JIM Original Article

doi: 10.1111/joim.13442

Changes in eicosapentaenoic acid and docosahexaenoic acid and risk of cardiovascular events and atrial fibrillation: A secondary analysis of the OMEMI trial

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Abstract. PL Myhre, AA Kalstad, SH Tveit, K Laake, EB Schmidt, P Smith, et al. Changes in eicosapentaenoic acid and docosahexaenoic acid and risk of cardiovascular events and atrial fibrillation: a secondary analysis of the OMEMI trial. *J Intern Med.* 2022;**291:**637–647.

Background. The cardiovascular benefit from n-3 polyunsaturated fatty acids (PUFAs) after acute myocardial infarction (AMI) is controversial, and the importance of serum eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) concentrations for clinical events is unclear.

Objectives. To assess changes in EPA and DHA serum concentrations during n-3 PUFA supplementation and their association with incident cardiovascular events.

Methods. In the OMEMI trial, elderly patients with a recent AMI were randomized to 1.8 g/day of EPA/DHA or control (corn oil) for 2 years. The primary outcome was a composite of AMI, coronary revascularization, stroke, heart failure hospitalization, or all-cause death (major adverse cardiovascular event [MACE]) and the secondary outcome was new-onset atrial fibrillation (AF).

Results. EPA and DHA measurements were available in 881 (92% of survivors) participants at randomization and study completion. EPA and DHA increased in the active treatment arm ($n = 438$) by a median of 87% and 16%, respectively. Greater on-treatment increases in EPA and DHA were associated with decreasing triglycerides, increasing high-density lipoprotein cholesterol, and lower baseline EPA and DHA concentrations. Greater on-treatment increases in EPA were associated with lower risk of MACE (adjusted hazard ratio 0.86 [95% confidence interval, CI, 0.75–0.99], $p = 0.034$), and higher risk of AF (adjusted hazard ratio (HR) 1.36 [95% CI 1.07–1.72], $p = 0.011$). Although there were similar tendencies for DHA changes and outcomes, these associations were not statistically significant (HR 0.84 [0.66–1.06] for MACE and 1.39 [0.90–2.13] for AF).

Conclusion. Greater on-treatment increases in EPA were associated with lower risk of MACE and higher risk of new-onset AF. These data suggest that the cardiovascular effects of increasing n-3 PUFA levels through supplements are complex, involving both potential benefits and harm.

Keywords: atrial fibrillation, cardiovascular events, docosahexaenoic acid, eicosapentaenoic acid, omega-3

Introduction

Higher concentrations of the omega-3 polyunsaturated fatty acids (n-3 PUFAs) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in blood and adipose tissue have been associated with lower risk of cardiovascular events in the general population [1–4] and among patients with established cardiovascular disease [5–7]. The GISSI-Prevenzione trial demonstrated that supplementation with combined EPA and DHA after an acute myocardial infarction (AMI) reduced the risk of subsequent AMI and death [8]. Later trials conducted in the era of modern secondary prevention have, however, failed to demonstrate a clear benefit of mixed EPA and DHA supplementation after AMI [9–11]. In the OMega-3 fatty acids in Elderly patients with Myocardial Infarction (OMEMI) trial, we confirmed these neutral results even when using a higher dose (1.8 g) of mixed EPA and DHA than in previous trials [12].

In patients with hypertriglyceridemia, supplementation with very high dose icosapent ethyl (i.e., purified EPA) of 4 g significantly reduced the risk of cardiovascular events [13], and the magnitude of risk reduction was associated with the achieved serum EPA levels in the active treatment arm. A similar type of study testing the same high dose of mixed EPA and DHA found no significant risk reduction, and no association between risk and changes in EPA or DHA [14, 15].

Concerns related to an increased risk of incident atrial fibrillation (AF) from n-3 PUFAs supplementation have emerged from the results of recent trials [12–14, 16]. The underlying mechanism for this association and whether there is a dose-dependent gradient remain unknown.

In the current prespecified substudy of OMEMI, we aimed to investigate changes in serum concentrations of EPA and DHA in association with the risk of major adverse cardiovascular events (MACE) and new-onset AF in patients treated for 2 years with mixed EPA and DHA.

Material and methods

The OMEMI trial (NCT01841944) was a randomized, double-blind, parallel group, placebo-controlled trial testing the cardiovascular effect of 1.8 g/day of n-3 PUFAs in elderly patients with a recent AMI [12, 17]. Criteria for inclusion were age 70–82 years and hospitalization for AMI 2–8 weeks before randomization. Eligible patients were randomized in a 1:1 ratio to three capsules of n-3 PUFAs (total 1800 mg, comprising 930/660 mg EPA/DHA; Pikasol, Orkla Health, Norway) or matching placebo (corn oil). Treatment other than the intervention was standard secondary prevention according to current guidelines and by the discretion of the treating physician. Although patients were instructed not to use other n-3 PUFA supplements in the study period, one small spoon of cod liver oil was permitted for users due to local tradition for this in Norway. The OMEMI protocol was approved by the Regional Committee for Medical and Health Research Ethics (#2012/1422). All participants provided written informed consent and the trial was conducted in compliance with the Declaration of Helsinki and Good Clinical Practice.

Laboratory analysis

Venous blood samples were drawn in the fasting state at randomization and the final visit (24 months). Serum was prepared within 1 hour by centrifugation at 2000× g for 10 min and kept frozen at −80°C. Fatty acid (FA) composition of serum phospholipids was analyzed by gas chromatography in thawed samples at the Lipid Research Laboratory (Aalborg University Hospital, Denmark), with results presented as percent weight (%wt) of total FAs in serum phospholipids [18]. Routine laboratory analyses were performed by conventional methods in core laboratories.

Outcome measures

The primary outcome was a composite of MACE, including nonfatal AMI, unscheduled revascularization, stroke, hospitalization for heart failure (HF), or all-cause death, whichever occurred first. The secondary outcome was new-onset AF, which was screened for by hand-held single-lead rhythm monitoring for 30 s twice daily for 14 consecutive days following the 12-month visit (Zenicor Medical Systems AB, Stockholm, Sweden), in addition to standard 12-lead ECG and review of hospital records at each study visit (3, 12, and 24 months). Patients with known AF or new-onset AF between the index AMI and randomization were excluded from this analysis. The primary safety outcome was serious bleeding, defined as Bleeding Academy Research Consortium (BARC) classification ≥2 [12]. All outcomes were adjudicated by an independent endpoint committee.

Statistical analysis

Values are reported as *N* (%) and median (quartiles 1 to 3 [Q1, Q3]) for skewed and mean ± SD for normally distributed variables. Categorical and continuous variables were compared using the chi-square test for binary variables, ANOVA for parametric continuous variables, and the Kruskal–Wallis test for nonparametric continuous variables. Clinical and laboratory variables were presented by quartiles of EPA and DHA levels at baseline and change from baseline to 24 months, and compared for trend across quartiles by linear and logistic regression. Absolute changes in EPA and DHA were calculated by subtracting the baseline level from the 24 month level, and ratios of change by dividing the 24 month level with the baseline level. Correlations between changes in EPA and DHA were calculated by Spearman's rho. Changes in EPA and DHA in serum phospholipids were assessed in association with the risk of MACE and the risk of new-onset AF by Cox proportional hazard regression models, stratified by treatment arm. The analyses conducted with respect to incident MACE and incident AF were conducted separately without censoring patients who experienced the other event, that is, patients who experienced MACE were not censored and still followed for AF subsequently. The Cox models were adjusted for covariates determined *a priori* based on clinical factors known to be associated with risk (i.e., age, sex, current smoking, body mass index [BMI], systolic blood pressure, New York Heart Association functional class [NYHA], preexisting hypertension, diabetes mellitus, and HF), in addition to baseline levels of each n-3 PUFA to account for regression to the mean. Restricted cubic spline models tested for 2–7 knots (best linear or nonlinear fit based on Bayesian Information Criterion), and adjusted for the same covariates as the Cox model, were used to plot the flexible relationship between changes in serum EPA and DHA as continuous variables and the incidence of MACE and AF. All statistical analyses were performed using Stata Software (v16, Stata Corp., College Station, TX). A two-sided *p*-value of <0.05 was considered statistically significant.

Results

In total, 1002 of the 1027 patients enrolled in the trial had available FA measurements at randomization. Their mean age was 74.7 ± 3.6 years. A total of 287 (28.6%) were female and 1000 (99.8%) were Caucasian.

Baseline EPA and DHA serum phospholipid levels and their association with outcomes

EPA and DHA levels at baseline were median 2.5 (Q1–Q3 1.8–3.5) and 5.6 (Q1–Q3 4.8–6.6) %wt, respectively. Higher EPA and DHA levels were associated with intake of pretrial n-3 PUFA supplements, less frequent current smoking and diabetes mellitus, better NYHA functional class, higher left ventricular ejection fraction, lower plasma triglycerides and higher high-density lipoprotein (HDL)–cholesterol (Table 1; Table S1).

Serum concentrations of EPA and DHA at baseline ($n = 1002$), were not associated with incident MACE or all-cause death ($N = 208$): hazard ratio (HR) 0.93 (95% confidence interval [CI] 0.84–1.03), $p = 0.18$ and HR 0.93 (0.84–1.03), $p = 0.15$, respectively. This null effect persisted even after adjusting for age, sex, BMI, current smoking, systolic blood pressure, NYHA class, hypertension, diabetes mellitus, and HF (HR 0.99 [0.89–1.10], $p = 0.82$ for EPA and HR 0.96 [0.86–1.07], $p = 0.44$ for DHA). There were no associations between baseline serum EPA and DHA levels and new-onset AF ($N = 43$): HR 1.09 (0.89–1.33), $p = 0.42$ and HR 1.19 (0.96–1.43), $p = 0.11$, respectively. This was also consistent in adjusted models (HR 1.14 [0.92–1.40], $p = 0.22$ for EPA and HR 1.20 [0.97–1.50], $p = 0.10$ for DHA).

Changes in EPA and DHA levels during the study

FA measurements at the final 24-month study visit were available in 881 patients. Patients without follow-up samples included 55 nonsurvivors and 66 survivors who did not have measurements of EPA and DHA available (only 27 of these attended the final visit). Overall, patients without available blood samples at both time points were older, with more comorbidities and a greater incidence of MACE (Table S2). At the 24-month visit, median EPA was 3.5 (Q1–Q3 2.0–5.4) %wt and DHA 6.0 (Q1–Q3 4.9–7.1) %wt for the total population. In patients randomized to n-3 PUFAs, EPA increased by 2.4 (Q1–Q3 1.0–3.6) %wt, corresponding to a relative median 87% (Q1–Q3 32%, 166%) increase, and DHA increased by 0.9 (Q1–Q3 0.13–1.8) %wt, corresponding to a median 16% (Q1–Q3 2%, 33%) increase (Fig. 1). The on-treatment changes in EPA and DHA correlated moderately (rho 0.57, $p < 0.001$; Fig. S1). In the placebo group, there was a small decrease in both EPA, −0.3 (Q1–Q3 −1.1–0.5) %wt (−13% [Q1–Q3 -35%, +21%]), and DHA, −0.4 (Q1–Q3 −1.1–0.3) %wt (−8% [Q1–Q3 −18%,

Table 1. *Baseline characteristics by quartiles of baseline eicosapentaenoic acid (EPA) concentrations*

Baseline EPA, %wt	Baseline EPA Q1 ≤1.82 $n = 253$	Baseline EPA Q2 1.84–2.52 $n = 250$	Baseline EPA Q3 2.53–3.51 $n = 251$	Baseline EPA Q4 ≥3.52 $n = 248$	*p*-value for trend
Age, years	74.2 ± 3.5	75.3 ± 3.7	74.6 ± 3.6	74.8 ± 3.5	0.23
Female sex	71 (28.1%)	74 (29.6%)	73 (29.1%)	69 (27.8%)	0.93
Current smoker	38 (15.0%)	33 (13.2%)	23 (9.2%)	24 (9.7%)	0.027
Body mass index, kg/m^2	26.4 ± 4.1	27.4 ± 9.8	26.8 ± 4.0	26.5 ± 3.9	0.85
Systolic blood pressure	135.8 ± 21.0	137.4 ± 19.7	137.2 ± 19.5	138.1 ± 18.8	0.23
Heart rate, per min	70.6 ± 42.5	66.1 ± 13.1	65.6 ± 12.0	66.5 ± 40.9	0.14
NYHA 3 or 4	31 (12.4%)	21 (8.4%)	19 (7.6%)	16 (6.5%)	0.020
Prev. LV ejection fraction, %	48.9 ± 9.0	49.3 ± 8.7	50.7 ± 8.7	51.2 ± 7.4	0.006
Medical history					
Hypertension	166 (65.6%)	137 (54.8%)	154 (61.4%)	146 (58.9%)	0.32
Diabetes mellitus	64 (25.3%)	53 (21.2%)	56 (22.3%)	35 (14.1%)	0.005
Prev. acute myocardial infarction	69 (27.3%)	74 (29.6%)	60 (23.9%)	54 (21.8%)	0.07
Prev. coronary revascularization	71 (28.1%)	70 (28.0%)	78 (31.1%)	74 (29.8%)	0.51
Prev. atrial fibrillation	38 (15.0%)	34 (13.6%)	36 (14.3%)	46 (18.5%)	0.27
Prev. heart failure	18 (7.1%)	19 (7.6%)	18 (7.2%)	9 (3.6%)	0.12
Index acute myocardial infarction					
STEMI	88 (34.8%)	96 (38.4%)	76 (30.3%)	75 (30.2%)	0.10
Troponin T maximum	678 (157, 2214)	844 (186, 3771)	603 (123, 2221)	479 (112, 1929)	0.021
Medications					
Aspirin	238 (94.1%)	239 (95.6%)	231 (92.0%)	236 (95.2%)	0.96
Statin	238 (94.1%)	241 (96.4%)	245 (97.6%)	243 (98.0%)	0.012
Beta blocker	220 (87.0%)	203 (81.2%)	207 (82.5%)	201 (81.0%)	0.12
n-3 PUFA supplement	55 (21.9%)	81 (32.5%)	122 (48.8%)	154 (63.1%)	<0.001
Laboratory measurements					
Creatinine, umol/L	91 (77, 110)	87 (76, 105)	86 (77, 102)	84 (72, 97)	<0.001
Hemoglobin A1c, %	5.9 (5.5, 6.5)	5.8 (5.5, 6.4)	5.8 (5.5, 6.3)	5.8 (5.5, 6.1)	0.12
Total cholesterol, mmol/L	3.65 (3.10, 4.20)	3.60 (3.10, 4.20)	3.55 (3.10, 4.10)	3.50 (3.10, 4.00)	0.02
HDL cholesterol, mmol/L	1.10 (0.91, 1.40)	1.20 (1.00, 1.57)	1.20 (1.00, 1.49)	1.30 (1.05, 1.56)	<0.001
LDL cholesterol, mmol/L	1.92 (1.50, 2.40)	1.90 (1.50, 2.38)	1.87 (1.47, 2.30)	1.80 (1.50, 2.22)	0.022
Triglycerides, mmol/L	1.39 (1.00, 1.79)	1.14 (0.88, 1.55)	1.06 (0.81, 1.42)	0.92 (0.75, 1.18)	<0.001

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; LV, left ventricular; NYHA, New York Heart Association; PUFA, polyunsaturated fatty acids; STEMI, ST-elevation myocardial infarction.

+6%]). Compared to placebo, EPA levels increased by median 100% and DHA by median 24% in the active treatment arm.

Greater increases in EPA and DHA in the active treatment arm were associated with decreasing plasma triglycerides and increasing HDL-cholesterol concentrations throughout the study. (Table 2; Table S3). Patients with lower EPA and DHA concentrations at baseline experienced greater increases in EPA and DHA.

Changes in EPA and DHA levels and their association with MACE

In patients with available FA samples at baseline and final study visit ($n = 881$), a total of 128 experienced MACE during follow-up—comprising of 54

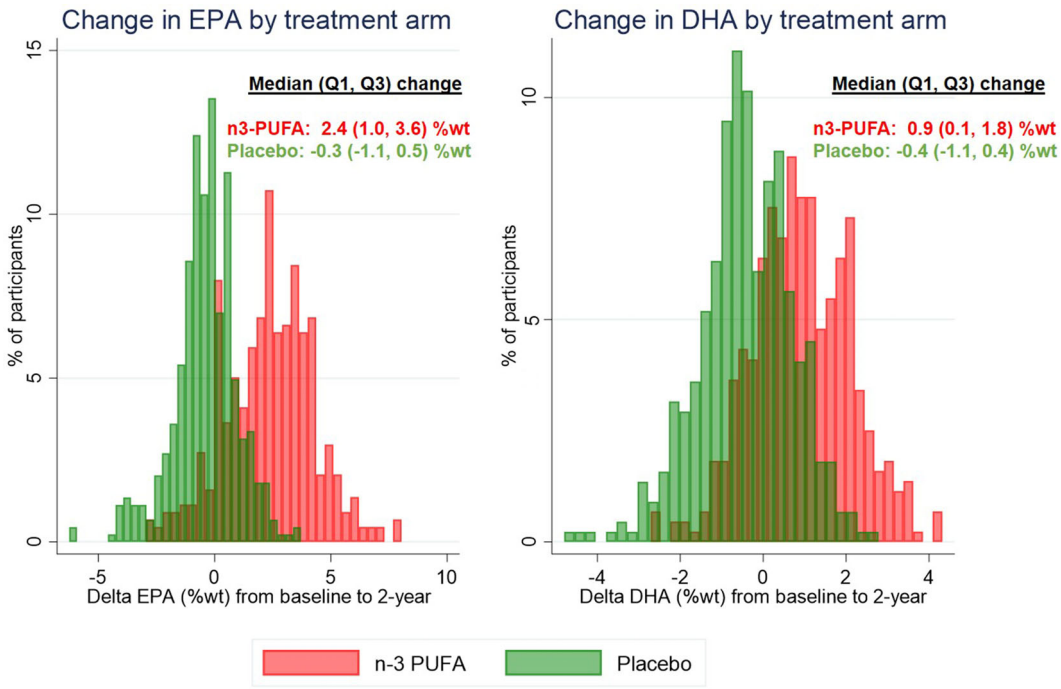

Fig 1 *Changes in eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from baseline to 2 years in patients randomized to 1.8 g/day of n-3 polyunsaturated fatty acids (n-3 PUFAs) and in patients randomized to placebo.*

Table 2. *Baseline values and absolute changes in serum lipids and fatty acid concentrations, by quartiles of change in eicosapentaenoic acid (EPA) in the n-3 PUFA arm (n = 438)*

	EPA change Q1 $n = 110$	EPA change Q2 $n = 110$	EPA change Q3 $n = 110$	EPA change Q4 $n = 108$	*p*-value for trend
Change in EPA (%wt)	*<1.0*	*1.0–2.4*	*2.5–3.6*	*>3.6*	
Baseline biomarkers					
HDL cholesterol, mmol/L	1.16 (1.00, 1.41)	1.27 (1.00, 1.51)	1.20 (1.00, 1.40)	1.20 (1.00, 1.58)	0.48
LDL cholesterol, mmol/L	1.80 (1.40, 2.10)	1.80 (1.40, 2.23)	1.90 (1.50, 2.30)	1.90 (1.48, 2.52)	0.01
Triglycerides, mmol/L	1.19 (0.89, 1.60)	1.04 (0.84, 1.45)	1.12 (0.88, 1.52)	1.13 (0.88, 1.51)	0.44
EPA, %wt	3.16 (2.17, 4.67)	2.92 (2.11, 3.76)	2.38 (1.83, 3.19)	2.09 (1.55, 2.92)	<0.001
Docohexaenoic acid, %wt	5.8 (4.9, 6.7)	5.7 (4.9, 6.9)	5.6 (4.8, 6.5)	5.5 (4.7, 6.4)	0.05
Change in biomarkers					
HDL cholesterol, mmol/L	0.06 (−0.04, 0.29)	0.10 (−0.03, 0.28)	0.10 (−0.02, 0.30)	0.20 (0.05, 0.40)	<0.001
LDL cholesterol, mmol/L	0.10 (−0.20, 0.28)	−0.02 (−0.30, 0.30)	−0.10 (−0.40, 0.30)	0.06 (−0.30, 0.38)	0.79
Triglycerides, mmol/L	0.05 (−0.28, 0.32)	−0.07 (−0.24, 0.13)	−0.10 (−0.40, 0.14)	−0.21 (−0.45, −0.03)	<0.001
n-3 PUFA supplement (*n*, %)					
n-3 PUFA suppl. baseline	49 (45.0)	50 (46.3)	39 (35.8)	42 (38.9)	0.18
n-3 PUFA suppl. study end	17 (15.9)	16 (15.1)	20 (18.5)	27 (25.7)	0.05

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; PUFA, polyunsaturated fatty acids.

Table 3. *Cox regression models of changes in EPA and DHA levels (absolute values, per percentage weight of total fatty acids increase) from baseline to 24 months in association with the risk of major adverse cardiovascular events (MACE) (n = 881) and new-onset atrial fibrillation (AF) in participants free of AF at baseline (n = 759)*

	n-3 PUFAs		Placebo	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
MACE				
Delta EPA, unadjusted	0.89 (0.78–1.00)	0.059	1.02 (0.85–1.23)	0.85
Delta EPA, adjusted[a]	0.86 (0.70–0.99)	0.034	1.05 (0.84–1.31)	0.67
Delta DHA, unadjusted	0.86 (0.70–1.05)	0.13	1.16 (0.92–1.46)	0.22
Delta DHA, adjusted[a]	0.84 (0.66–1.06)	0.14	1.19 (0.92–1.53)	0.20
New- onset AF				
Delta EPA, unadjusted	1.31 (1.06–1.62)	0.012	0.91 (0.64–1.31)	0.63
Delta EPA, adjusted[a]	1.36 (1.07–1.72)	0.011	1.01 (0.69–1.50)	0.90
Delta DHA, unadjusted	1.29 (0.91–1.83)	0.16	0.75 (0.50–1.13)	0.16
Delta DHA, adjusted[a]	1.39 (0.90–2.13)	0.13	0.82 (0.51–1.33)	0.42

AF, atrial fibrillation; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; HR, hazard ratio; MACE, major adverse cardiovascular events; PUFA, polyunsaturated fatty acids.
[a]Adjusted for age, sex, current smoking, body mass index, systolic blood pressure, New York Heart Association class, preexisting hypertension, diabetes, heart failure, and baseline levels of the fatty acid of interest (EPA or DHA).

with AMI, 34 nonscheduled revascularizations, 23 strokes, and 17 hospitalizations for HF as the first event. In patients randomized to n-3 PUFAs (n = 438), there was an association between greater increases in EPA levels and lower risk of MACE (N = 68): unadjusted HR 0.89 (95% CI 0.78–1.00) per %wt increase, $p = 0.059$ and HR 0.86 (0.75–0.99), $p = 0.034$ after adjusting for age, sex, BMI, current smoking, systolic blood pressure, NYHA class, hypertension, diabetes mellitus, HF, and baseline concentrations of EPA (Table 3; Fig. 2), and the association was linear (Table S4). Similarly, there was an association between the achieved EPA level (concentrations at the final study visit) and incident MACE in adjusted models: HR 0.86 (0.75–0.99) per %wt, $p = 0.034$. The lowest risk was seen in the top three quartiles of EPA increase, and these patients had a 61% lower risk of MACE compared to the lowest quartile (HR 0.39 [0.19–0.79], $p = 0.009$) (Figure S2). There was no significant association between changes in DHA and incident MACE in the active treatment arm: unadjusted HR 0.86 (0.70–1.05), $p = 0.13$ and adjusted HR 0.83 (0.66–1.05), $p = 0.14$. Similarly, there was no association between achieved DHA level and risk of MACE: adjusted HR 0.91 (0.74–1.10), $p = 0.35$. The ratio of changes in EPA and DHA was not associated with incident MACE (Table S4). There was no effect modification by treatment arm on the association between change in EPA and MACE (adjusted p for interaction = 0.30), while there was a borderline interaction for change in DHA and MACE (adjusted p for interaction = 0.05). In the placebo arm (n = 443), there were no significant associations between changes in EPA and DHA and incident MACE (N = 60; Table 3).

Changes in EPA and DHA levels and their association with new-onset AF

Of the 881 patients with FA samples available at both time points, 759 (86%) had no history of AF at randomization. During follow-up, a total of 43 (6%) patients had new-onset AF, of whom two were detected by thumb ECG following the 12-month visit. In patients randomized to n-3 PUFAs, there was a significant association between a greater increase in EPA and a higher risk of incident AF: adjusted HR 1.36 (1.07–1.72), $p = 0.011$. (Table 3; Fig. 2; Fig. S3), and the association was linear (Table S4). Similarly, achieved EPA serum phospholipid levels were associated with new-onset AF: adjusted HR 1.36 (1.07–1.72), $p = 0.011$. Changes in DHA were not significantly associated with incident AF in the active treatment arm: adjusted HR 1.29 (0.91–1.83), $p = 0.16$. Similarly, no associations were observed for achieved DHA levels: adjusted HR 1.29 (0.91–1.83), $p = 0.15$. The ratio of change in EPA was associated with incident AF in the active treatment arm: HR 1.35 (1.06–1.72), $p = 0.01$, while this was not significant for the ratio of change in DHA (Table S5). In patients randomized to placebo also there was no significant

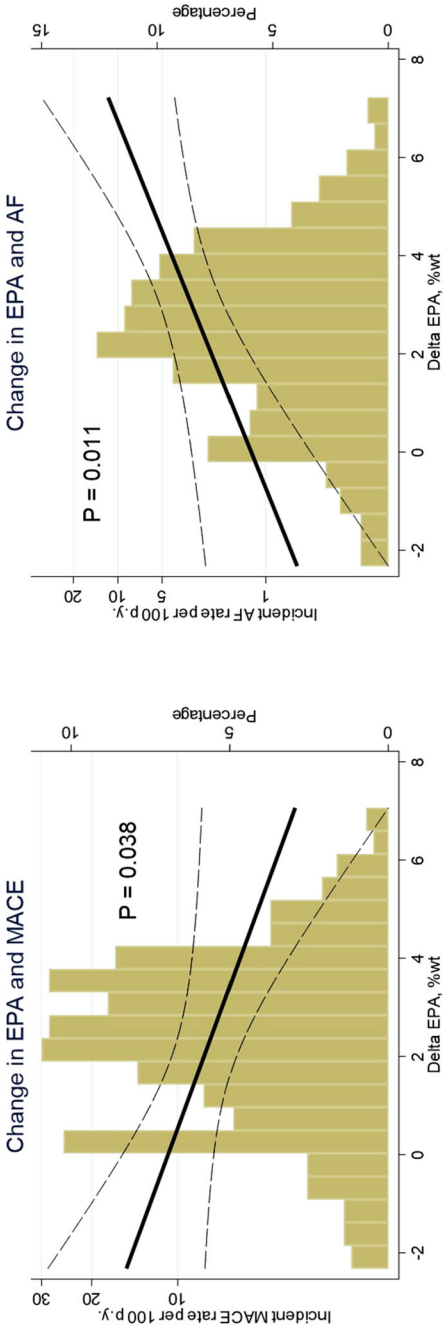

Fig 2 *Changes in eicosapentaenoic acid (EPA) and incident rates of major adverse cardiovascular events (*left panel, *n = 438) and new-onset atrial fibrillation (*right panel, *n = 339 free of atrial fibrillation at study inclusion) in patients randomized to 1.8 grams per day of n-3 polyunsaturated fatty acids for 2 years. Models are adjusted for age, sex, current smoking, body mass index, systolic blood pressure, New York Heart Association class, preexisting hypertension, diabetes, heart failure, and baseline levels of EPA. The flexible associations were tested with 2–7 knots, and 2 knots (linear) yielded the best fit for both analyses using the lowest Bayesian Information Criterion. The histogram represents the distribution of patients by change in EPA (right Y-axis) and the black line represents the association between change in EPA and incident rate of each outcome (left Y-axis) with 95% confidence intervals as dashed lines.*

association between changes in EPA and DHA for incident AF.

Changes in EPA and DHA levels in association to bleeding

Serious bleeding occurred in 90 (10.2%) of the 881 patients with FA samples available at both time points, of which 45 were in the active treatment arm. There was no association between changes in EPA or DHA and serious bleeding in the active treatment arm: OR 1.02 (0.77–1.33), $p = 0.91$, and OR 0.94 (0.71–1.23), $p = 0.64$ (Table S6). Similar results were present when analyzing the total study population.

Discussion

In elderly patients with a recent AMI treated with 1.8 g/day of n-3 PUFAs, greater increases in serum phospholipid EPA were independently associated with lower risk of incident MACE and higher risk of new-onset AF. Despite tendencies in the same direction, there was no significant association between changes in DHA and cardiovascular events. In the OMEMI trial, patients treated with n-3 PUFA had a borderline significant 84% increased risk of new-onset AF, and we now extend these findings by showing an association between increases in EPA and AF risk in the active treatment arm. These data suggest that potential beneficial effects on MACE of increasing n-3 PUFA levels through supplements may be counteracted by an increased risk of AF.

Circulating levels of n-3 PUFAs at baseline and cardiovascular risk

Higher circulating levels of EPA and DHA have consistently been shown to be associated with lower risk of cardiovascular events and all-cause death in large cohort studies and epidemiological studies [1–7, 19, 20]. In OMEMI, we found no significant association between baseline concentrations of EPA or DHA in serum phospholipids and cardiovascular risk. However, higher levels were associated with lower plasma triglycerides and low-density lipoprotein (LDL) cholesterol and higher HDL-cholesterol levels. Moreover, patients with higher serum levels of n-3 PUFAs were less likely to smoke, had less diabetes mellitus, higher functional class, and used more statins after the index AMI. These associations suggest that patients with higher baseline levels of n-3 PUFAs have fewer risk factors and fewer adverse health behaviors. This

highlights the core challenge with clinical nutrition research—detangling association from causation.

Supplementation with EPA and DHA and cardiovascular risk

The n-3 PUFA dose used in the OMEMI trial was moderate, that is, higher than the majority of trials that were using <1 g/day [9–11], but lower than 4 g/day used in the recent landmark trials STRENGTH and REDUCE-IT [13, 14]; whereas STRENGTH and OMEMI, which used a carboxylic acid formulation of EPA and DHA, showed neutral results, REDUCE-IT demonstrated a striking 25% reduction in cardiovascular events from pure EPA (icosapent ethyl) [13, 14]. The cardiovascular benefits from pure EPA supplementation in the open-label JELIS [21] and the finding of coronary plaque regression in a recent mechanistic trial [22] support the findings in REDUCE-IT.

Changes in serum phospholipid n-3 PUFAs and effects on cardiovascular events

In the active treatment arm in OMEMI, EPA levels increased by 100% and DHA by 24%, compared to placebo. In REDUCE-IT, EPA increased by 386%, while DHA decreased by 3% compared to placebo, and in STRENGTH, EPA, and DHA, they increased by 269% and 40%, respectively. Thus, the magnitude of increase in the circulating n-3 PUFA levels seems to reflect both the dose and formulation of the treatment. In REDUCE-IT, greater on-treatment increases in EPA were associated with lower risk of cardiovascular events [23], and a similar association was observed in the JELIS trial [24]. In contrast, there was no association between changes or achieved levels in EPA (or DHA) and the risk of cardiovascular events in STRENGTH [15]. We now add to this body of evidence by reporting an independent association between greater on-treatment increases in EPA and lower incidence of cardiovascular events in elderly post-AMI patients. Contrary to this, there was no significant association between DHA changes and cardiovascular events. Although there are different mechanisms by which EPA and DHA may exert their effects [25, 26], they are difficult to detangle given that the study drug included both FAs, and on-treatment changes in EPA and DHA were correlated.

Importantly, we found no significant association for the ratio of change (as opposed to absolute change) in EPA and MACE. These findings suggest that patients who achieve high levels of EPA from n-3 PUFA supplementation may derive clinical benefit from this therapy. Indeed, changes in EPA were directly associated with changes in HDL cholesterol, and inversely associated with changes in triglycerides and LDL cholesterol, which may at least in part explain the effect. Moreover, patients with greater increases in EPA had lower baseline EPA and were less likely to use n-3 PUFA supplements prior to the trial. Pretrial n-3 PUFA supplement use and baseline EPA levels had no impact on the primary results of the OMEMI trial.

We did not find any association between changes in EPA or DHA and incident serious bleeding. This is in contrast to findings from REDUCE-IT and JELIS, which found a higher rate of bleeding events in patients randomized to EPA as compared to placebo, suggesting that there may be an antithrombotic mechanism of action [13, 21].

The effect of changes in serum n-3 PUFAs and AF

Some epidemiological studies have suggested that fish intake is associated with lower incidence of AF [27], while others have found no association between intake of EPA and DHA and new-onset AF [28]. A large Danish cohort study found a U-shaped association between consumption of marine n-3 PUFAs and risk of incident AF in a study of 57,053 subjects, with the lowest risk close to the median intake of 0.6 g/day [29]. Several clinical trials have tested the effect of n-3 PUFAs on AF. Overall, the results are inconsistent, and a systematic review and meta-analysis of randomized control trials (RCTs) do not support n-3 PUFAs as useful agents for prevention of AF [30]. An emerging signal from the more recent trials even suggests that n-3 PUFA supplements may increase the risk of new-onset AF. Thus, in STRENGTH and REDUCE-IT, there were significant 69% and 36% increased risks of AF, respectively, after a supplementation with n-3 PUFAs [13, 14], while there was a borderline-significant 84% increased risk in OMEMI [12]. In primary prevention trials of low-dose n-3 PUFAs, nonsignificant trends towards increased risk of AF have been reported [31, 32]. A meta-analysis of these recent trials found an incident ratio of 1.37 (95% CI 1.22–1.54) for incident AF, with no statistically significant heterogeneity between the studies included [33]. We now report a significant and independent association between on-treatment increases (both absolute and ratio) in EPA and the risk of new-onset AF in OMEMI.

Although the tendency was similar, changes in DHA did not associate with incident AF. Importantly, we screened for AF through 2 weeks of thumb-ECG recordings, which is a unique aspect compared to other trials in the field. Our findings agree with an observation of higher levels of EPA in patients with AF, with the highest levels in those with persistent and permanent AF [34]. The underlying mechanisms linking n-3 PUFAs, and especially EPA, to AF are incompletely understood. Experimental studies suggest that n-3 PUFAs reduce asynchronous contractile activity in atrial myocytes, lengthen the atrial conduction times, and reduce the inducibility of AF, but increase the inducibility of atrial flutter [35, 36]. Although we currently rely on evidence from post hoc analysis of RCTs designed for different outcomes, our findings support the recent concerns related to a dose-related risk of AF with n-3 PUFA intake [16], which seems to particularly relate to EPA. More research is needed to better understand the balance of pro-arrhythmic and anti-arrhythmic properties of n-3 PUFAs dependent on formulation, dose, and clinical setting (i.e., HF).

Limitations

This was a prespecified substudy of the OMEMI trial restricted to patients with available FA measurements at randomization for the baseline analysis (98%), and at the final study visit for the analysis of FA changes (86%). Accordingly, 55 deceased and 66 nondeceased patients (7% of survivors) were not included in the analysis assessing FA changes, and these patients were older and with more comorbidities. The exclusion of these patients introduces both survival bias and attendance bias, and we cannot extrapolate our findings to these patients at the highest risk. However, as we investigated individual changes of FA with risk, we still believe our findings are of importance. All the investigated events occurred between the time points of EPA and DHA measurements, which limits the temporal interpretation of changes in these FAs with events. Moreover, the predefined primary endpoint, which included all-cause death, was modified to only comprise incident AMI, coronary revascularization, stroke, or HF hospitalization in the analysis investigating FA changes. The number of new-onset AF was low, despite efforts to detect this by screening, and thus there is a risk for type 2 errors and overfitting of the adjusted regression models. There was a moderate correlation between changes in EPA and DHA, which precludes independent assessment in association with outcome. Patients in OMEMI previously using cod liver oil were allowed to continue throughout the trial, as previously explained [12]. Although this may introduce bias to the current analysis, we believe this is of minor importance as we investigated changes within each treatment arm, and adjusted for baseline n-3 PUFA supplementation.

Conclusions

In elderly post-AMI patients, greater increases in EPA during treatment with n-3 PUFA supplements were independently associated with lower risk of incident MACE and a higher risk of new-onset AF. Despite tendencies in the same direction as for EPA, changes in DHA did not associate significantly with either MACE or AF. Our findings suggest that potentially beneficial vascular effects of n-3 PUFA supplementation may be counterbalanced by increased risk of AF. Mechanistic studies are needed to address the discrepancy in cardiovascular effects from n-3 PUFAs on MACE and AF, and to explore whether there are differences in the effects related to type of patient, doses and formulation.

Conflict of interest

Peder L. Myhre has served on advisory boards and received speaker fees from AmGen, AstraZeneca, Boehringer Ingelheim, Novartis, and Novo Nordisk, unrelated to this work. All other authors report no relevant disclosures.

Acknowledgments

We thank the staff and coworkers at all the institutions involved for invaluable help. A special acknowledgment is given to Charlotte Holst Hansen, Sissel Åkra, Jeanette K.Steen, and Vibeke Bratseth at Center for Clinical Heart Research, Solfrid Moen at Stavanger University Hospital, Sophia Onarheim and Dr Trygve Berge at Vestre Viken Hospital Trust, Bærum Hospital, and Dr. Linn M. Nordby and Marit Buvarp at Akershus University Hospital for tremendous and immeasurable help and assistance throughout this project. We thank the laboratory technicians at the Lipid Clinic, Aalborg University Hospital, for the valuable help with the fatty acid measurements. We also thank the End-point Committee, which consisted of cardiologists Tor Ole Klemsdal MD, PhD, Svend Aakhus, Professor, MD, PhD, and Tonje Aksnes MD, PhD. The work was supported by grants from Stein Erik Hagen Foundation for Clinical Heart Research,

Oslo, Norway, Olav Thons Foundation, Oslo, Norway, and Tom Wilhelmsen Foundation, Oslo, Norway. The grants were unrestricted and the foundations did not have any impact on any part of the study.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1 Baseline characteristics by quartiles of baseline DHA concentrations.

Table S2 Baseline characteristics of patients with and without available blood sample at the final study visit.

Table S3 Baseline values and changes in serum lipids and fatty acid concentrations, by quartiles of absolute change in DHA in the n-3 PUFA arm (n = 438).

Table S4 Results from the restricted cubic splines testing linear (2 knots) and non-linear (3-7 knots) for the association between changes in EPA and incident MACE and incident AF.

Table S5 Cox regression models of relative changes in EPA and DHA levels (ratios) from baseline to 24-months in association with the risk of major adverse cardiovascular events (MACE) and new-onset atrial fibrillation (AF) in patients randomized to n-3 PUFAs (n = 438).

Table S6 Serious bleeding defined as Bleeding Academy Research Consortium (BARC) classification ≥2 and quartiles of changes in EPA and DHA levels from baseline to study completion.

Figure S1 Correlation between absolute changes in EPA (Delta EPA) and changes in DHA (Delta DHA) from randomization to the final study visit (24 months) in the n-3 PUFA treatment arm (n = 438).

Figure S2 Kaplan Meier plots of quartiles of absolute changes in EPA in patients randomized to n-3 PUFA (n = 438) and cumulative proportion with major adverse cardiovascular events (MACE).

Figure S3 Kaplan Meier plots of quartiles of absolute changes in EPA in patients randomized to n-3 PUFA (n = 339 without previous AF) and cumulative proportion with new-onset atrial fibrillation (AF). ■

