# Effects of n-3 Fatty Acid Supplements in Elderly Patients after Myocardial Infarction

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1   **ABSTRACT**

2   **Background**

3   High intake of marine n-3 polyunsaturated fatty acids (PUFA) has been associated with reduced risk

4   of cardiovascular events, however, this has not been confirmed in patients with a recent myocardial

5   infarction (MI). Elderly patients are at particularly increased cardiovascular risk after MI, but few

6   trials address this group specifically. Omega-3 fatty acids hold the potential to reduce cardiovascular

7   events, with limited adverse effects, in this vulnerable group.

8   **Hypothesis**

9   The hypothesis was that daily addition of 1.8g n-3 PUFA to standard of care secondary prophylaxis in

10   elderly patients who have survived an acute myocardial infarction (AMI) would reduce the risk of

11   subsequent cardiovascular events during 2 years follow-up.

12   **Methods**

13   The OMega-3 fatty acids in Elderly with Myocardial Infarction (OMEMI) trial is an investigator-

14   initiated, multi-center, randomized clinical trial adding 1.8 g n-3 PUFA (Pikasol®; 930 mg EPA and 660

15   mg DHA) versus placebo (corn oil) daily to standard of care in 70-82 years old patients with recent (2-

16   8 weeks) MI. The primary endpoint was a composite of non-fatal MI, unscheduled revascularization,

17   stroke, all-cause mortality, heart failure hospitalization after two years follow-up. The safety

18   outcome was major bleeding. Serum fatty acids were measured as biomarkers of adherence.

19   **Results**

20   In total, 1,027 patients were randomized. Follow-up data were available for 1,014 patients who were

21   included in the intention-to-treat analysis. Mean ± SD age was 75±3.6 years, 294 (29%) were female

22   and mean triglycerides were 1.26±0.70 mmol/L. The primary endpoint occurred in 108 (21.4%)

23   patients on n-3 PUFA vs 102 (20.0%) on placebo (HR 1.08 [95%CI 0.82-1.41], p=0.60). In post hoc

24   analysis, consistent results were seen for all components of endpoint and across key clinical

1    subgroups. Median changes in EPA and DHA were +87% and +16% for n-3 PUFA vs -13% and -8% for

2    placebo. Major bleeding occurred in 54 (10.7%) and 56 (11.0%) in the n-3 PUFA and placebo groups,

3    respectively (p=0.87). Similar results were found in per-protocol analysis (n=893).

4    **Conclusion**

5    Among elderly patients with a recent MI, treatment with 1.8 g n-3 PUFAs daily for 2 years did not

6    reduce the risk of clinical events.

7    **Study Registration:** OMEMI Study; ClinicalTrails.gov Identifier: NCT01841944

# CLINICAL PERSPECTIVE

## BACKGROUND

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 PUFA) 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 icosapen ethyl used in this trail is notably different from formulations typically used in other n-3 PUFA trials, in that it delivers almost exclusively eicosapentaenoic acid (EPA) as opposed to the typical mixed EPA/decosohexaenoic 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

1 and age-related decline in absorption and metabolic function contributes to an increased risk of

2 dietary deficiencies in the elderly[17].

3       The hypothesis of the OMega-3 fatty acids in Elderly patients with Myocardial Infarction

4 (OMEMI) trial [18] was that daily addition of 1.8 g n-3 PUFA to standard of care secondary prevention in

5 elderly patients who have survived an AMI would reduce the risk of subsequent cardiovascular

6 events during 2 years follow-up.

7

## METHODS

**Trial design**

10 The OMEMI trial was designed as a multi-center, placebo-controlled, double-blind clinical trial

11 conducted by independent investigators at Center for Clinical Heart Research, Department of

12 Cardiology, Oslo University Hospital, Ullevål, Oslo, Norway. The study design and methods have

13 previously been published [18]. The protocol was approved by the Regional Committee for Medical and

14 Health Research Ethics (#2012/1422), and all participants provided written informed consent. The

15 trial was conducted in compliance with the declaration of Helsinki and with the rules outlined in the

16 guidelines for Good Clinical Practice. The trial was registered at ClinicalTrials.gov (NCT01841944).

17 This registration was late as we originally submitted an application for registration to the European

18 Union Drug Regulating Authorities Clinical Trial Database before November 1. An application for

19 registration was subsequently submitted to the ClinicalTrials.gov registry on April 16, 2013 and

20 formally posted on April 29, 2013. Between November 1, 2012 and April 29, 2013, 47 patients were

21 enrolled in the trial.

22  Capsules containing n-3 PUFA and matching placebo were provided by Orkla Health, Oslo, Norway,

23 who had no role in data collection, data analysis, interpretation of results or decision to submit the

24 manuscript for publication.

1   The manuscript was prepared by the authors, who vouch for the completeness and accuracy of the

2   data and analysis, and for the fidelity of the trial to the study protocol and statistical data analysis

3   plan. Requests for data sharing will be handled according to the regulation by Data Protection Officer

4   at Oslo University Hospital.

5

6   **Patients**

7   Hospitalized patients between 70 and 82 years old who were able to provide verbal and written

8   informed consent, were screened during admission for the index AMI of any type at four centers in

9   Norway (Oslo University Hospital, Ullevål, Oslo; Akershus University Hospital, Lørenskog; Vestre

10  Viken, Bærum Hospital, Gjettum; and Stavanger University Hospital, Stavanger). Exclusion criteria

11  were documented intolerance for n-3 fatty acids, participation in other clinical trials, additional

12  disease state deemed to be incompatible with adherence to the study protocol and life expectancy

13  <2 years. Examples of the latter could be malignancy with ongoing or deferred treatment, suspected

14  or confirmed cognitive impairment or obvious frailty.

15  **Trial procedures**

16  Eligible patients willing to participate were scheduled for baseline visit 2-3 weeks after the index

17  AMI. This was later changed up to 2-8 weeks to enhance inclusion rate. At the baseline visit, patients

18  were randomized in a 1:1 ratio to receive either 1.8 g n-3 PUFA (930 mg eicosapentaenoic acid (EPA)

19  + 660 mg docosahexaenoic acid (DHA) (Pikasol®), Orkla Health, Oslo, Norway) or matching placebo

20  (corn oil; 56% linoleic acid, 32% oleic acid, 10% palmitic acid). Total dose divided by 3 capsules to be

21  taken once daily. Permuted block randomization was used, stratified for participating centers.

22  Consecutively numbered sealed non-translucent envelopes were opened by the study physician at

23  randomization to reveal the treatment code. The study physician was blinded for the treatment

24  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. Detailed method description is given in supplementary material.

**Outcomes**

The pre-specified primary efficacy outcome was the first major adverse cardiovascular event (MACE), consisted 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 n3-PUFA[19-21], 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 [22]. 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-scpecified secondary outcome was new-onset atrial fibrillation, defined according to accepted diagnostic definitions. In addition to access to clinical records and EKGs taken at study visits, patients were screened with ambulant hand-held single lead rhythm monitoring (Zenicor, Zenicor Medical Systems AB, Stockholm, Sweden) for 2x30 minutes per day for 14 days,following the study visit at 12 months.

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All outcomes were adjudicated centrally by an independent endpoint committee of experienced clinicians, blinded to the treatment allocation (Suppl. Mat. 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, 23-25], 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 [26] 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). 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.

The same regression model was applied for the secondary endpoint, with time to first new-onset atrial fibrillation as the outcome. This was performed only for patients free from all previous known atrial fibrillation 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.

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.

1

## RESULTS

3 **Patients**

4 A total of 4,027 patients were screened across the four study sites, and 1,027 patients underwent

5 randomization. The first patient underwent randomization November 28, 2012 and the last on July 5,

6 2018. Of these, follow-up data were available for 1,014 patients (98.7%) to be included in the

7 intention-to-treat analysis (**Figure 1**). In this analysis, 505 patients (49.8%) were randomized to n-3

8 PUFA and 509 (50.2%) to placebo. Data according to the randomized groups are given in **Table 1.**

9 Clinical characteristics were well balanced between the groups. Of these patients, 29.0 % were

10 female, 99.8 % were of Caucasian ethnicity, median (Q1, Q3) age was 74 (72, 78) years, and 467

11 (46.1%) had known previous CVD at the time of the index AMI. At enrollment 415 (41.3%) reported

12 use of some form of n-3 PUFA supplement.

13 **Adherence**
14 Self-reported adherence to the study medication was present in 893 (88.1%) patients, forming the

15 set of the per-protocol analysis.

16 In the intention-to-treat analysis, levels of EPA and DHA at baseline and at the 24-month follow-up

17 were available in 881 (86.9%) patients. Patients in the n-3 PUFA group experienced a median (Q1-Q3)

18 of +87% (+32%, +165%) change in the concentration of EPA and +16% (+2%, +34%) change in DHA,

19 while in the placebo group changes were -13% (-34%, +20%) and -8% (-18%, +6%) in EPA and DHA,

20 respectively, expressed as relative change from baseline **(Figure 2)**. Changes in the per-protocol set

21 showed more pronounced differences **(Table S2)**.

22 Cod liver oil (up to one child spoon per day) was used by 202 (21.4%) at 3 months, 187 (21.2%) at 12

23 months and 174 (19.4%) at 24 months.

1 **Outcomes**

2 A primary outcome event according to intention-to-treat analysis occurred in 108 (21.0%) patients in

3 the n-3 PUFA group and in 102 (19.8%) in the placebo group (hazard ratio [HR] 1.07 [95% confidence

4 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

5 9.5 – 14.0) per 100 patient years, respectively (**Figure 3A)**. Consistent results were present for each

6 component of the primary end-point (**Table 2**). There were also no differences between the n-3 PUFA

7 and placebo groups in all-cause mortality: 28 (5.5%) vs 28 (5.5%); HR 1.01 [95% CI 0.60 – 1.71],

8 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

9 years, respectively (**Figure 3B)**.

10 The treatment effect on the primary outcome did not differ by age, sex, body mass index, diabetes,

11 previous hypertension, previous MI, previous HF, previous hyperlipidemia, levels of triglycerides, or

12 use of n-3 PUFA supplement at baseline (**Figure 4**).  Triglycerides changes by median (Q1, Q3) were -

13 8.1% (-27.5%, +15.3%) in the n-3 PUFA group vs +5.1% (-17.0%, +33.3%) in the placebo group

14 (p<0.001); between-group median absolute difference 13.2%. LDL changes were 0 %( - 15.8 %,

15 18.8 %) vs 0.7 % (-13.3 %, 19.3 %), respectively (p=0.57).

16 A total of  (25.1 % )of patients had experienced a form of atrial fibrillation at the time of

17 randomization, and759 patients were included in the intention-to-treat analysis for the secondary

18 endpoint. A secondary enpoint occurred in 28 (7.2 %) in the n-3 PUFA group and in 15 (4.0 %) in the

19 placebo group [HR] 1.84 [95% confidence interval [CI] 0.0.98-3.44], p=0.056) (**Table 2)**, with event

20 rates 4.0 (95% CI 2.7 – 5.7) and 2.2 (95% CI 1.3 – 3.6) per 100 patient years, respectively. Subgroup

21 analysis was not performed.

22 Analyses performed in per-protocol analyses yielded similar results (**Tables S3**).

23 **Adverse events**

24 Major bleeding occurred in 54 (10.7%) in the n-3 PUFA group and in 56 (11.0%) in the placebo group

25 (p=0.87). No patients withdrew from the trial because of bleeding problems.

1  Reasons for discontinuing treatment were well balanced between the groups, with 14 due to GI-

2  symptoms, 25 due to difficulty swallowing capsules and 36 due to other disease burden deemed not

3  related to the study intervention. Complete data are shown in **Table S4**.

4

## DISCUSSION

6

7  Elderly patients with a recent AMI who received 1.8 g of n-3 PUFA did not have a lower incidence of

8  MACE or death than those randomized to placebo after two years of follow-up. Analyses of the

9  different components of the primary endpoint as well as of key clinical subgroups equally did not

10  differ between patients given n-3 PUFA or placebo, either in intention-to-treat or in per protocol

11  analysis. There was also no effect on all-cause mortality. The changes in serum phospholipid levels of

12  EPA and DHA support good adherence among patients, limiting a problem that has been debated in

13  previous trials.

14  Early randomized clinical trials in the 1990s suggested cardiovascular benefits of n-3 PUFA after an

15  AMI. Thus, the Diet and Reinfarction Trial (DART) randomized patients to dietary advice and

16  demonstrated a 29% reduction in 2-year mortality in patients advised to eat fatty fish twice per

17  week. [6] The GISSI Prevenzione trial demonstrated a 21% reduction in all-cause mortality and 45%

18  reduction in sudden cardiac death in patients given 850 mg EPA/DHA compared to placebo for 3.5

19  years [5]. These promising results were however, not confirmed by three large RCTs published in 2010

20  using mixed EPA/DHA from 400 mg to 840 mg per day, all showing neutral results [7-9] The dosage used

21  in our trial was approximately the double that of these studies, including also the ORIGIN trial[27].

22  These contrasting results may be due to improved secondary prevention therapy after AMI, with the

23  introduction of statins and double antiplatelet therapy. In addition to difference in n-3 PUFA dosage,

24  differences in baseline risk have also been suggested to play an important role. The effect of 1 g

25  EPA/DHA in low-risk subjects from the general population was tested in the Vitamin-D and Omega-3

26  Trial (VITAL), with neutral results [28]. Similarly, A Study of Cardiovascular Events in Diabetes (ASCEND)

1     showed no risk reduction by 1 g EPA/DHA in patients with diabetes free of cardiovascular disease[29].

2     Patients in the OMEMI trial were at considerably higher risk than subjects in those studies, being

3     older and with a recent AMI. The n-3 PUFA dosage in OMEMI was also higher than in the afore-

4     mentioned trials. Accordingly, our findings extend the lack of effect by mixed EPA/DHA to reduce

5     cardiovascular risk.

6     The remarkable results from the REDUCE-IT trial[14], which demonstrating a 25% reduction in

7     cardiovascular events with 4 g of icosapent ethyl in statin-treated patients with hypertriglyceridemia

8     and established CVD or diabetes, and confirmed previous results of the JELIS trial[30], have shed new

9     light to the field of treatment with EPA. Icosapent ethyl is an ethyl-EPA, which is metabolized to EPA

10     after ingestion, and allows substantially higher content of EPA compared to over-the-counter

11     products. The substantial risk reduction in REDUCE-IT is unlikely to be explained by the moderate

12     22% reduction in triglyceride levels, and mechanistic studies suggest direct effects of icosapent ethyl

13     on coronary plaque regression[31]. Serum levels of EPA increased by 386% compared to placebo after

14     the first year in REDUCE-IT. This is considerably higher than the 113% between-group difference in

15     increase we observed in the OMEMI trial, and seems to reflect the difference in EPA-dosage (4000

16     mg versus 930 mg). Of note, the decrease in EPA and DHA concentration in the placebo arm may

17     relate to the reduced number of patients who reported additional use n-3 PUFA supplement (415

18     patients at baseline and 174 patients at 24 months). It is also worth noting that the that the baseline

19     median levels in our material (2.5 % EPA and 5.6 % DHA) are notably higher than corresponding

20     values from population studies in the USA (0.5 % EPA and 2.9 % DHA) [32], suggesting higher

21     background consumption of n-3 PUFA in our Norwegian study population. Equally notable is the

22     modest reduction in triglycerides in the n-3 PUFA group compared to the placebo group (median

23     13 %) in the OMEMI study, which is less than previous n-3 PUFA studies in patients who were

24     younger and with higher baseline triglyceride levels [33].

The safety of n-3 PUFA is well documented. However, due to their potential of in vitro inhibition of platelets, bleeding is a potential 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 double 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.

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 trials not targeting elderly patients[27-30]. 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 trials, however few of these are restricted to the geriatric population. We note that the PROSPER trial had an indentical age range as our trial, and an inclusion rate of 24 %[34]. Although specific frailty assessment or comprehensive comorbidity review was not part of screening or the trial, it is plausible that these conditions are a contributing cause to the low inclusion rate.

Although the OMEMI trial was moderately sized compared to other recent RCTs in the field, 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 sufficient 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, daily supplementation with 1.8 g EPA/DHA for two years in elderly patients with a recent AMI did not reduce the incidence of cardiovascular events or all-cause mortality.

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**FIGURE LEGENDS**

**Figure 1.** Flow chart of screening, randomization, treatment, and follow-up of the participants

**Figure 2** Changes in serum phospholipid concentration of EPA and DHA from baseline to 24 months

(n=806), according to randomization to n-3 PUFA or Placebo.

**Figure 3** Cumulative incidence rates of the primary outcome and all-cause death, according to months of follow-up in the randomized groups.

**Figure 4.** The ratios for the primary outcome in selected subgroups in the n-3 PUFA and the placebo groups TABLES

**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 > 150 µmol/L) | 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 from acute phase to inclusion | 94 (18.6) | 117 (23.0) |
| **Serum lipids** | | |
| Low-density lipoprotein cholesterol (mmol/L) | 1.9 ± 0.7 | 2.0 ± 0.7 |
| High-density liporpotein cholesterol (mmol/L) | 1.3 ± 0.4 | 1.3 ± 0.4 |
| Triglycerides (mmol/L) | 1.3 ± 0.8 | 1.2 ± 0.6 |
| 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 atrial fibrillation* | 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 arrhythmias (n-3 PUFA n=372, placebo n=387)

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



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 intention-to-treat analysis

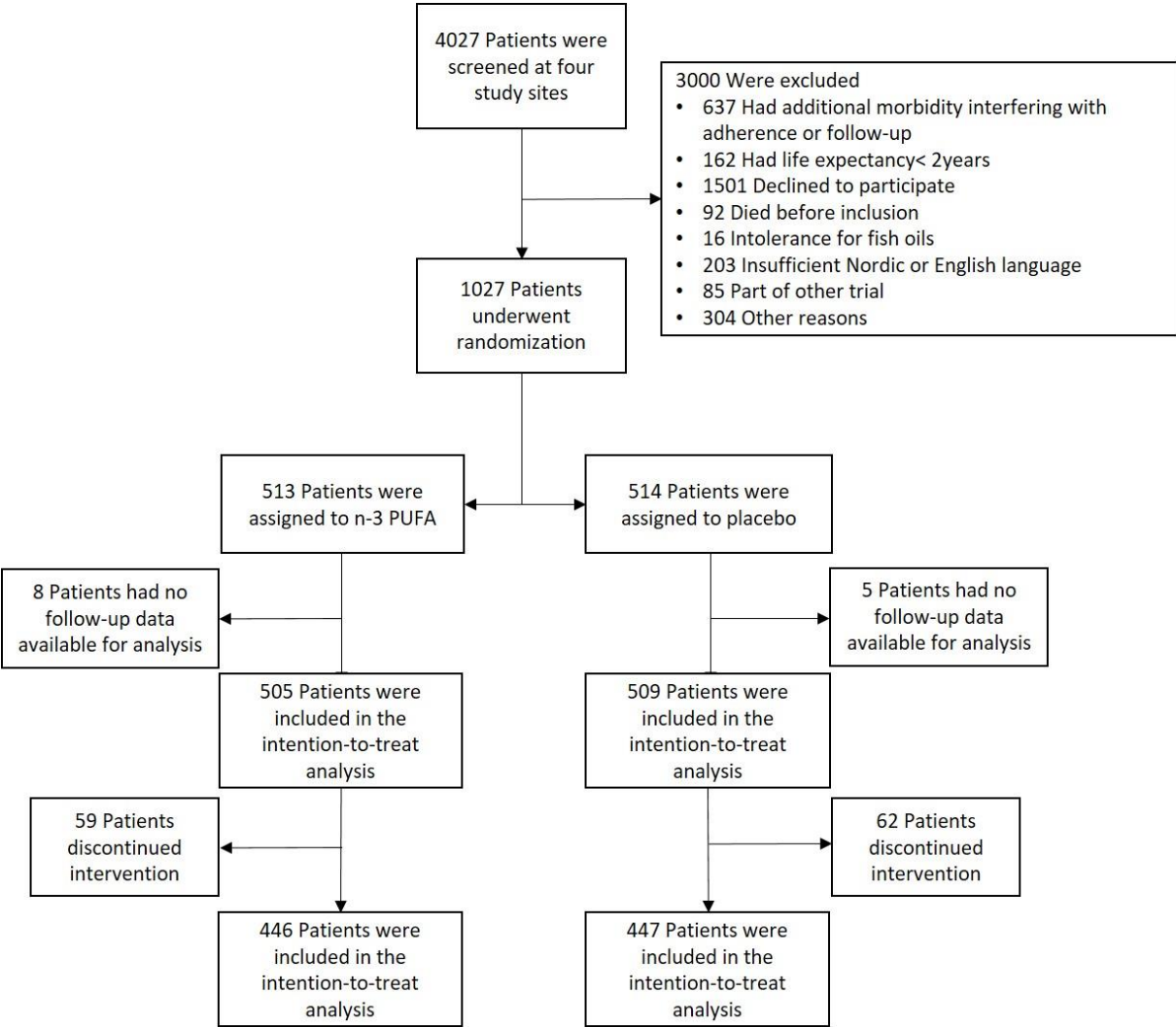447 Patients were included in the intention-to-treat analysis

**Figure 2.** Changes in serum phospholipid concentration of EPA and DHA, assessed as ratio (relative change) from baseline to 24 months. Samples were available for 881 patients.
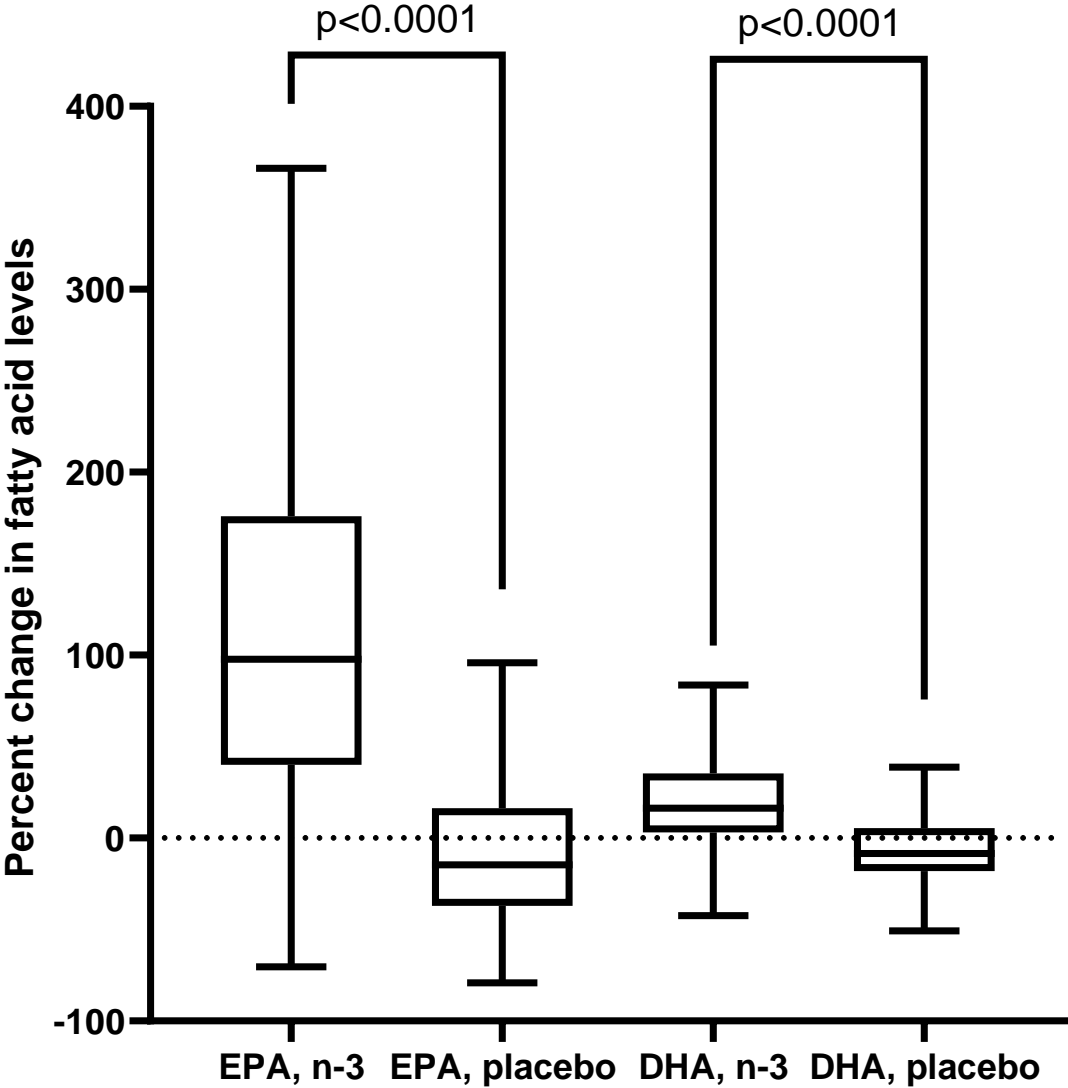
Figure 3. Kaplan–Meier estimation of the first events (A) and of all-cause death (B) during follow-up
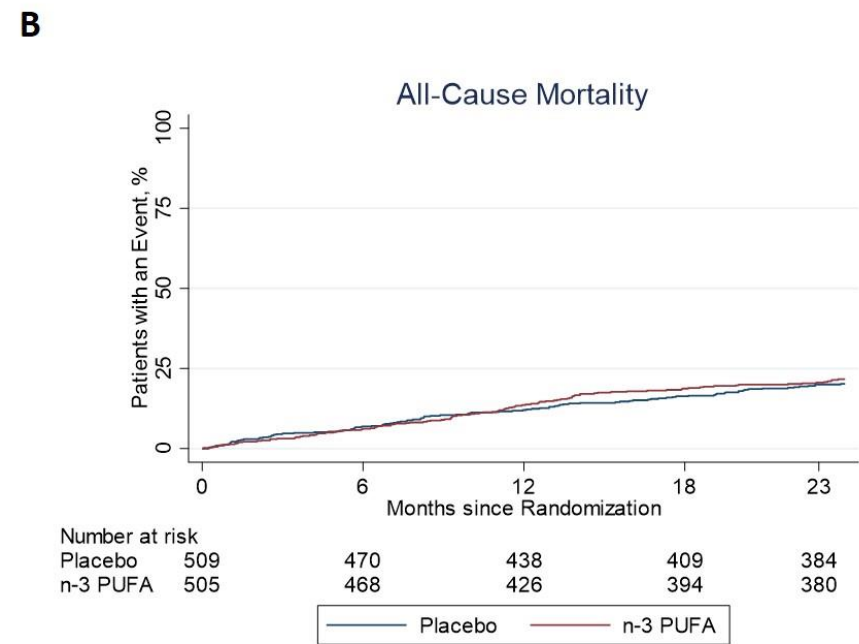
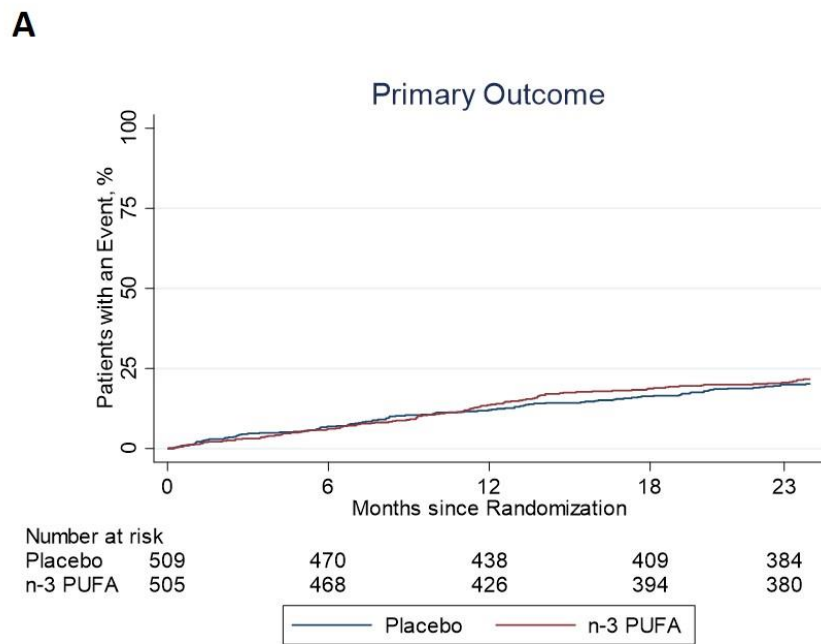**Figure 3.** Primary outcomes.

**A**



**B**

**Figure 4.** Treatment effect on the primary composite endpoint overall and by key clinical subgroups