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# Effects of n-3 Fatty Acid Supplements in Elderly Patients after Myocardial Infarction: A Randomized Controlled Trial

**Running Title:** *Kalstad & Myhre, et al.; Omega-3 in Elderly with Recent AMI*

Are Annesønn Kalstad, MD[1,2*]; Peder Langeland Myhre, MD, PhD[2,3*]; Kristian Laake MD, PhD[1]; Sjur Hansen Tveit, MD[2,3]; Erik Berg Schmidt, MD PhD[4]; Paal Smith P, MD PhD[2,3]; Dennis Winston Trygve Nilsen, MD PhD[6,7]; Arnljot Tveit, MD, PhD[2,5]; Morten Wang Fagerland, PhD[8]; Svein Solheim, MD PhD[1]; Ingebjørg Seljeflot, PhD[1,2**]; Harald Arnesen, MD PhD[1,2**]; on behalf of the OMEMI investigators

[1]Center for Clinical Heart Research, Department of Cardiology, Oslo University Hospital Ullevål, Oslo, Norway; [2]Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Norway; [3]Department of Cardiology, Division of Medicine, Akershus University Hospital, Lørenskog, Norway; [4]Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark; [5]Department of Medical Research, Vestre Viken Hospital Trust, Bærum Hospital, Gjettum, Norway; [6]Department of Cardiology, Stavanger University Hospital, Stavanger, Norway; [7]Department of Clinical Science, Faculty of Medicine, University of Bergen, Bergen, Norway; [8]Oslo Centre for Biostatistics and Epidemiology, Research Support Services, Oslo University Hospital, Norway

[*]Contributed equally to this article as first authors

[**]Contributed equally to this article as last authors

**Address for Correspondence:**
Are A. Kalstad, MD
Center for Clinical Heart Research
Department of Cardiology
Oslo University Hospital
Ullevål, Pb 4956 Nydalen, 0424, Oslo, Norway
Tel: +47 22117521; +47 48221822
Email: arekal@ous-hf.no

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## Abstract

**Background:** High intake of marine n-3 polyunsaturated fatty acids (PUFA) has been associated with reduced risk of cardiovascular events; however, this has not been confirmed in patients with a recent acute myocardial infarction (AMI). Elderly patients are at particularly increased cardiovascular risk after MI, but few trials address this group specifically. Omega-3 fatty acids hold the potential to reduce cardiovascular events with limited adverse effects in this vulnerable group. The hypothesis was that daily addition of 1.8g n-3 PUFA to standard of care secondary prophylaxis in elderly patients who have survived an AMI would reduce the risk of subsequent cardiovascular events during 2 years follow-up.
**Methods:** The OMega-3 fatty acids in Elderly with Myocardial Infarction (OMEMI) trial is an investigator-initiated, multi-center, randomized clinical trial adding 1.8 g n-3 PUFA (930 mg EPA and 660 mg DHA) versus placebo (corn oil) daily to standard of care in 70-82 years old patients with recent (2-8 weeks) AMI. The primary endpoint was a composite of non-fatal AMI, unscheduled revascularization, stroke, all-cause death, heart failure hospitalization after two years. The secondary outcome was new atrial fibrillation. The safety outcome was major bleeding. Serum fatty acids were measured as biomarkers of adherence.
**Results:** In total, 1,027 patients were randomized. Follow-up data were available for 1,014 patients who were included in the intention-to-treat analysis. Mean ± SD age was 75±3.6 years, 294 (29%) were female and mean triglycerides were 111.4±61.9 mg/dL. The primary endpoint occurred in 108 (21.4%) patients on n-3 PUFA vs 102 (20.0%) on placebo (HR 1.08 [95%CI 0.82-1.41], p=0.60). The secondary endpoint occurred in 28 (7.2%) patients on n-3 PUFA vs 15 (4.0%) on placebo (1.84 [0.98 -3.45], p=0.06). Median changes in EPA and DHA were +87% and +16% for n-3 PUFA vs -13% and -8% for placebo. Major bleeding occurred in 54 (10.7%) and 56 (11.0%) in the n-3 PUFA and placebo groups, respectively (p=0.87). Similar results were found in per-protocol analysis (n=893).
**Conclusions:** We could not detect reduction in clinical events in our elderly patients with a recent AMI, treated with 1.8 g n-3 PUFAs daily for 2 years.
**Clinical Trial Registration:** OMEMI Study; URL: https://clinicaltrials.gov Unique Identifier: NCT01841944


**Key Words:** Elderly; Myocardial infarction; Omega-3 fatty acids; Eicosapentaenoic acid; Docosahexaenoic acid; Randomized Clinical Trial; Cardiovascular events; Secondary prevention

**Non-standard Abbreviations and Acronyms**

| | |
|---|---|
| AF | Atrial fibrillation |
| AMI | Acute myocardial infarction |
| BARC | Bleeding Academic Research Consortium |
| BMI | Body mass index |
| CABG | Coronary artery bypass grafting |
| CI | Confidence intervals |
| CVD | Cardiovascular disease |
| DHA | Docosahexaenoic acid |
| EPA | Eicosapentaenoic acid |
| HF | Heart failure |
| HR | Hazard ratio |

LDL Low-density lipoprotein
LVEF Left ventricle ejection fraction
MACE Major adverse cardiovascular event
PUFA Polyunsaturated Fatty acids

**Clinical Perspective**

**What is new?**

- An investigator-initiated, randomized clinical trial adding 1.8g of n-3 PUFA (930mg EPA and 660mg DHA) versus placebo (corn oil) to standard of care daily to a population of elderly patients (70-82 years) with a recent MI followed for 2 years.
- Serum fatty acid concentrations (EPA and DHA) were measured at baseline and after 2 years follow-up as measures of objective compliance, limiting a problem that has been debated in previous trials.

**What are the clinical implications?**

- In the present population of elderly patients with relatively high levels of EPA and DHA and relatively low levels of triglycerides, supplementation with 1.8 g n-3 PUFA did neither influence on the clinical end-points non-fatal AMI, unscheduled revascularization, stroke, hospitalization for heart failure or all-cause mortality, nor on major bleeding, when compared to placebo.
- More patients were registered with first time episodes of atrial fibrillation in the n-3 PUFA group compared to the placebo group during the study period, thus raises concerns with regard to moderate doses of n-3 PUFA supplements and risk of new-onset AF.

## Introduction

Despite significant improvements in secondary prophylaxis, the risk of subsequent events remains high in elderly after myocardial infarction. Even when optimally treated with lipid-lowering and antiplatelet therapy, the residual risk, particularly in elderly, is considerable[1]. The risk of adverse effects from modern secondary prevention therapy is also elevated in elderly[2]. Unfortunately, this vulnerable group is vastly underrepresented in cardiovascular clinical trials and therapeutic recommendations are typically extrapolated from younger subjects[3, 4].

Marine derived, very long chain n-3 polyunsaturated fatty acids (n-3 PUFAs) have been studied for decades in patients with cardiovascular disease (CVD) states, yielding conflicting results with respect to the effects on cardiovascular events. Earlier randomized clinical trials have demonstrated significant reduction in cardiovascular events and mortality both with increased fatty fish intake and with n-3 PUFA supplements in post-MI patients [5, 6], while more recent trials have shown no such benefit in middle-aged post-MI populations with low-dose n-3 PUFA supplement [7-9]. Furthermore, meta-analyses have shown inconsistent benefits of marine n-3 PUFA in secondary prevention [10-13]. More recently, the Reduction of Cardiovascular Events with Icosapent Ethyl – Intervention Trial (REDUCE-IT) found a highly significant 25% reduction in ischemic events in patients treated with 4g icosapent ethyl daily [14]. It is worth noting that icosapent ethyl used in this trial is notably different from formulations typically used in other n-3 PUFA trials, almost exclusively containing eicosapentaenoic acid (EPA) as opposed to the typical mixed EPA/docosohexaenoic acid (DHA) formulations used in other trials, and in a considerably higher dose. The American Heart Association scientific statements currently recommend n-3 PUFA supplements for secondary prevention of coronary heart disease[15] and in management of hypertriglyceridemia[16]. Marine n-3 PUFAs are essential and primarily obtained

through diet, and reduced nutrient consumption with age and age-related decline in absorption and metabolic function contributes to an increased risk of dietary deficiencies in the elderly[17].

The hypothesis of the OMega-3 fatty acids in Elderly patients with Myocardial Infarction (OMEMI) trial [18] was that daily addition of 1.8 g n-3 PUFA to standard of care secondary prevention in elderly patients who have survived an AMI would reduce the risk of subsequent cardiovascular events during 2 years follow-up.

## Methods

### Trial design

The OMEMI trial was designed as a multi-center, placebo-controlled, double-blind clinical trial conducted by independent investigators at Center for Clinical Heart Research, Department of Cardiology, Oslo University Hospital, Ullevål, Oslo, Norway. The study design and methods have previously been published [18]. The protocol was approved by the Regional Committee for Medical and Health Research Ethics (#2012/1422), and all participants provided written informed consent. The trial was conducted in compliance with the declaration of Helsinki and with the rules outlined in the guidelines for Good Clinical Practice. The trial was registered at ClinicalTrials.gov (NCT01841944). This registration was late as we originally submitted an application for registration to the European Union Drug Regulating Authorities Clinical Trial Database before November 1. An application for registration was subsequently submitted to the ClinicalTrials.gov registry on April 16, 2013 and formally posted on April 29, 2013. Between November 1, 2012 and April 29, 2013, 47 patients were enrolled in the trial.

Capsules containing n-3 PUFA and matching placebo were provided by Orkla Health, Oslo, Norway, who had no role in data collection, data analysis, interpretation of results or decision to submit the manuscript for publication.

The manuscript was prepared by the authors, who vouch for the completeness and accuracy of the data and analysis, and for the fidelity of the trial to the study protocol and statistical data analysis plan. Requests for data sharing will be handled according to the regulation by Data Protection Officer at Oslo University Hospital.

**Patients**

Hospitalized patients between 70 and 82 years old who were able to provide verbal and written informed consent were screened during admission for the index AMI of any type at four centers in Norway (Oslo University Hospital, Ullevål, Oslo; Akershus University Hospital, Lørenskog; Vestre Viken, Bærum Hospital, Gjettum; and Stavanger University Hospital, Stavanger). Exclusion criteria were documented intolerance for n-3 fatty acids, participation in other clinical trials, additional disease state deemed to be incompatible with adherence to the study protocol and life expectancy <2 years. Examples of the latter could be malignancy with ongoing or deferred treatment, suspected or confirmed cognitive impairment or obvious frailty.

**Trial procedures**

Eligible patients willing to participate were scheduled for baseline visit 2-3 weeks after the index AMI. This was later changed to 2-8 weeks to enhance inclusion rate. At the baseline visit, patients were randomized in a 1:1 ratio to receive either 1.8 g n-3 PUFA (930 mg eicosapentaenoic acid (EPA) + 660 mg docosahexaenoic acid (DHA) (Pikasol®), Orkla Health, Oslo, Norway) or matching placebo (corn oil; 56% linoleic acid, 32% oleic acid, 10% palmitic acid). Total dose divided by 3 capsules to be taken once daily. Permuted block randomization

was used, stratified for participating centers. Consecutively numbered sealed non-translucent envelopes were opened by the study physician at randomization to reveal the treatment code. The study physician was blinded for the treatment code, and blinding was maintained until general unblinding after study completion.

Patients were seen by a study physician at baseline visit and after 3, 12 and 24 months. Patients who could not attend follow-up visits, were offered interview by telephone and study capsules were sent by mail. Each study visit included clinical examination, ECG recordings, and collection of blood samples in the fasting state between 8.00 and 11.30 am. Adherence to study drug was assessed by interview at each study visit. Patient reported adherence was defined as no more than four consecutive weeks without taking the study drug. As an assessment of adherence at group level, measurement of serum fatty acid profiles at randomization and at the final visit (24 months) were performed, and changes calculated. Treatment other than the intervention was standard-of-care, according to current guidelines and by the discretion of the treating physician. Patients were instructed not to use other n-3 PUFA supplements in the study period, however one child spoon of cod liver oil was permitted, as this habit is fairly common among elderly Norwegians, and denying this could lead to selection bias and lower inclusion rate.

Routine blood analyses were performed by regular hospital laboratory services. Serum was prepared and frozen at -80°C for analyses of fatty acid composition of serum phospholipids, performed at the Lipid Research Laboratory, Aalborg University Hospital, Denmark, by gas chromatography and expressed as percent weight of total fatty acid[19, 20]. Detailed method description is given in supplementary material.

**Outcomes**

The pre-specified primary efficacy outcome was the first major adverse cardiovascular event (MACE), consisting of a composite of non-fatal MI, unscheduled revascularization, stroke or all-cause death. While recruitment was still ongoing, hospitalization for heart failure (HF) was added to the definition of MACE by protocol amendment. This modification was made due to increased focus on HF in the elderly, studies showing reduction in adverse left ventricular remodeling with n-3 PUFA[21-23], and potentially to increase statistical power of the trial. The primary safety outcome was serious bleeding, defined according to Bleeding Academic Research Consortium (BARC) criteria [24]. Bleeding ≥ BARC 2 was registered as serious adverse events. Outcomes were registered by accessing electronic medical records and by interviewing the patients at follow-up visits. Norwegian national summary care records, including contacts with hospitals and the specialist health service, were available to the investigators for identifying endpoints. Total mortality at the end of the trial was retrieved from Statistics Norway.

The pre-specified secondary outcome was new-onset atrial fibrillation (AF), defined as a standard 12-lead ECG recording or a single-lead ECG tracing of > 30 s showing heart rhythm with no discernible repeating P waves and irregular RR intervals[25]. In addition to access to clinical records and ECGs taken at study visits, patients were screened with ambulant hand-held single lead rhythm monitoring (Zenicor, Zenicor Medical Systems AB, Stockholm, Sweden) for 2x30 seconds per day for 14 days, following the study visit at 12 months. Data for paroxysmal, persistent and chronic AF were combined for all analyses.

All outcomes were adjudicated centrally by an independent endpoint committee of experienced clinicians, blinded to the treatment allocation **(Suppl. Material, p5)**.

**Statistical analysis**

Initial power calculations were performed for a composite endpoint of non-fatal MI, unscheduled revascularizations, stroke and all-cause death, whatever came first. Based on previous studies[5, 26-28], we postulated a 30 % reduction in MACE from 20% to 14% during two years follow-up. With an α of 0.05 and a power of 80 %, 611 patients would be required in each study arm with an estimated dropout rate of 10%. With the protocol amendment including hospitalization for HF in the primary outcome, we anticipated an increase in the two-year event rate from 20% to 35%, but reduced the estimated effect of the intervention from 30% to 25%. Accordingly, the estimated number of participants needed was 500 in each study arm, and including dropouts, the total number needed was calculated to be 1100 patients.

The data analysis plan according to Gamble et al [29] was finalized by the steering committee being unaware of the trial results according to group assignment (Suppl. Material, Statistical Analysis Plan). We used Cox proportional hazard regression models with time to the first occurrence of a primary outcome event as the outcome and group assignment (n-3 PUFA vs placebo) and participating center as covariates. Based on the models, we report hazard ratios (HRs) with 95% confidence intervals (CIs) using the Breslow method for ties, and P-values for the null hypothesis of no treatment effect (HR=1.0). The proportional hazard assumption was assessed with log-log plots of the estimated survival curves against time. We used the Kaplan-Meier estimator to estimate the survival curves of patients randomized to n-3 PUFA or placebo. For analyses of each component of the primary outcome, we did not count non-fatal events that occurred after another primary outcome event. Additional analysis was performed for total mortality irrespective of whether a non-fatal primary outcome event had occurred. Patients

without events were censored after two years of follow-up or at the date of last participation to a visit for patients lost to follow-up.

Potential treatment effect modification by key clinical subgroups (age </≥ 75 years, sex, obesity, diabetes mellitus, hypertension, previous MI, previous HF, hyperlipidemia, creatinine </≥ 1.4 mg/dL, LVEF </≥50%, triglycerides </≥ 124.0 mg/dL and use n-3 PUFA supplementation at baseline) was assessed by including an interaction term in the Cox proportional hazard regression model.

The same Cox regression model was also applied for the secondary endpoint, with time to first new-onset AF as the outcome. This was performed only for patients free from all previous known AF at the time of inclusion. Patients without a secondary event, and with only a primary outcome as available follow-up data, were censored at the time of the primary event for analysis of the secondary outcome. Subgroup analysis was not performed for AF.

Analyses were performed both according to an intention-to-treat and per-protocol principle for the primary outcome. The intention-to-treat analysis included all randomized patients with follow-up data, either in the form of a clinical outcome or attending study visits. The per-protocol analysis included all patients with self-reported adherence as defined in the protocol. Occurrence of major bleeding was compared between n-3 PUFA and placebo with Pearson chi-squared test. Changes in serum phospholipids of EPA and DHA and of serum triglycerides were expressed as the relative change from baseline to 24 months, and compared between the treatment groups by the Mann-Whitney U test. A two-tailed P value of less than 0.05 was considered statistically significant.

## Results

### Patients

A total of 4,027 patients were screened across the four study sites, and 1,027 patients underwent randomization. The first patient underwent randomization November 28, 2012 and the last on July 5, 2018. Of these, follow-up data were available for 1,014 patients (98.7%) to be included in the intention-to-treat analysis (**Figure 1**). In this analysis, 505 patients (49.8%) were randomized to n-3 PUFA and 509 (50.2%) to placebo. Data according to the randomized groups are given in **Table 1.** Clinical characteristics were well balanced between the groups. Of these patients, 29.0 % were female, 99.8 % were of Caucasian ethnicity, median (Q1, Q3) age was 74 (72, 78) years, and 467 (46.1%) had known previous CVD at the time of the index AMI. At enrollment 415 (41.3%) reported use of some form of n-3 PUFA supplement.

Data for the per-protocol set is given in **Supplemental Table I**

### Adherence

Self-reported adherence to the study medication was present in 893 (88.1%) patients, forming the set of the per-protocol analysis.

In the intention-to-treat analysis, levels of EPA and DHA at baseline and at the 24-month follow-up were available in 881 (86.9%) patients. Patients in the n-3 PUFA group experienced a median (Q1-Q3) of +87% (+32%, +165%) change in the concentration of EPA and +16% (+2%, +34%) change in DHA, while in the placebo group changes were -13% (-34%, +20%) and -8% (-18%, +6%) in EPA and DHA, respectively, expressed as relative changes from baseline **(Figure 2)**. Changes in the per-protocol set showed more pronounced differences **(Supplemental Table II).**

Cod liver oil (up to one child spoon per day) was used by 202 (21.4%) at 3 months, 187 (21.2%) at 12 months and 174 (19.4%) at 24 months, well balanced between the study groups.

**Outcomes**

A primary outcome event according to intention-to-treat analysis occurred in 108 (21.0%) patients in the n-3 PUFA group and in 102 (19.8%) in the placebo group (hazard ratio [HR] 1.07 [95% confidence interval [CI] 0.82-1.40], p=0.62) (**Table 2)**, with event rates 12.4 (95% CI 10.3 – 15.0) and 11.5 (95% CI 9.5 – 14.0) per 100 patient years, respectively (**Figure 3A)**. Consistent results were present for each component of the primary end-point (**Table 2**). There were also no differences between the n-3 PUFA and placebo groups in all-cause mortality: 28 (5.5%) vs 28 (5.5%); HR 1.01 [95% CI 0.60 – 1.71], p=0.97 **(Table 2),** with event rates 2.92 (95%CI 2.01-4.22) vs 2.92 (95%CI 2.02-4.23) per 100 patient years, respectively (**Figure 3B)**.

The treatment effect on the primary outcome did not differ by age, sex, body mass index, diabetes, previous hypertension, previous MI, previous HF, previous hyperlipidemia, levels of triglycerides, or use of n-3 PUFA supplement at baseline (**Figure 4**). Triglycerides changes by median (Q1, Q3) were -8.1% (-27.5%, +15.3%) in the n-3 PUFA group vs +5.1% (-17.0%, +33.3%) in the placebo group; between-group median absolute difference 13.2% (p<0.001). LDL cholesterol changes were 0 %( - 15.8 %, 18.8 %) vs 0.7 % (-13.3 %, 19.3 %), respectively (p=0.57).

A total of 255 (25.1 %) patients had experienced a form of AF before the time of randomization, and 759 patients were included in the intention-to-treat analysis for the secondary endpoint. A secondary endpoint occurred in 28 (7.2 %) in the n-3 PUFA group and in 15 (4.0 %) in the placebo group [HR] 1.84 [95% CI 0.98-3.44], p=0.056) (**Table 2)**, with event rates 4.0

(95% CI 2.7 – 5.7) and 2.2 (95% CI 1.3 – 3.6) per 100 patient years, respectively **(Figure 5)**. Subgroup analysis was not performed for AF.

Analyses performed in per-protocol analyses yielded similar results **(Supplemental Table III**).

**Adverse events**

Major bleeding occurred in 54 (10.7%) in the n-3 PUFA group and in 56 (11.0%) in the placebo group (p=0.87). No patients withdrew from the trial because of bleeding problems.

Reasons for discontinuing treatment were well balanced between the groups, with 14 due to GI-symptoms, 25 due to difficulty swallowing capsules and 36 due to other disease burden deemed not related to the study intervention. Complete data for all randomized patients are shown in **Supplemental Table IV**.



**Discussion**

Elderly patients with a recent AMI who received 1.8 g of n-3 PUFA did not have a lower incidence of MACE or death than those randomized to placebo after two years of follow-up. Analyses of the different components of the primary endpoint as well as of key clinical subgroups equally did not differ between patients given n-3 PUFA or placebo, either in intention-to-treat or in per protocol analysis. There was also no effect on all-cause mortality. The occurrence of primary events was lower than estimated, but nevertheless, higher than that observed in the REDUCE-IT trial [14]. The incidence of new-onset AF was higher in the n-3 PUFA arm; however, the difference did not reach statistical significance. The changes in serum phospholipid levels of EPA and DHA support good adherence among patients, limiting a problem that has been debated in previous trials.

Early randomized clinical trials in the 1990s suggested cardiovascular benefits of n-3 PUFA after an AMI. The Diet and Reinfarction Trial (DART) randomized patients to dietary advice and demonstrated a 29% reduction in 2-year mortality in patients advised to eat fatty fish twice per week. [6] The GISSI Prevenzione trial demonstrated a 21% reduction in all-cause mortality and 45% reduction in sudden cardiac death in patients given 850 mg EPA/DHA compared to placebo for 3.5 years [5]. These promising results were however, not confirmed by three large RCTs published in 2010 using mixed EPA/DHA from 400 mg to 840 mg per day, all showing neutral results [7-9] The dosage used in our trial was approximately twice that of these studies, including also the ORIGIN trial[30]. These contrasting results may be due to improved secondary prevention therapy after AMI, with the introduction of statins and double antiplatelet therapy. In addition to difference in n-3 PUFA dosage, differences in baseline risk have also been suggested to play an important role. The effect of 1 g EPA/DHA in low-risk subjects from the general population was tested in the Vitamin-D and Omega-3 Trial (VITAL), with neutral results [31]. Similarly, A Study of Cardiovascular Events in Diabetes (ASCEND) showed no risk reduction by 1 g EPA/DHA in patients with diabetes free of cardiovascular disease[32]. Patients in the OMEMI trial were at considerably higher risk than subjects in those studies, being older and with a recent AMI. The n-3 PUFA dosage in OMEMI was also higher than in the afore-mentioned trials. Accordingly, our findings extend the lack of effect by mixed EPA/DHA to reduce cardiovascular risk.

The remarkable results from the REDUCE-IT trial[14], which demonstrated a 25% reduction in cardiovascular events with 4 g per day of icosapent ethyl in statin-treated patients with hypertriglyceridemia and established CVD or diabetes, confirming previous results of the JELIS trial[33], have shed new light to the field of treatment with EPA. Icosapent ethyl is an ethyl-

EPA, which is metabolized to EPA after ingestion, and allows substantially higher content of EPA compared to over-the-counter products. The substantial risk reduction in REDUCE-IT is unlikely to be explained by the moderate 22% reduction in triglyceride levels, and mechanistic studies suggest direct effects of icosapent ethyl on coronary plaque regression[34]. Serum levels of EPA increased by 386% compared to placebo after the first year in REDUCE-IT. This is considerably higher than the 100% between-group difference in increase we observed in the OMEMI trial, and seems to reflect the difference in EPA-dosage (4000 mg versus 930 mg). Of note, the decrease in EPA and DHA concentration in the placebo arm may relate to the reduced number of patients who reported additional use n-3 PUFA supplement (415 patients at baseline and 174 patients at 24 months). It is also worth noting that the baseline median levels in our material (2.5 % EPA and 5.6 % DHA) are notably higher than corresponding values from population studies in the USA (0.5 % EPA and 2.9 % DHA) [35], suggesting higher background consumption of n-3 PUFA in our Norwegian study population. Equally notable is the modest reduction in triglycerides in the n-3 PUFA group compared to the placebo group (median 13.2 %) in the OMEMI trial, which is less than previous n-3 PUFA studies in patients who were younger and with higher baseline triglyceride levels [36]. It should nevertheless, be noted that the beneficial effects seen in the REDUCE-IT trial was probably not attributed to reduction in triglycerides[14]. As also observed in other studies, LDL cholesterol levels did not change.

The safety of n-3 PUFA was considered well documented at the initiation of the trial. However, due to their potential of in vitro inhibition of platelets, bleeding is a concern. A tendency to increased bleeding risk with icosapent ethyl was present in REDUCE-IT, supporting this hypothesis. As most patients after AMI are treated with dual antiplatelet therapy, and because of the increased bleeding risk among elderly, bleeding was a highly relevant concern in

the OMEMI trial. Still, we found no differences in bleeding events between the groups. This applied both to major and minor bleeding. Reasons reported for stopping the study drug was well balanced between the treatment groups, with no serious adverse events.

Although our secondary endpoint of AF was originally included because of a potentially beneficial antiarrhythmic effect of n-3 PUFA[37], the increased occurrence of AF in the REDUCE-IT trial has raised safety concerns about high dose n-3 PUFAs[14]. Although the increased risk of new onset AF in the n-3 PUFA arm in our study was not statistically significant, we believe that the results are of interest. Our elderly patient population with multiple cardiovascular risk factors is at high risk of AF. The relatively high prevalence at inclusion (25.1 %) is not surprising, compared to a high prevalence in the same age group in the general population in Norway[38]. The REDUCE-IT trial reported new-onset or worsening of AF in 5.3 % in those receiving Icosapent Ethyl and 3.9 % in the placebo group with a median follow-up of 4.9 years. In the OMEMI trial, new-onset AF was found in 7.2 % in the n-3 PUFA group and in 4.0 % in the placebo group with a follow-up of 2 years, illustrating a higher risk population. Taken together, the findings in these two studies raise concerns regarding high doses of n-3 PUFA supplements and risk of new-onset AF.

The OMEMI-study stands out among other n-3 PUFA studies by being performed in what is by all standards a very high-risk group. A limitation to the study is the inclusion rate of 26 % of screened candidates, which is relatively low compared to other n-3 PUFA trials not targeting elderly patients[30-33]. Of the excluded patients, 27 % were not eligible due to comorbidities that limited their ability to attend study visits or with life expectancy <2 years. This is markedly lower than other n-3 PUFA trials, however few of these are restricted to the geriatric population. We also note that the PROSPER trial had an identical age range as our trial,

and an inclusion rate of 24 %[39]. Although specific frailty assessment or broad comorbidity review was not part of screening for the trial, it is plausible that these conditions are a contributing cause to the low inclusion rate.

This trial also has additional important limitations. Notably, assumptions for power calculation proved too optimistic, largely due to a lower event rate than expected. Also, the addition of the endpoint component of heart failure hospitalization did not add the number of events that might be expected in an elderly population. With the benefit of hindsight, and the results of the REDUCE-IT trial, where survival curves seem to separate at 14—18 months[14], changing the protocol to a longer observation time or an event-driven trial would have added to the power of the study. For a number of reasons this was abandoned, notably because earlier trials showed benefit at a much earlier stage[5, 33], the challenge with continued adherence in these elderly patients over longer time, and also because supply of study drugs could not be assured. . As already discussed, the choice of dosage is still a matter of debate. Nevertheless, the dosage used in OMEMI was about twice that used in comparable earlier trials[5, 7, 23, 30], although considerably lower than the dosage used in REDUCE-IT[14], and also in the STRENGTH trial [36]. The latter study was terminated for futility, and so far, data remain unpublished and thus difficult to speculate on.

Patients in the OMEMI trial using cod-liver oil were allowed to continue with one child spoon daily, as explained. This corresponds to approximately 600 mg EPA + DHA. Although this adds to the total dose of n-3 PUFAs, the use was equally distributed between the two groups, and as follows from Figure 5, clinical outcome was not significantly affected.

Although the OMEMI trial was moderately sized compared to other recent RCTs in the field, and eventually proved to be underpowered, we believe that our study is an important

contribution to the field given the dosage of EPA/DHA used and the unique patient population. Even if the duration of follow-up was somewhat shorter than in most studies, a potential effect of intervention would have been expected in elderly, very high-risk patients after 2 years.

Our results, seen in concert with other neutral trials, should provide important answers to the question of whether mixed n-3 PUFA dietary supplements are effective as cardiovascular protection. Still, we cannot rule out Type 2 errors as the trial ended up not being sufficiently powered to answer the original research question. However, based on the clarity of the results, with no signs of effect in none of the components of the primary outcomes or in key subgroups, we believe these results provide a clinically relevant answer.

In conclusion, we could not detect reduced incidence of cardiovascular events or all-cause death in our elderly patients with a recent AMI, treated with 1.8 g n-3 PUFAs daily for 2 years.



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**Disclosures**

All other authors declare no conflict related to this paper.

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**Supplementary Materials**

Supplementary Methods - Measurement of fatty acid composition of serum phospholipids

Steering committee

Endpoint committee

Supplementary tables I-IV

Statistical Analysis Plan

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**Table 1.** Baseline characteristics of patients, according to randomized assignment to n-3 PUFA or placebo included in intention to treat analysis. Continuous variables are given as mean±SD or median (Q1, Q3). Proportions are given as n (%).

| **Characteristics** | **n-3PUFA (n=505)** | **Placebo (n=509)** |
|---|---|---|
| Age (years) | 74.0 [72.0 , 78.0 ] | 74.0 [72.0 , 78.0 ] |
| Female sex | 148 (29.3) | 146 (28.7) |
| Caucasians | 503 (99.6 ) | 509 (100 ) |
| Body mass index (kg/m$^2$) | 26.8 ± 7.5 | 27.2 ± 11.9 |
| Systolic BP (mmHg) | 137.7 ± 20.1 | 136.5 ± 19.4 |
| **General medical history** | | |
| Hypertension | 321 (63.6) | 290 (57.0) |
| Hyperlipidemia | 234 (46.3) | 235 (46.2) |
| Current smokers | 63 (12.5) | 58 (11.4) |
| Chronic kidney disease (creat > 1.7 mg/dL) | 19 (3.8 ) | 26 (5.1 ) |
| Any diabetes | 114 (22.6) | 96 (18.9) |
| History of major bleeding | 12 (2.4 ) | 10 (2.0 ) |
| **Previous cardiovascular disease** | | |
| Any cardiovascular disease | 227 (45.0) | 240 (47.2) |
| Myocardial infarction | 125 (24.8) | 136 (26.7) |
| Previous percutaneous coronary intervention | 119 (23.6) | 119 (23.4) |
| Previous coronary artery bypass graft | 53 (10.4) | 59 (11.7) |
| Previous heart failure | 34 (6.7 ) | 31 (6.1 ) |
| Ischaemic stroke | 44 (8.7 ) | 54 (10.6) |
| Previous atrial fibrilliation | 71 (14.0) | 83 (16.3) |
| **Index myocardial infarction details** | | |
| ST-elevation myocardial infarction | 174 (34.5) | 166 (32.6) |
| Type 1 myocardial infarction | 456 (90.3) | 453 (89.0) |
| Acute coronary angiography | 490 (97.0) | 486 (95.5) |
| Percutaneous coronary intervention | 358 (70.9) | 372 (73.1) |
| Coronary artery bypass graft | 34 (6.7 ) | 28 (5.5 ) |
| Heart failure in acute phase | 59 (11.7) | 53 (10.4) |
| Atrial fibrillation, acute phase to inclusion | 94 (18.6) | 117 (23.0) |
| **Serum lipids** | | |
| Low-density lipoprotein cholesterol (mg/dL) | 75.1 ± 25.9 | 77.0 ± 26.1 |
| High-density lipoprotein cholesterol (mg/dL) | 49.3 ± 15.2 | 49.8 ± 15.2 |
| Triglycerides (mg/dL) | 115.4 ± 72.1 | 107.4 ± 49.5 |
| Serum eicosapentaenoic acid (%wt) | 2.8 ± 1.4 | 2.9 ± 1.5 |
| Serum docosahexaenoic acid (%wt) | 5.7 ± 1.4 | 5.7 ± 1.3 |
| **Medication at baseline** | | |
| Aspirin | 474 (93.9) | 480 (94.3) |
| Other antiplatelet therapy | 452 (88.7) | 452 (89.6) |
| Dual antiplatelet therapy | 433 (85.7) | 438 (86.1) |
| Anticoagulation | 83 (16.4) | 103 (20.2) |
| Statin | 488 (96.6) | 490 (96.3) |
| Antihypertensives (excluding beta-blockers) | 360 (71.3) | 367 (72.1) |
| Beta-blockers | 413 (81.8) | 428 (84.1) |
| n-3 fatty acids supplements /cod liver oil | 203 (40.7) | 212 (41.8) |

**Table 2.** Components of the primary and secondary outcomes and bleeding, according to randomized assignment to n-3 PUFA or placebo

| | **n-3PUFA, (n=505)** | **Placebo (n=509)** | | |
|---|---|---|---|---|
| **Primary endpoint** | **N (%)** | **N (%)** | **HR [95% CI]** | **P** |
| Composite primary outcome | 108 (21.4) | 102 (20.0) | 1.07 [0.82 – 1.40] | 0.62 |
| Death as first event | 20 (4.0) | 20 (4.0) | 1.01 [0.54 – 1.88] | 0.98 |
| Non-fatal acute myocardial infarction | 39 (7.7) | 35 (6.9) | 1.14 [0.72 – 1.80] | 0.57 |
| Stroke | 17 (3.4) | 12 (2.4) | 1.37 [0.65 – 2.88] | 0.41 |
| Unscheduled revascularization | 14 (2.8) | 21 (4.1) | 0.66 [0.34 – 1.30] | 0.23 |
| Hospitalization for heart failure | 20 (4.0) | 17 (3.3) | 1.19 [0.62 – 2.26] | 0.61 |
| All-cause mortality | 28 (5.54 ) | 28 (5.50) | 1.01 [0.60 – 1.71] | 0.97 |
| **Secondary endpoint** | | | | |
| New AF* | 28 (7.2) | 15 (4.0) | 1.84 [0.98 – 3.45] | 0.06 |
| **Bleeding** | | | | |
| Major bleeding (BARC≥2) | 54 (10.7) | 56 (11.0) | N/A | 0.87 |
| All bleeding | 183 (36.2) | 178 (35.0) | N/A | 0.67 |

*Analysis performed in patients free of previous AF (n-3 PUFA n=372, placebo n=387)

## Figure Legends

**Figure 1. Screening, enrollment, randomization, treatment allocation and follow-up.**

Flow chart of screening, randomization, treatment, and follow-up of the participants

**Figure 2. Adherence assessment by serum fatty acid measurements.**

Changes in serum phospholipid concentration of EPA and DHA from baseline to 24 months (n=881), according to randomization to n-3 PUFA or Placebo.

**A.** Values in %wt of serum fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), measured at 0 and 24 months. **B**. Changes in serum phospholipid concentration of EPA and DHA, assessed as percent change from baseline to 24 months. Samples were available for 881 patients.



**Figure 3. Primary outcomes.**

Kaplan–Meier estimation of the first events (A) and of all-cause death (B) during follow-up

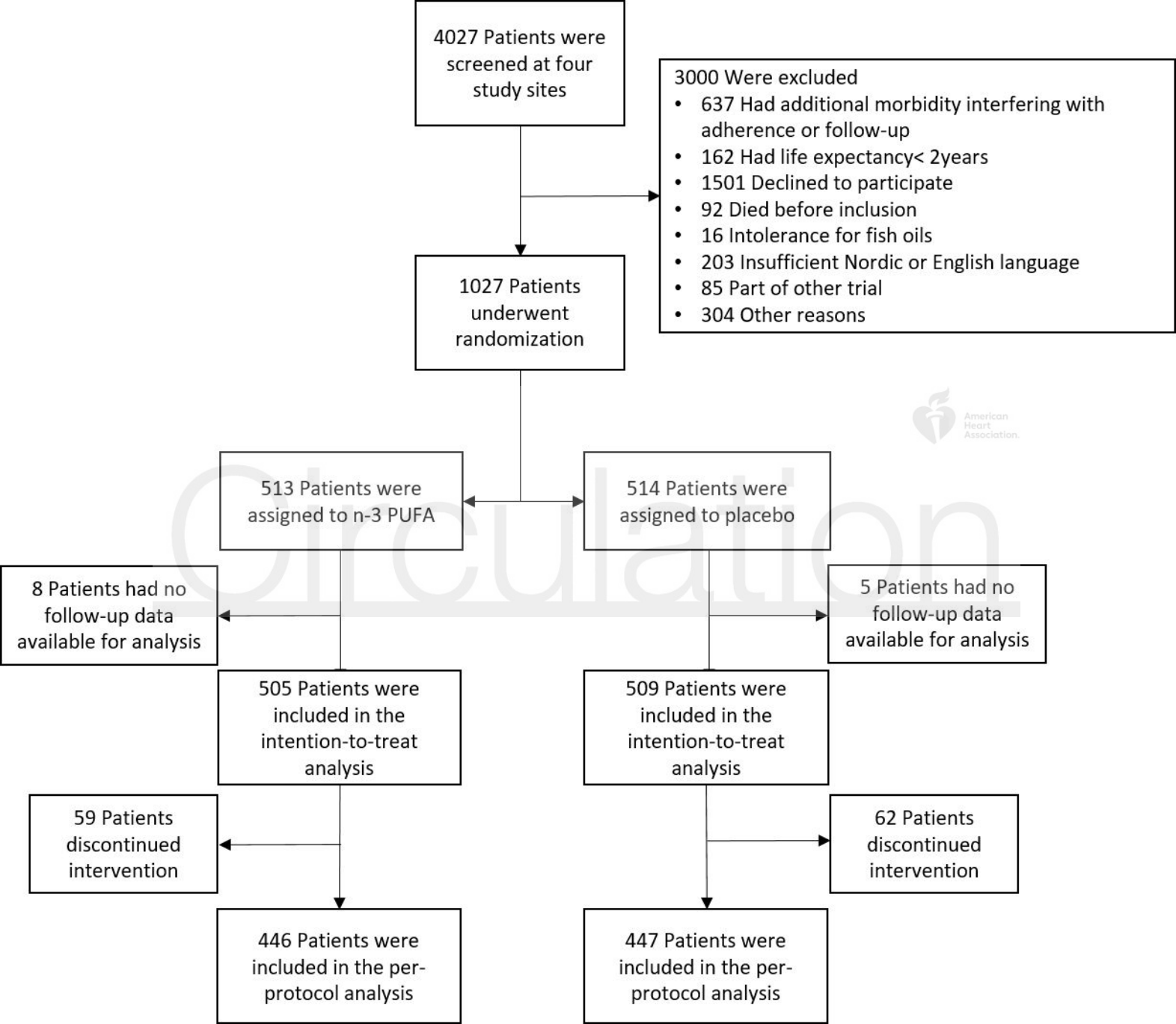
Cumulative incidence rates of the primary outcome and all-cause death, according to months of follow-up in the randomized groups.

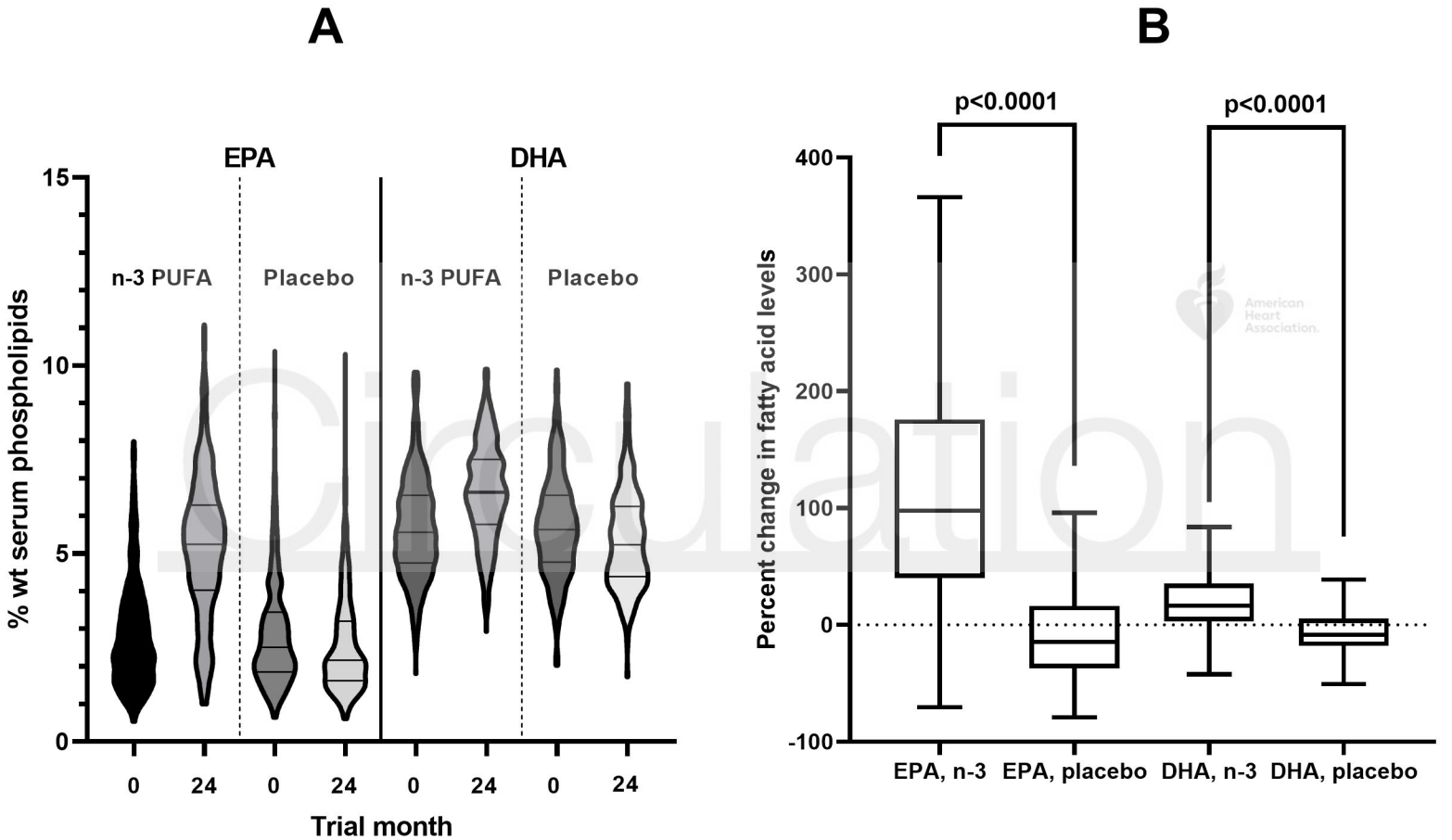
**Figure 4. Key clinical subgroups.**

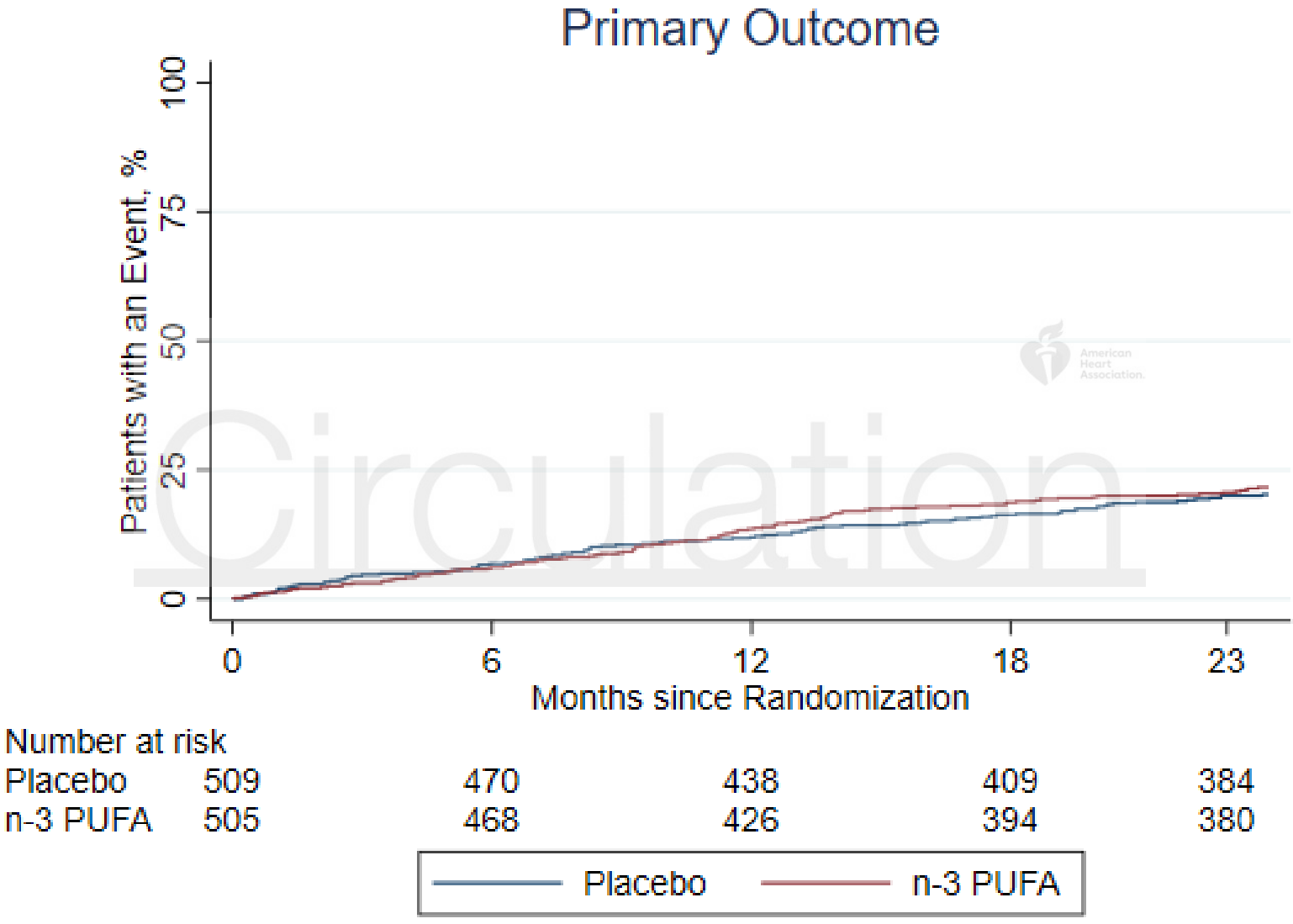
Treatment effect on the primary composite endpoint overall and by key clinical subgroups. The hazard ratios for the primary outcome in selected subgroups in the n-3 PUFA and the placebo groups

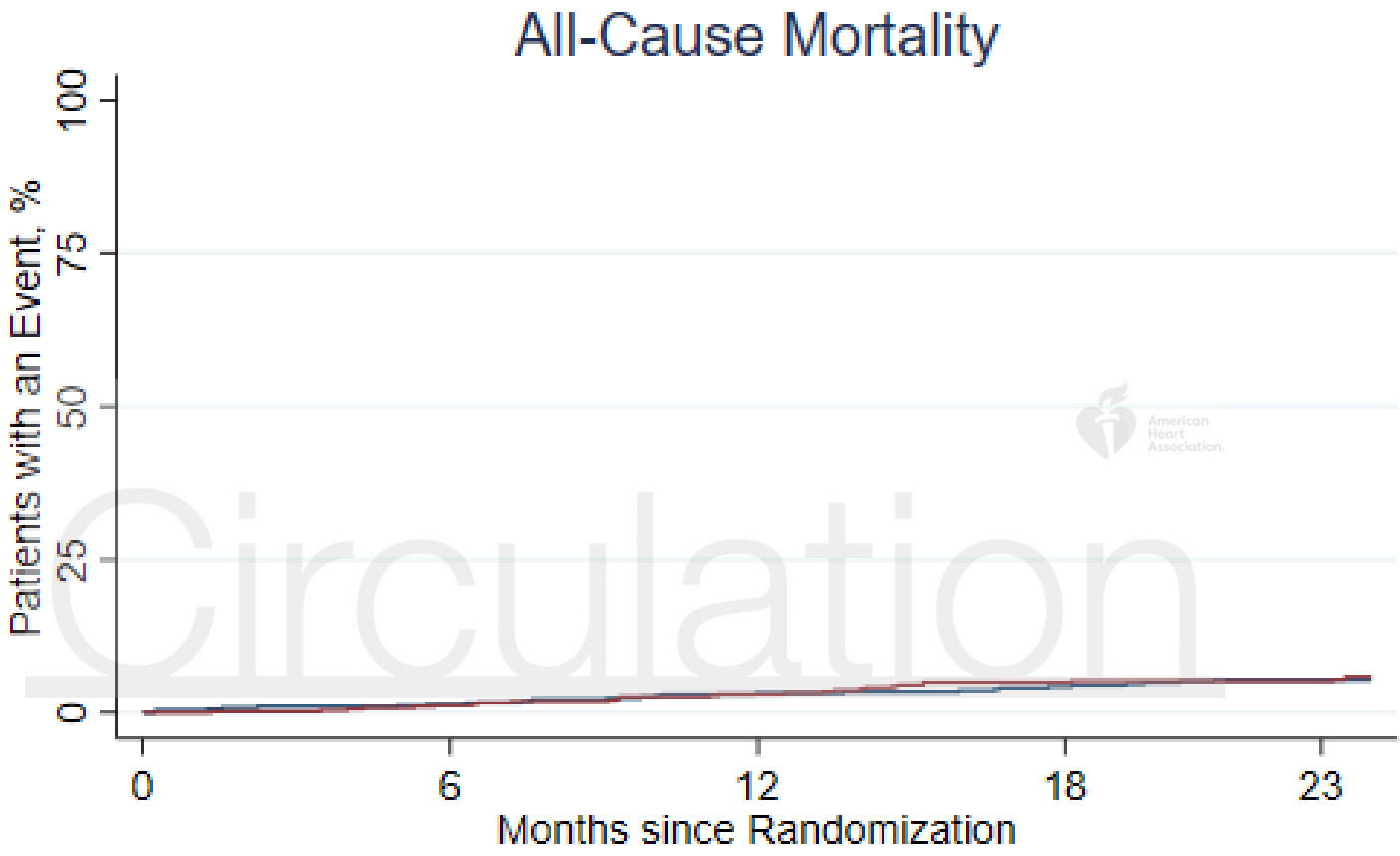
**Figure 5. Secondary outcome, new onset atrial fibrillation.**

Cumulative incidence rates of the secondary outcome, according to months of follow-up in the randomized groups


4027 Patients were screened at four study sites
3000 Were excluded
• 637 Had additional morbidity interfering with adherence or follow-up
• 162 Had life expectancy< 2years
• 1501 Declined to participate
• 92 Died before inclusion
• 16 Intolerance for fish oils
• 203 Insufficient Nordic or English language
• 85 Part of other trial
• 304 Other reasons
1027 Patients underwent randomization
513 Patients were assigned to n-3 PUFA
514 Patients were assigned to placebo
8 Patients had no follow-up data available for analysis
5 Patients had no follow-up data available for analysis
505 Patients were included in the intention-to-treat analysis
509 Patients were included in the intention-to-treat analysis
59 Patients discontinued intervention
62 Patients discontinued intervention
446 Patients were included in the per-protocol analysis
447 Patients were included in the per-protocol analysis


A
EPA
DHA
n-3 PUFA
Placebo
n-3 PUFA
Placebo
% wt serum phospholipids
15
10
5
0
0
24
0
24
0
24
0
24
Trial month
B
p<0.0001
p<0.0001
Percent change in fatty acid levels
400
300
200
100
0
-100
EPA, n-3
EPA, placebo
DHA, n-3
DHA, placebo


Primary Outcome
Patients with an Event, %
0
25
50
75
100
0
6
12
18
23
Months since Randomization
Number at risk
Placebo 509 470 438 409 384
n-3 PUFA 505 468 426 394 380
Placebo
n-3 PUFA

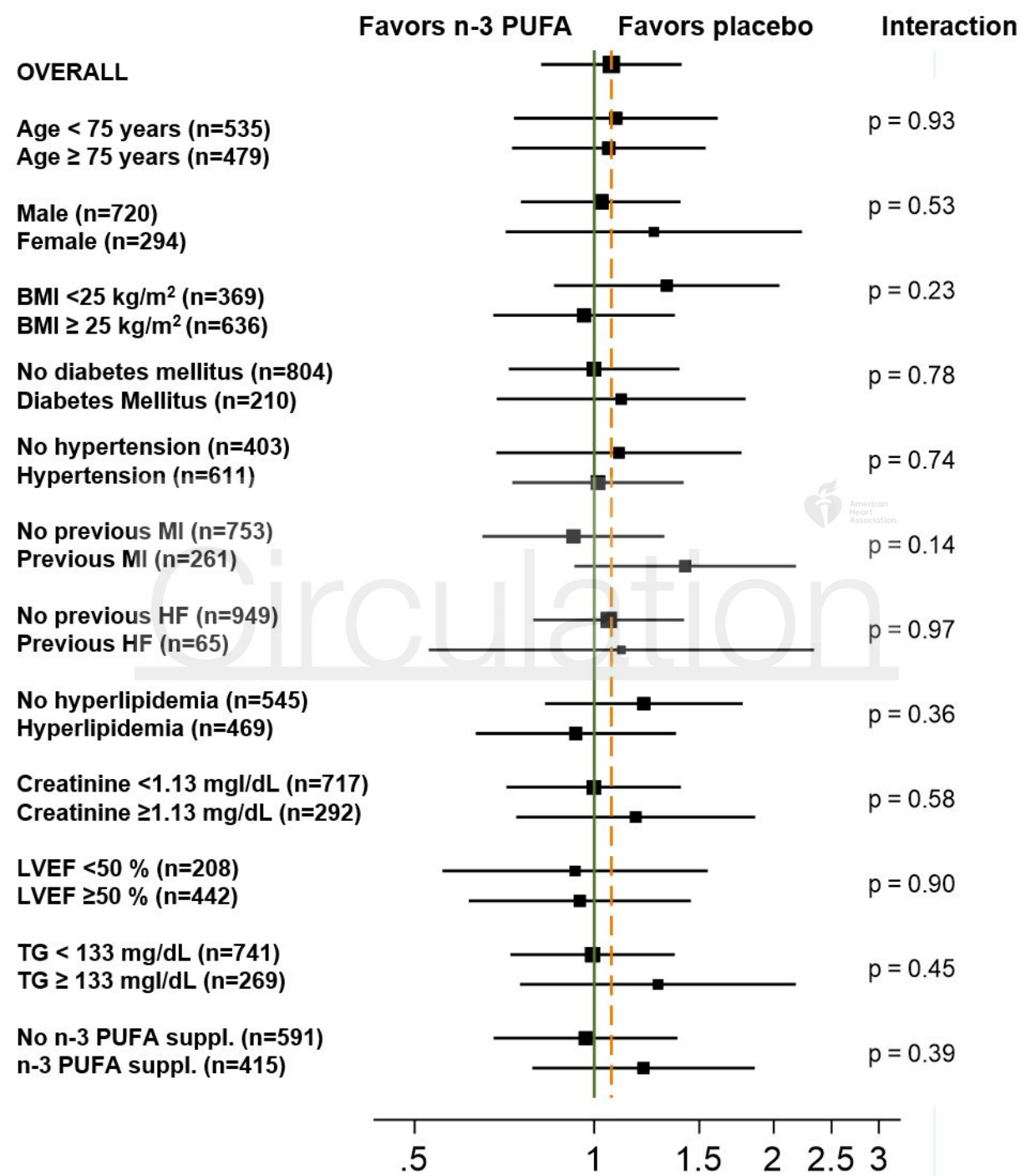


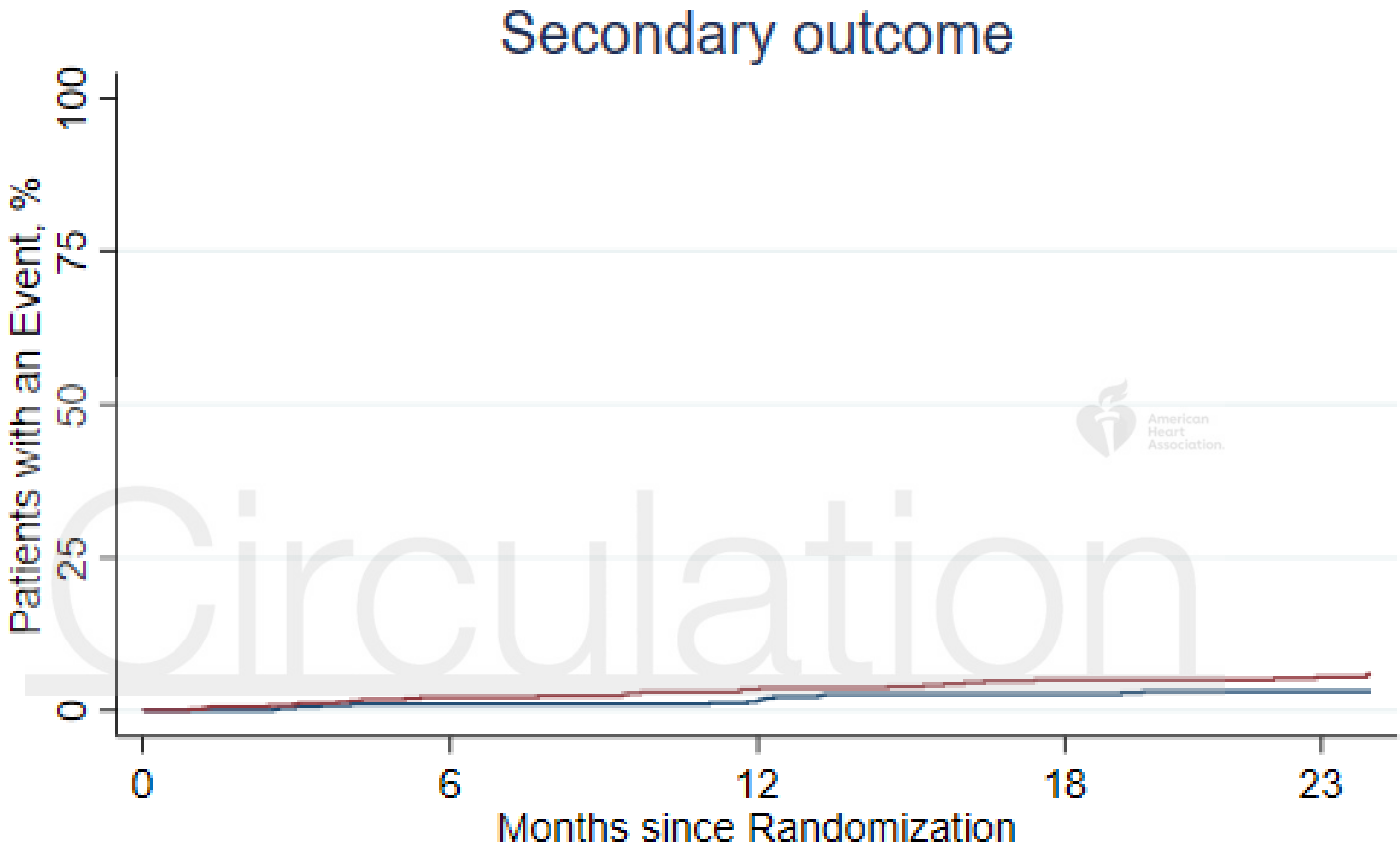



Number at risk

| | | | | | |
|---|---|---|---|---|---|
| Placebo | 509 | 495 | 477 | 459 | 445 |
| n-3 PUFA | 505 | 492 | 476 | 457 | 447 |

Placebo n-3 PUFA


Favors n-3 PUFA
Favors placebo
Interaction
OVERALL
Age < 75 years (n=535)
Age ≥ 75 years (n=479)
p = 0.93
Male (n=720)
Female (n=294)
p = 0.53
BMI <25 kg/m² (n=369)
BMI ≥ 25 kg/m² (n=636)
p = 0.23
No diabetes mellitus (n=804)
Diabetes Mellitus (n=210)
p = 0.78
No hypertension (n=403)
Hypertension (n=611)
p = 0.74
No previous MI (n=753)
Previous MI (n=261)
p = 0.14
No previous HF (n=949)
Previous HF (n=65)
p = 0.97
No hyperlipidemia (n=545)
Hyperlipidemia (n=469)
p = 0.36
Creatinine <1.13 mgl/dL (n=717)
Creatinine ≥1.13 mg/dL (n=292)
p = 0.58
LVEF <50 % (n=208)
LVEF ≥50 % (n=442)
p = 0.90
TG < 133 mg/dL (n=741)
TG ≥ 133 mgl/dL (n=269)
p = 0.45
No n-3 PUFA suppl. (n=591)
n-3 PUFA suppl. (n=415)
p = 0.39
.5
1
1.5
2
2.5
3






Number at risk

| | | | | | |
|---|---|---|---|---|---|
| Placebo | 509 | 477 | 462 | 441 | 430 |
| n-3 PUFA | 505 | 473 | 453 | 436 | 426 |

Placebo n-3 PUFA