 fatty acids were modeled both as continuous variables as well as categorized using quartiles. Adjusted odds ratios were determined using logistic regression models that included the following variables: age, sex, estimated glomerular filtration rate (estimated with the Modification of Diet in Renal Disease formula), hypertension, prior myocardial infarction, heart failure, diabetes mellitus, smoking, statin use, baseline low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, body mass index, race, region, index diagnosis, and randomized treatment arm. The logistic regression models included a weighted likelihood approach using inverse probability weighting using design weight (for cases weight=1, controls weight=1 over the sampling fraction of noncases) to account for oversampling of cases and adjusted variance using robust standard error estimation/sandwich estimator for consistent estimation of variance in the presence of upweighting of controls.[18] Sensitivity analyses were performed in subjects in whom fasting plasma samples were available (n=1384, 57.5%). Subgroup analyses were conducted for the outcome of sudden cardiac death stratified by low-density lipoprotein cholesterol (≤ or >130 mg/dL), triglycerides (< or ≥150 mg/dL), TIMI Risk Score (≤ or >3), and high-sensitivity C-reactive protein (≤ or >5 mg/L). Tests for heterogeneity were determined by including an interaction term in the adjusted models. Splines were modeled by restricted cubic splines with 3 knots at the 10th, 50th, and 90th percentile based on Frank Harrell's SAS macro.

All analyses were performed using SAS (version 9.4; SAS Institute). Given the exploratory nature of the analysis, a *P* value (2-tailed) <0.05 was considered statistically significant. The authors had full access to and take full responsibility for the integrity of the data. All statistical analyses were performed at the TIMI Study Group using an independent copy of the trial database.

RESULTS

ω3-PUFA Plasma Content at Baseline

The long-chain ω3-PUFAs (EPA, DHA, DPA) comprised 85.6% of the total ω3-PUFA content in plasma samples. Among the individual ω3-PUFAs, the fatty acid that contributed the highest relative proportion to the total ω3 content was DHA (52.5%), followed by EPA (19.6%), ALA (14.4%), and DPA (13.5%) (Figure 1). A moderate-to-strong correlation (r=0.46 to 0.67, all P<0.001) was seen among the 3 long-chain ω3-PUFAs EPA, DPA, and DHA, whereas the correlation was weaker between ALA and the 3 long-chain ω3-PUFAs (r=–0.14 to 0.26, all P<0.001; Table S1).

Baseline Characteristics

Overall, the mean age of the study population was 63.9 years; 36.2% were female. Patients with higher long-chain marine-based ω3-PUFA content (ie, the arithmetic sum of EPA, DPA, and DHA fractions) were more likely to be female, older, have lower estimated

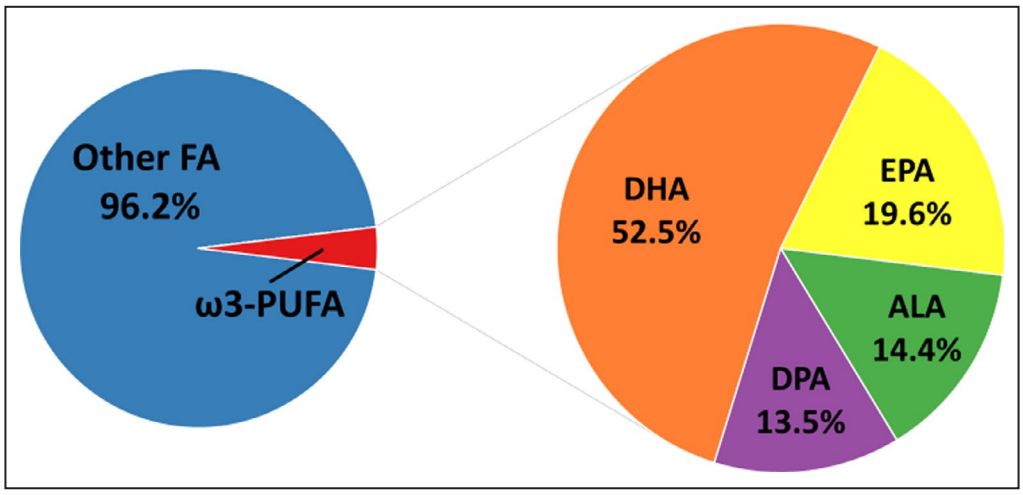

Figure 1. Relative proportion of ω3-polyunsaturated fatty acids subtypes as compared with total ω3-PUFA content and total fatty acid (FA) content overall.
ALA indicates α-linolenic acid; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EPA, eicosapentaenoic acid; and ω3-PUFA, ω3-polyunsaturated fatty acids.

glomerular filtration rate, a history of hypertension, lower triglycerides and higher high-density lipoprotein concentrations, and were less likely to be smokers (Table). Patients with higher quartiles of ALA were more likely to be male, have a history of diabetes mellitus, lower low-density lipoprotein cholesterol and high-density lipoprotein cholesterol levels, and be less likely to have a history of hypertension and heart failure (Table S2).

ω3-Polyunsaturated Fatty Acid Plasma Content and Cardiovascular Outcomes

After multivariable adjustment, patients with higher plasma content of the long-chain ω3-PUFAs had 18% lower odds of cardiovascular death (adjusted odds ratio per 1 SD, 0.82; 95% CI, 0.68–0.98; Figure 2A). Although directional consistency was seen across all individual ω3-PUFA subtypes, the magnitude of the relationship was not as strong for ALA (adjusted odds ratio per 1 SD, 0.92; 95% CI, 0.74–1.14) when compared with the long chain ω3-PUFAs. Notably, the observed relationship between the long-chain ω3-PUFAs and risk of cardiovascular death was largely driven by a 27% lower odds of sudden cardiac death (adjusted odds ratio per 1 SD, 0.73; 95% CI, 0.55–0.97; Figure 2B), whereas there was no significant association with cardiovascular death unrelated to sudden cardiac death (Figures S1 and S2).

When considered by quartile, a stepwise decrease in the odds of sudden cardiac death was observed with higher long-chain ω3-PUFA content (*P* trend=0.025) (Figure 3). Although underpowered, a qualitatively similar gradient of risk was seen for the individual fatty acids DPA (*P* trend=0.061) and EPA (*P* trend=0.079) (Figure 3). Adjusted natural cubic regression splines suggest a consistent, nearly linear decrease in the probability of sudden cardiac death for increasing proportions of the long-chain ω3-PUFAs (Figure 4).

There was a consistent relationship between the long-chain ω3-PUFAs and the odds of sudden cardiac death among prespecified subgroups (all *P* values for interaction >0.32), including stratification on the basis of high versus low baseline triglyceride concentration (Figure S3).

No significant associations were found for any of the ω3 fatty acids, either alone or in combination, with any of the other outcomes of interest, including myocardial infarction, atrial fibrillation, or early post-ACS ventricular tachycardia, either when tested as a continuous variable (Figure S1) or categorized by quartiles (Figure S2). These relationships were all directionally consistent when the association between total ω3-PUFA (ie, combining long-chain ω3-PUFAs and ALA) and outcomes was examined (Figure S4). Sensitivity analyses using only fasting samples yielded similar results with directionally concordant point estimates (Figures S5 through S7).

DISCUSSION

In a large clinical trial population of patients after a non–ST-segment–elevation ACS, we observed an inverse relationship between plasma long-chain ω3 fatty acid content and the odds of cardiovascular and sudden cardiac death independent of traditional risk factors. Although directional consistency was seen across the ω3 subtypes, the magnitude of the effect appeared to be greatest for the long-chain marine-based ω3-PUFAs

Table. Baseline Characteristics by Quartiles of Long-Chain ω3-Polyunsaturated Fatty Acids (EPA, DPA, DHA)

Characteristic	Total, N=2407	Q1, n=602	Q2, n=602	Q3, n=602	Q4, n=601	*P* Value for Trend
Age, y	63.9±10.8	61.5±11.1	63.6±11.1	65.0±10.3	65.4±10.2	<0.0001
Female sex	871 (36.2%)	207 (34.4%)	208 (35.0%)	215 (35.7%)	241 (40.1%)	0.037
White	2347 (97.5%)	581 (96.5%)	583 (96.8%)	592 (98.3%)	591 (98.3%)	0.014
Current smoker	578 (24.0%)	189 (31.4%)	154 (25.6%)	137 (22.7%)	98 (16.3%)	<0.0001
Diabetes mellitus	800 (33.2%)	228 (37.9%)	196 (32.6%)	188 (31.2%)	188 (31.3%)	0.014
Prior HF	573 (23.8%)	140 (23.3%)	137 (22.8%)	133 (22.1%)	163 (27.1%)	0.16
Index event NSTEMI	1169 (49.7%)	282 (47.8%)	302 (51.6%)	304 (51.5%)	281 (48.0%)	0.96
Prior MI	886 (37.2%)	202 (33.8%)	214 (35.9%)	225 (37.9 %)	245 (41.2%)	0.007
Prior coronary revascularization	620 (25.8%)	170 (28.3%)	167 (27.8%)	132 (21.9%)	151 (25.1%)	0.054
Hypertension	1826 (76.3%)	433 (72.2%)	458 (76.6%)	461 (77.1%)	474 (79.4%)	0.004
Hyperlipidemia	1441 (66.4%)	388 (69.9%)	357 (66.7%)	342 (63.2%)	354 (65.7%)	0.071
BMI, kg/m^2	29.0±5.5	29.5±5.5	29.0±5.1	28.9±6.8	28.5±4.5	0.002
eGFR, mL/min per 1.73 m^2	75.5±23.6	77.1±25.1	75.9±23.2	75.4±23.2	73.6±22.6	0.011
Total cholesterol, mg/dL	198.1±54.9	198.8±55.8	198.7±57.5	195.6±53.0	199.5±53.3	0.92
LDL-C, mg/dL	119.9±48.3	116.9±46.5	120.5±52.5	119.4±45.9	122.7±48.2	0.080
HDL-C, mg/dL	45.1±15.3	41.3±15.4	44.1±13.7	46.2±15.6	49.0±15.5	<0.0001
Triglycerides, mg/dL	176.0±141.9	223.5±218.0	181.7±122.5	155.3±86.3	143.0±81.2	<0.0001
hs-CRP, mg/dL	13.8±20.8	13.6±19.7	14.9±21.8	14.0±21.1	12.7±20.5	0.37
Aspirin	2316 (96.2%)	575 (95.5%)	577 (95.9%)	584 (97.0%)	580 (96.5%)	0.23
β-blocker	2179 (90.5%)	552 (91.7%)	534 (88.7%)	548 (91.0%)	545 (90.7%)	0.89
Statin	1843 (76.6%)	457 (75.9%)	470 (78.1%)	461 (76.6%)	455 (75.7%)	0.78

Continuous variables reported as mean (SD). BMI indicates body mass index; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; eGFR, estimated glomerular filtration rate; EPA, eicosapentaenoic acid; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; and NSTEMI, non–ST-segment–elevation myocardial infarction.

including DHA, DPA, and EPA. Together, these findings lend support to the emerging evidence that suggests that certain types of ω3 supplementation may reduce the risk of adverse cardiovascular outcomes in higher-risk populations.

Current guidelines of the American Heart Association suggest ω3-PUFA supplementation or consumption from seafood may be reasonable to help prevent sudden cardiac death in patients with coronary heart disease.[19,20] However, despite supportive evidence from observational studies, data from clinical trials remain inconsistent.[5–7,21–23] Some of the inconsistency between findings may be explained partly by the patient population studied and differences in the dosing, type, and quality of the ω3-PUFAs.[3–8]

To date, the relationship between circulating ω3-PUFA content and cardiovascular events in patients after ACS is not well established. Prior observational studies have suggested an association between plasma ω3-PUFA and lower risk of sudden cardiac death in patients without a history of cardiovascular disease or those with stable atherosclerotic disease.[24,25] In contrast, in a relatively small investigation among 460 patients after recent ACS, red blood cell ω3-PUFA content was not significantly associated with cardiac or all-cause death.[26]

Building on this evidence, earlier trials demonstrated that low-dose (up to 1 g/d) ω3-PUFA supplementation may offer protective effects among patients with recent acute myocardial infarction with reduced risk of cardiovascular death and in particular sudden cardiac death.[8] In contrast, 2 large and well-conducted randomized controlled trials in primary prevention were unable to demonstrate a significant benefit for low-dose ω3 supplementation for reducing major adverse cardiovascular events,[6,7] although a significant reduction in the secondary outcome of coronary heart disease was seen in one of the studies.[7]

At higher doses (4 g/d), the REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention) trial showed significant reductions in major adverse cardiovascular events including cardiovascular death in patients with hypertriglyceridemia and either known atherosclerotic cardiovascular disease or diabetes mellitus.[5] Unlike the trials with neutral findings that studied a low-dose (up to 1 g/d) combination of DHA and EPA, the REDUCE-IT trial tested a substantially higher dose regimen of icosapent ethyl,

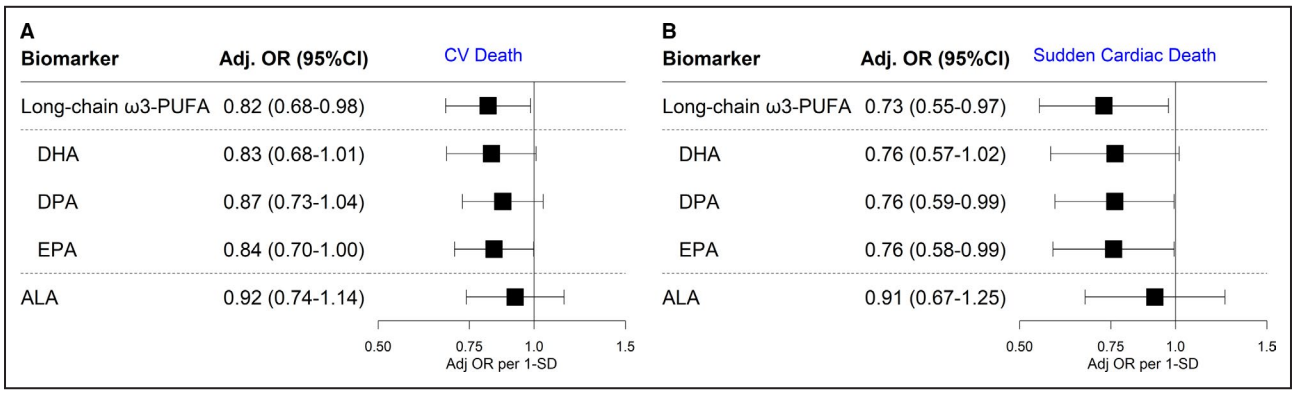

Figure 2. Multivariable adjusted odds ratios per 1-SD increase in ω3-polyunsaturated fatty acid subtype content for cardiovascular death (A) and sudden cardiac death (B).
The models were adjusted for age, sex, estimated glomerular filtration rate, hypertension, prior myocardial infarction, heart failure, diabetes mellitus, smoking, statin use, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, body mass index, race, region, index diagnosis, and randomized treatment arm. The long chain ω3-polyunsaturated fatty acids include EPA, DPA, and DHA. Adj. OR indicated adjusted odds ratio; ALA, α-linolenic acid; CV, cardiovascular; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; and EPA, eicosapentaenoic acid.

a purified EPA ethyl ester. It remains elusive whether the type of the ω3-PUFA or the higher dose may have contributed to the observed salutary effects, in addition to the potentially harmful use of mineral oil in the control arm.[27] Although several distinct effects of DHA and EPA have been suggested to be exert cardioprotective mechanisms,[28] the STRENGTH (A Long-Term Outcomes Study to Assess Statin Residual Risk Reduction With Epanova in High CV Risk Patients With Hypertriglyceridemia) trial (ClinicalTrials.gov Identifier: NCT02104817) studying the combination of higher-dose DHA and EPA (4 g) was more recently stopped early for futility.[29,30] It is possible that the specific formulation of icosapent ethyl

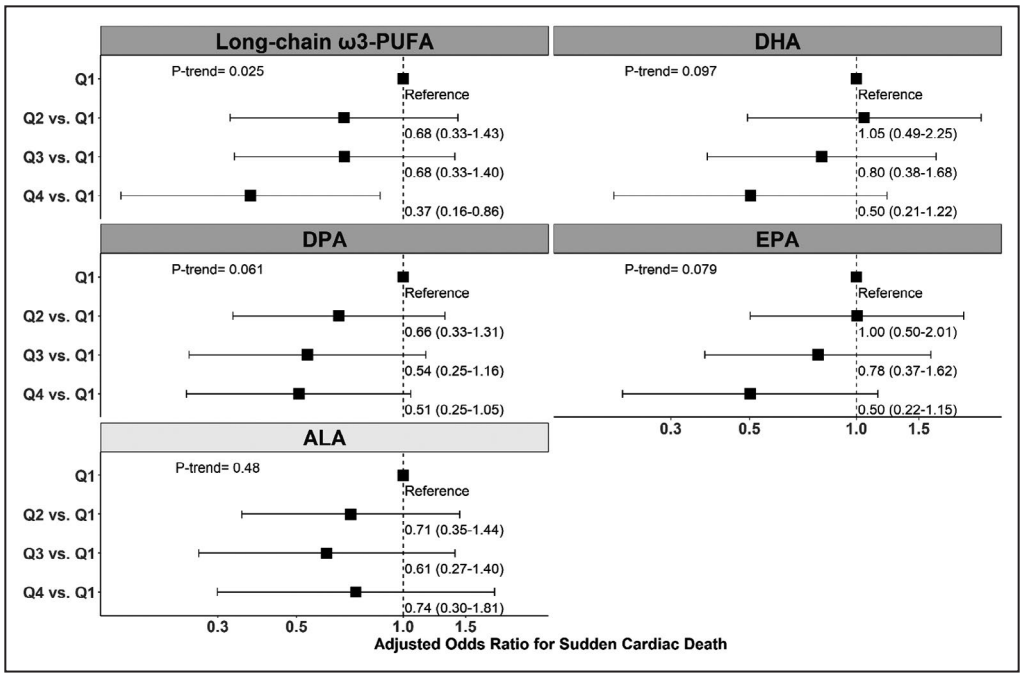

Figure 3. Multivariable adjusted odds ratios for quartiles of ω3-polyunsaturated fatty acid (ω3-PUFA) subtypes for sudden cardiac death.
The models were adjusted for age, sex, estimated glomerular filtration rate, hypertension, prior myocardial infarction, heart failure, diabetes mellitus, smoking, statin use, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, body mass index, race, region, index diagnosis, and randomized treatment arm. ALA indicates α-linolenic acid; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; and EPA, eicosapentaenoic acid.

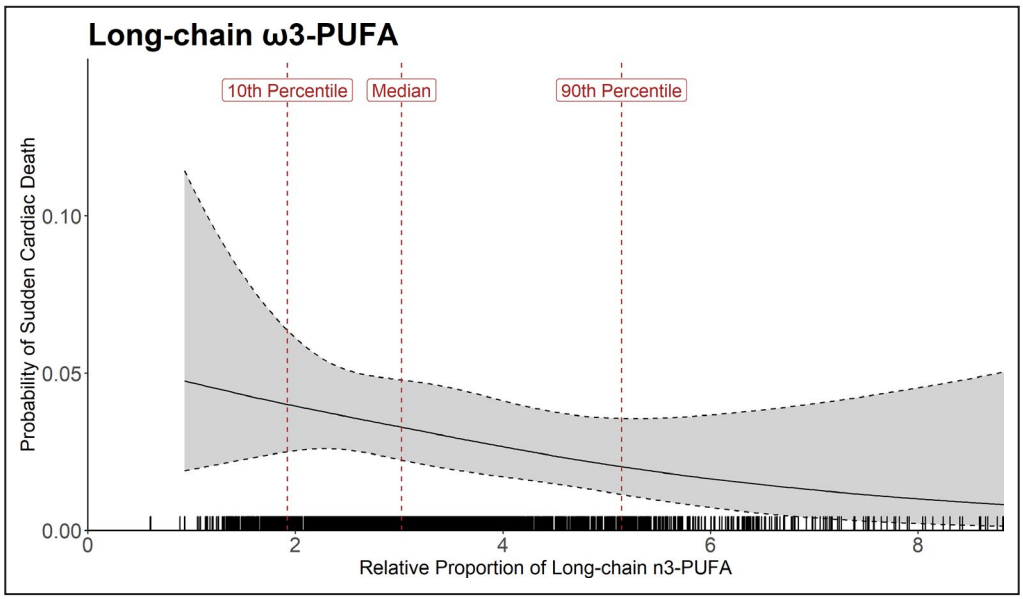

Figure 4. Multivariable adjusted splines for long-chain marine-based ω3-polyunsaturated fatty acid (ω3-PUFA) content (EPA, DHA, DPA) and sudden cardiac death.
The *x* axis is truncated at the 99.5 percentile of the distribution. Adjusted for age, sex, estimated glomerular filtration rate, hypertension, prior myocardial infarction, heart failure, diabetes mellitus, smoking, statin use, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, body mass index, race, region, index diagnosis, and randomized treatment arm. ALA indicates α-linolenic acid; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; and EPA, eicosapentaenoic acid. P-linearity = 0.87 (indicating that non-linearity cannot be rejected).

is responsible for the beneficial treatment effects or that DHA counters the beneficial effects.[28]

In the current study, although the individual subtypes of long-chain ω3-PUFAs showed a directionally concordant relationship with sudden cardiac death, the relationship appeared to be more attenuated for ALA. However, the proportion of omega-3 fatty acids represented by ALA, as with the other subtypes, was relatively small and therefore underpowered. ALA also serves as a biologic precursor to the long chain ω3-PUFAs; therefore, marine-sourced intake is not required to increase long-chain ω3-PUFA content. However, the conversion efficiency of ALA to DHA or EPA is low. Furthermore, the relationship between ALA and risk of sudden cardiac death appeared stronger when assessed in fasting samples. Nonetheless, evidence on ALA has been more limited, and previous observational studies and clinical trials provide conflicting evidence on its protective effects.[23,31–33]

Several pathobiological mechanisms have been suggested to be responsible for the favorable effects of increased ω3-PUFA intake, although their dose-response relationship and clinical implications at usual dietary intake remains unclear.[2] Despite conflicting data,[34] the antiarrhythmic properties of ω3-PUFAs have been described as their predominant salutary effect.[11,20,35,36] Interestingly, we did not observe any association between ω3-PUFAs and early post-ACS ventricular tachycardia that may have accounted for the observed decrease in odds of sudden cardiac death. The continuous electrocardiogram monitoring was only recorded for the first 7 days after randomization, and a possible effect could have emerged at a later time point. Similarly, no association between ω3-PUFAs and risk of atrial fibrillation was found. However, atrial arrhythmias may be more related to atrial structural abnormalities, rather than the change in ischemia-induced resting membrane depolarization that has been hypothesized to be influenced by ω3-PUFAs. However, the hypothesis of a membrane-stabilizing effect through ω3-PUFAs has been challenged by a few studies that even suggested possible proarrhythmic properties.[37,38] In the REDUCE-IT and STRENGTH trials, a surprising increase in risk of atrial fibrillation was reported despite substantial reductions in sudden cardiac death.[5,30] However, this was a secondary safety end point, and differences in risk of atrial fibrillation have not been reported in prior trials of n-3 PUFA supplements, whereas observational studies of fish consumption have shown inverse associations with risk of atrial fibrillation.

Limitations

Although this study benefited from a large and well-characterized patient cohort, with cardiovascular events that were adjudicated by an independent and blinded clinical end points committee, there are limitations that should be noted. First, because the study

population was hospitalized with an acute ACS, fasting samples were only available in a subset of the total patient cohort; however, sensitivity analyses provided qualitatively similar results. Furthermore, the effects of recent dietary intake on omega 3 fatty acids is not always predictable. In addition, Holter monitoring was performed for a period of 7 days, which allowed systematic capture of only early post-ACS ventricular tachycardia. Plasma levels of fatty acids may also reflect a shorter term of dietary fat intakes as compared with adipose tissue samples.[39] Moreover, as most patients in included in this trial were White, these results might not be generalizable to other races. Because this analysis was exploratory in nature, we did not control for multiple testing, and despite adjusting for a large number of clinically relevant variables, potential residual confounding cannot be ruled out.

CONCLUSIONS

In patients with a non–ST-segment–elevation ACS, a higher relative proportion of long-chain ω3-PUFA content in plasma is associated with lower odds of sudden cardiac death, independent of traditional risk factors and lipids.

ARTICLE INFORMATION

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Disclosures

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Supplementary Material

Tables S1–S2
Figures S1–S7

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SUPPLEMENTAL MATERIAL

Table S1. Correlation Matrix with the Spearman's correlation coefficient in the upper and the respective p-values in the lower triangular.

	EPA	DPA	DHA	ALA	LDL	HDL	TG	hsCRP
EPA	-	0.67	0.63	<.001	0.04	0.21	-0.14	-0.08
DPA	<.001	-	0.46	<.001	-0.06	0.11	-0.15	-0.11
DHA	<.001	<.001	-	<.001	0.05	0.22	-0.28	-0.05
ALA	0.25	0.26	-0.14	-	-0.15	-0.13	0.19	-0.09
LDL	0.046	0.003	0.015	<.001	-	0.07	0.21	0.04
HDL	<.001	<.001	<.001	<.001	<.001	-	-0.26	-0.05
TG	<.001	<.001	<.001	<.001	<.001	<.001	-	0.02
hsCRP	<.001	<.001	0.012	<.001	0.090	0.015	0.33	-

Table S2. Baseline Characteristics by Quartiles of Alpha-linolenic Acid.

Characteristic	Total (n=2407)	Q1 (n=602) (1.01-2.91%)	Q2 (n=602) (2.91-3.55%)	Q3 (n=602) (3.55-4.48%)	Q4 (n=601) (4.48-14.3%)	P-value for Trend
Age	63.9 ±10.8	63.7 ±10.5	64.1 ±10.7	64.2 ±10.9	63.6 ±11.1	0.98
Female Sex	871 (36.2%)	250 (41.5%)	219 (36.4%)	215 (35.7%)	187 (31.1%)	<0.001
White	2347 (97.5%)	593 (98.5%)	586 (97.3%)	584 (97.0%)	584 (97.2)	0.13
Current Smoker	578 (24.0%)	162 (26.9%)	148 (24.6%)	133 (22.1%)	135 (22.5%)	0.042
Diabetes mellitus	800 (33.2%)	169 (28.1%)	182 (30.2%)	205 (34.1%)	244 (40.6%)	<0.001
Prior HF	573 (23.8%)	271 (45.0%)	142 (23.6%)	100 (16.6%)	60 (10.0%)	<0.001
Index event NSTEMI	1169 (49.7%)	248 (41.5%)	276 (46.5%)	312 (54.1%)	333 (57.0%)	<0.001
Prior MI	886 (37.2%)	257 (43.3%)	230 (38.4%)	200 (33.8%)	199 (33.3%)	<0.001
Prior coronary revascularization	620 (25. 8%)	90 (15.0%)	153 (25.5%)	176 (29.3%)	201 (33.4%)	<0.001
Hypertension	1826 (76.3%)	520 (86. 7%)	467 (78.8%)	433 (72.3%)	406 (67.6%)	<0.001
Hyperlipidemia	1441 (66.4%)	307 (59.7%)	353 (66.0%)	380 (69.2%)	401 (70.1%)	<0.001
BMI (kg/m^2)	28.97 ±5.5	28.8 ±4.6	28.86 ±7.0	29.06 ±5.3)	29.2 ±4.8	0.17
eGFR <60 ml/min/1.73 m^2	593 (24.7%)	169 (28.1%)	142 (23.6%)	144 (24.0%)	138 (23.1%)	0.062
Total cholesterol (mg/dL)	198.1 ±54.9	207.7 ±54.7	201.6 ±59.2	192.22 ±49.9	191.2 ±53.9	<0.001
LDL-C (mg/dL)	119.9 ±48.3	130.4 ±49.8	123.7 ±52.6	115.52 ±43.1	109.1 ±44.3	<0.001
HDL-C (mg/dL)	45.1 ±15.3	46.9 ±15.0	45.7 ±14.5	44.58 ±15.6	43.2 ±15.9	<0.001
Triglycerides (mg/dL)	176.0 ±141.9	150.2 ±87.2	163.1 ±102.9	171.33 ±113.4	219.8 ±217.2	<0.001
hsCRP (mg/dL)	13.8 ±20.8	14.8 ±21.6	16.30 ±23.2	13.03 ±20.1	11.2 ±17.4	<0.001
Aspirin	2316 (96.2%)	572 (95.0%)	581 (96.5%)	582 (96.7%)	581 (96.7%)	0.14
Beta Blocker	2179 (90.5%)	545 (90.5%)	548 (91.0%)	546 (90.7%)	540 (89.9%)	0.66
Statin	1843 (76.6%)	337 (56.0%)	438 (72.7%)	523 (86.9%)	545 (90.7%)	<0.001

[#]Continuous variables reported as mean (standard deviation). Legend: BMI = body mass index, HDL-C = high-density lipoprotein cholesterol; HF = heart failure; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction, NSTEMI = non-ST-elevation myocardial infarction

Figure S1. Multivariable[#] adjusted odds ratios per 1 standard deviation increase of ω3-poly unsaturated fatty acid subtypes for non-sudden cardiac death, myocardial infarction, early post ACS ventricular tachycardia, and atrial fibrillation.

[#]The model was adjusted for age, sex, eGFR, hypertension, prior myocardial infarction, heart failure, diabetes mellitus, smoking, statin use, HDL-C, LDL-C, triglycerides, body mass index, race, region, index diagnosis, and randomized Rx arm.

ALA = alpha-linolenic acid; EPA = eicosapentaenoic acid; DPA = docosapentaenoic acid; DHA =docosahexaenoic acid

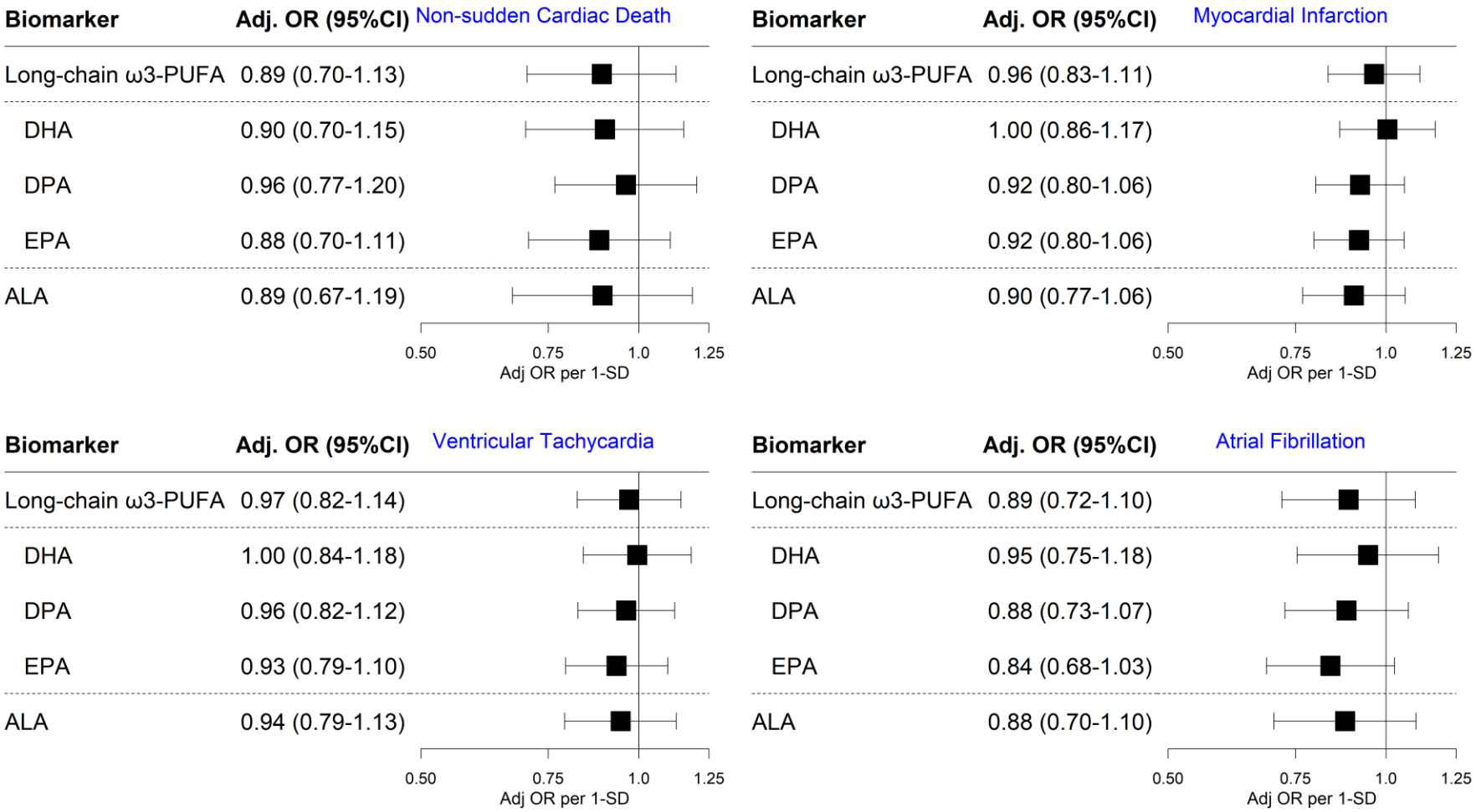

Figure S2. Multivariable[#] adjusted odds ratios for subtypes of ω3-poly unsaturated fatty acids in the top versus lowest quartile for non-sudden cardiac death, myocardial infarction, early post ACS ventricular tachycardia, and atrial fibrillation.

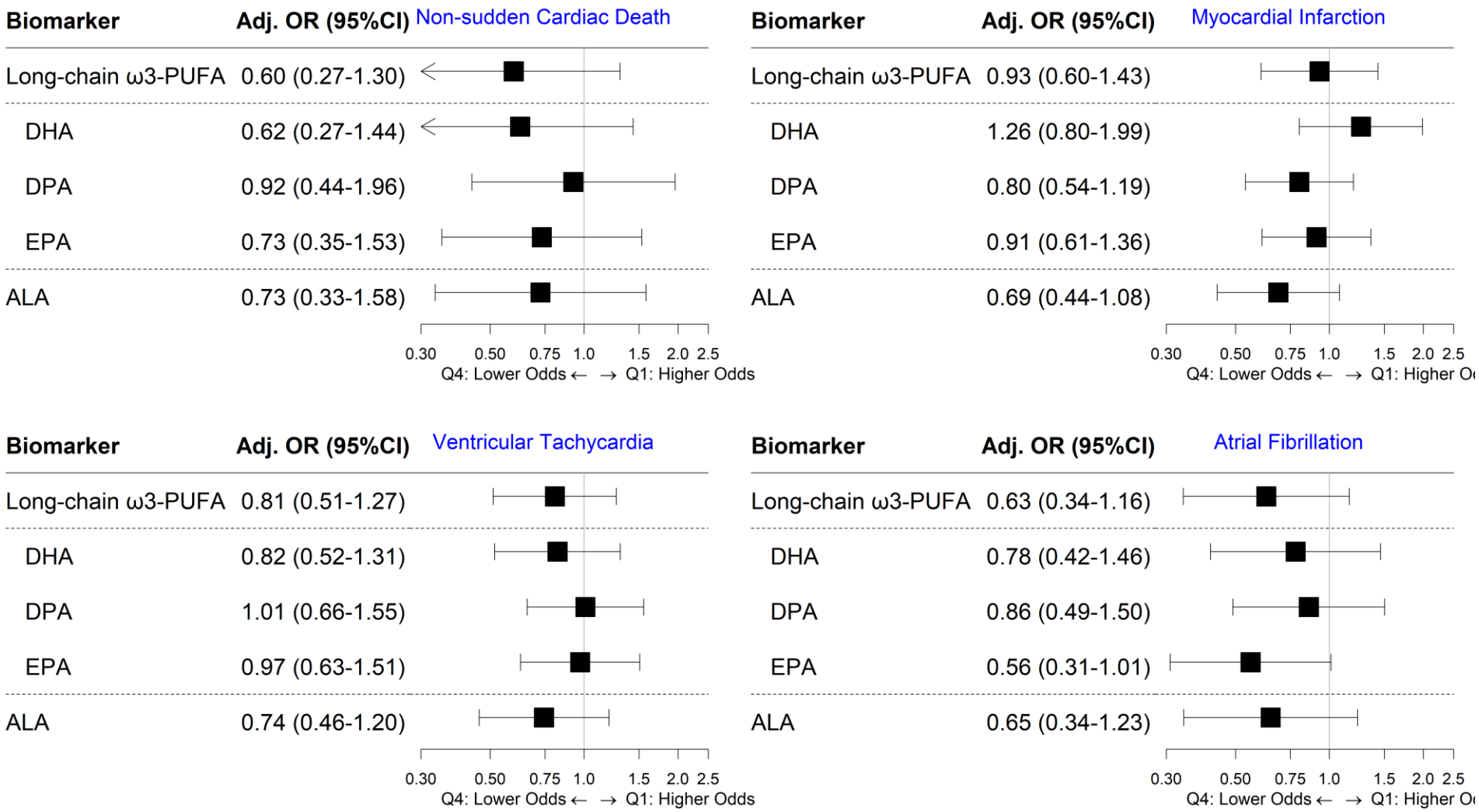

Figure S3. Association between long-chain ω3-poly unsaturated fatty acid and sudden cardiac death across different subgroups

HF = heart failure; hsCRP = high-sensitivity reactive protein C; LDL = low-density lipoprotein; TG = triglycerides, TRS = TIMI Risk Score

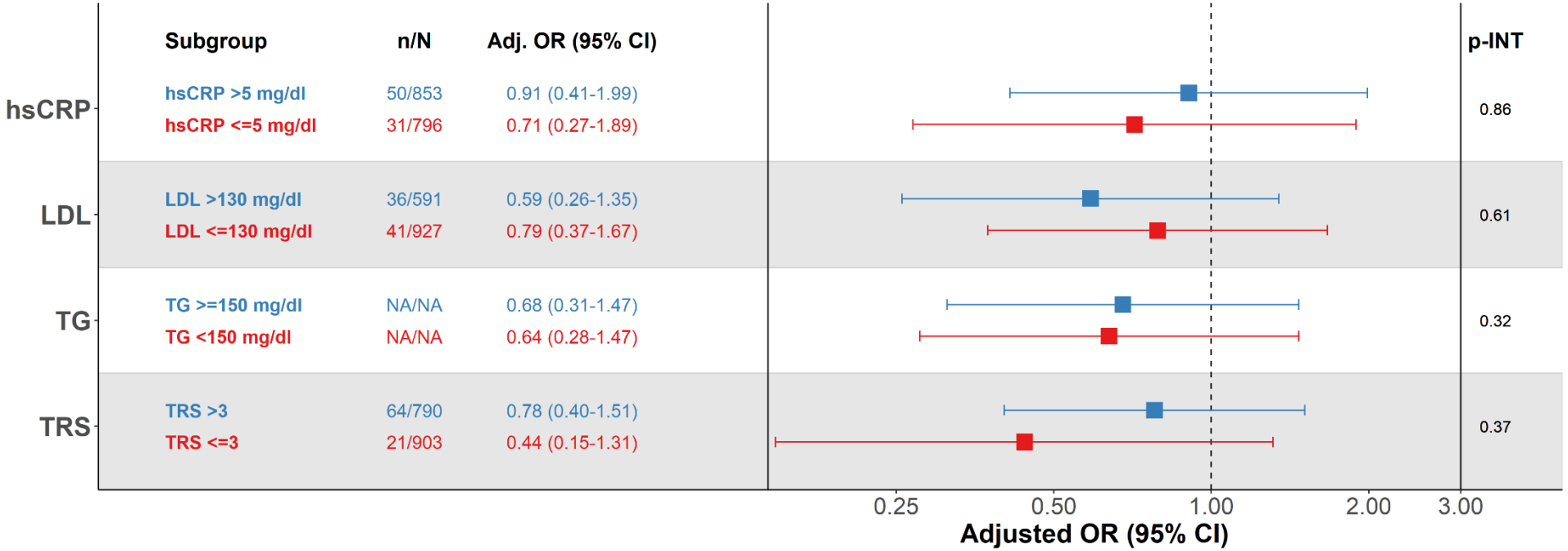

Figure S4. Multivariable adjusted odds ratios per 1-SD increase in total ω3-polyunsaturated fatty acid cardiovascular outcomes.

The models were adjusted for age, sex, eGFR, hypertension, prior myocardial infarction, heart failure, diabetes mellitus, smoking, statin use, HDL-C, LDL-C, triglycerides, body mass index, race, region, index diagnosis, and randomized treatment arm.

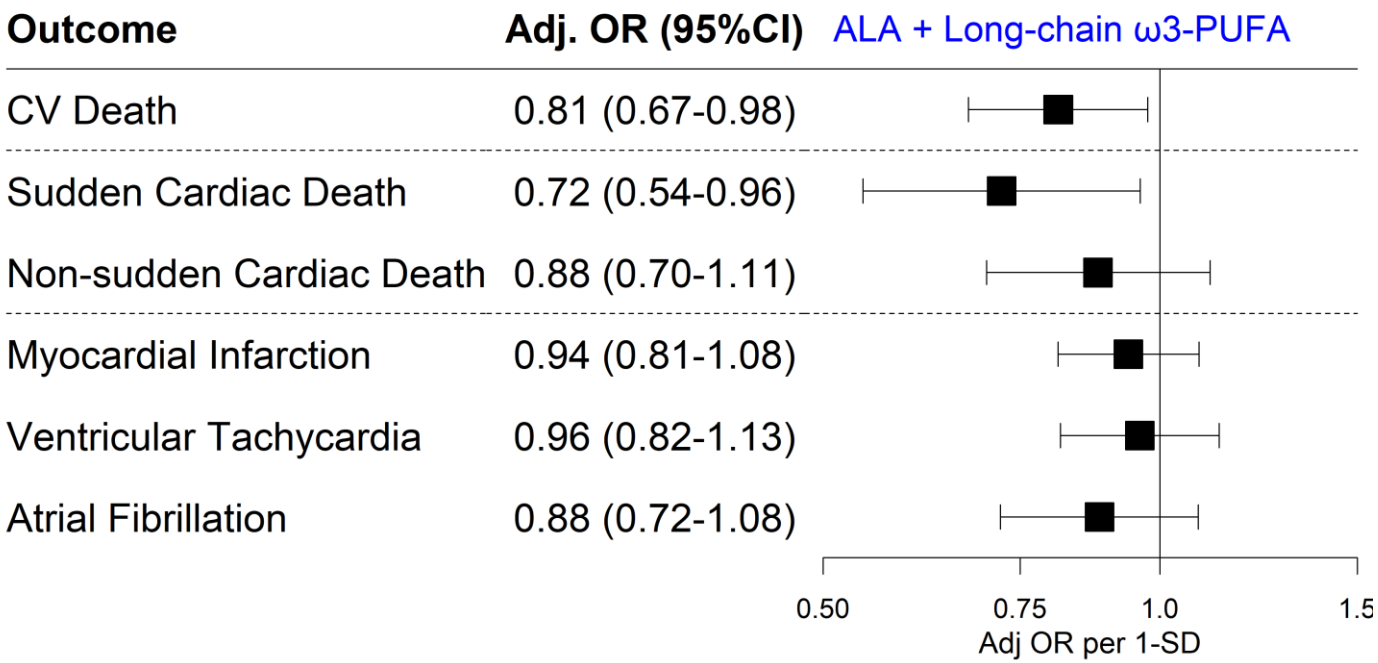

Figure S5. Multivariable adjusted odds ratios per 1-SD increase in levels of fasting ω3-poly unsaturated fatty acid subtypes for sudden cardiac death (n=1384 patients).

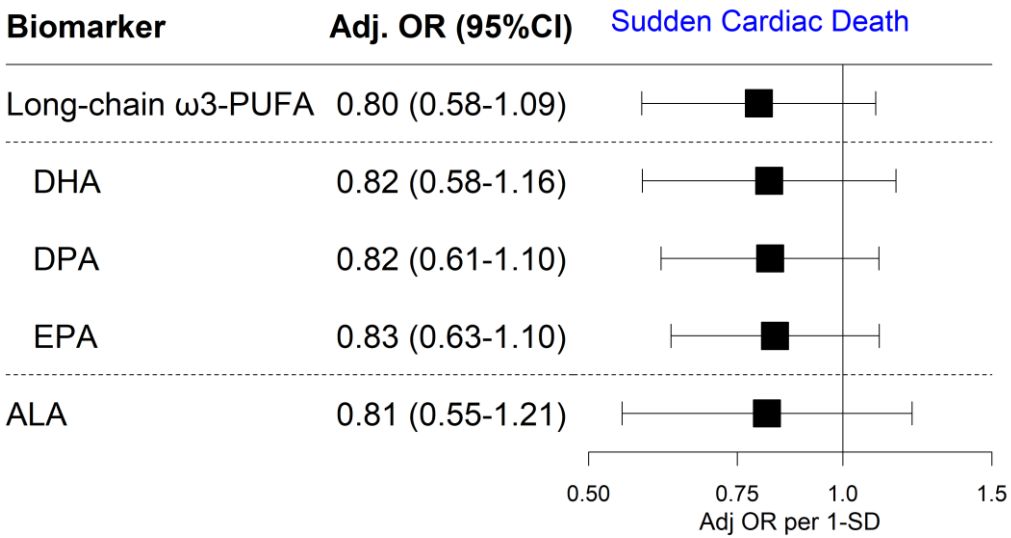

Figure S6. Multivariable adjusted odds ratios for quartiles of fasting ω3-poly unsaturated fatty acid subtypes for sudden cardiac death.

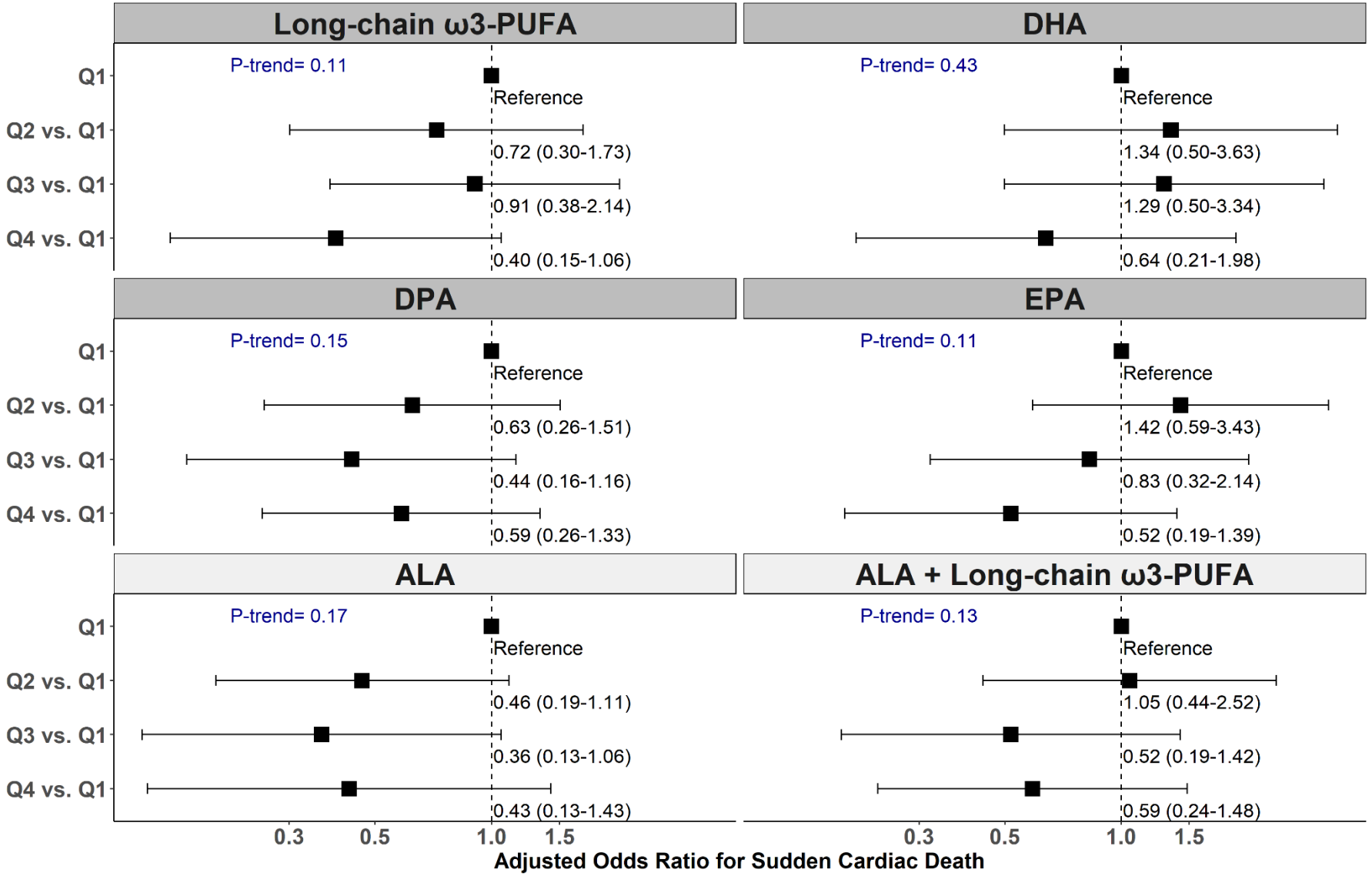

Figure S7. Multivariable adjusted odds ratios per 1 standard deviation increase of fasting ω3-poly unsaturated fatty acid subtypes for cardiovascular death, myocardial infarction, ventricular tachycardia, and atrial fibrillation.