Effects of \(n\)-3 fatty acids on major cardiovascular events in statin users and non-users with a history of myocardial infarction

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**Aims**

Recent secondary prevention trials have failed to demonstrate a beneficial effect of \(n\)-3 fatty acids on cardiovascular outcomes, which may be due to the growing use of statins since the mid-1990s. The aim of the present study was to assess whether statins modify the effects of \(n\)-3 fatty acids on major adverse cardiovascular events in patients with a history of myocardial infarction (MI).

**Methods and results**

Patients who participated in the Alpha Omega Trial were divided into consistent statin users (\(n=3740\)) and consistent statin non-users (\(n=413\)). In these two groups of patients, the effects of an additional daily amount of 400 mg eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA), 2 g \(\alpha\)-linolenic acid (ALA), or both on major cardiovascular events were evaluated. Multivariable Cox’s proportional hazard models were used to calculate adjusted hazard rate ratios (HRadj). Among the statin users 495 (13%) and among the statin non-users 62 (15%) developed a major cardiovascular event. In statin users, an additional amount of \(n\)-3 fatty acids did not reduce cardiovascular events [HRadj 1.02; 95% confidence interval (CI): 0.80, 1.31; \(P=0.88\)]. In statin non-users, however, only 9% of those who received EPA–DHA plus ALA experienced an event compared with 18% in the placebo group (HRadj 0.46; 95% CI: 0.21, 1.01; \(P=0.051\)).

**Conclusion**

In patients with a history of MI who are not treated with statins, low-dose supplementation with \(n\)-3 fatty acids may reduce major cardiovascular events. This study suggests that statin treatment modifies the effects of \(n\)-3 fatty acids on the incidence of major cardiovascular events.

ClinicalTrials.gov number: NCT00127452.

**Keywords**

\(n\)-3 fatty acids • Eicosapentaenoic acid • Docosahexaenoic acid • \(\alpha\)-linolenic acid • Cardiovascular diseases • Statins • Lipids

**Introduction**

The landmark Scandinavian Simvastatin Survival Study (4S)\(^1\) and subsequent randomized controlled trials\(^3\) showed beneficial effects of statins on mortality and morbidity in patients with and without previous myocardial infarction (MI) or other coronary heart disease (CHD). Ever since, statins have been the first choice of drug treatment for preventing and treating cardiovascular disease (CVD). The benefits of statins were first attributed solely to their ability to inhibit hepatic cholesterol synthesis, thereby improving serum lipid levels. Depending on the type, dose, and baseline levels, statins reduce LDL cholesterol by 18–55% and triglycerides by 7–30% and increase HDL cholesterol up to 15%\(^3\). Yet, over the years, multiple lipid-independent pleiotropic effects of statins have been described. Statins have, for example, beneficial effects on endothelial function, inflammation, and coagulation, independent of lipid lowering.\(^4\)
A healthy lifestyle is promoted for CVD prevention. Lifestyle changes include smoking cessation, increased physical activity level, and adopting a healthier diet. Dietary guidelines emphasize the importance of n-3 fatty acids, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). A meta-analysis of both prospective cohort studies and trials showed that 250 mg/day of EPA–DHA reduced fatal CHD by 36% compared with no EPA–DHA. Fish consumption, the major source of EPA–DHA in the diet, was inversely related to incident stroke in a meta-analysis of cohort studies. Less evidence exists for a protective effect of ω-3 fatty acids (ALA), the plant-derived n-3 fatty acid, against CVD.

Although adding n-3 fatty acids to statin therapy leads to significant reductions in triglyceride levels, it has also been suggested that the use of guideline-concordant statin therapy dilutes the effects of n-3 fatty acids such that no additional protective effect is observed. This hypothesis is supported by the reduction in cardiovascular events through either fatty fish or EPA–DHA in trials in which less than one-third of the participants were on statin therapy (DART12 and GISSI-Prevenzione13). n-3 fatty acids did not reduce major cardiovascular events in three recently conducted trials with a large number of statin users. The OMEGA trial showed that guideline-adjusted drug treatment—including statin use in >90% of the post-MI patients—resulted in a low risk of cardiovascular events which could not be further reduced by 840 mg EPA–DHA daily. Also in the SU.FOL.OM3 trial, no significant difference was detected in major vascular events between coronary artery disease patients allocated to 600 mg EPA–DHA daily and those allocated to placebo. Finally, we showed in the Alpha Omega Trial no reduction in cardiovascular events in 4837 post-MI patients who were randomized to an additional amount of EPA–DHA (400 mg/day) and/or ALA (2 g/day), compared with placebo.

The aim of the present study was to assess whether the effects of EPA–DHA and/or ALA on major cardiovascular events in the Alpha Omega Trial differed between statin users and statin non-users.

Methods

Study population

The Alpha Omega Trial is a multicentre, double-blind, placebo-controlled trial of low doses of n-3 fatty acids (400 mg/day EPA–DHA and/or 2 g/day ALA) on the risk of fatal and non-fatal major cardiovascular events. The trial was approved by a central medical Ethics Committee (Haga Hospital, Leyenburg, The Hague, The Netherlands) and by the Ethics Committee at each participating hospital. All subjects signed informed consent before entering the study. Details of the Alpha Omega Trial have been described elsewhere. Briefly, 4837 free-living Dutch post-MI patients aged 60–80 years were randomized to receive one of four margarines: an EPA–DHA-enriched, an ALA-enriched, an EPA–DHA plus ALA-enriched margarine, or a placebo margarine. Patients were enrolled from April 2002 through December 2006 and were followed for an average of 41 months.

At baseline, anthropometric measures were obtained and blood pressure, heart rate, lipid and glucose levels were determined. Information on demographic variables, lifestyle habits, current health status and medical history were collected by self-administered questionnaires. Baseline measurements were repeated after 20 months of the intervention in a random sample of 810 participants, and after 41 months in the 2531 participants who completed the trial before 1 January 2009. For the remaining participants, due to budgetary constraints, physical examination and blood sampling were not repeated and data were collected by questionnaires at the end of follow-up.

Assessment of statin use

Questionnaires on medication use were filled out by all participants at baseline and after 41 months. Subjects were asked to record changes in medication use in a structured diary, and medication was checked during structured telephone interviews after 12 and 24 months. All drugs were coded according to the Anatomical Therapeutic Chemical (ATC) classification by two of the authors (S.R.B.M.E. and O.H.K.). Subjects who reported the use of statins (ATC codes C10AA and C10B) at all measurements (at baseline and at 12-, 24-, and after an average 41-month follow-up) were classified as statin users. Those who were not using statins at any time point were classified as non-users. Subjects who initiated or stopped statin therapy during the trial and inconsistent statin users who used statins at some, but not all, time points were excluded.

Endpoint

The vital status of the participants was monitored via a computerized link with municipal registries. For patients who experienced a fatal event during follow-up, general practitioners, hospitals, and family members were approached to ascertain the primary and contributing causes of death. The occurrence of non-fatal major cardiovascular events (MI, cardiac arrest, and stroke) and cardiac interventions (percutaneous coronary intervention and coronary artery bypass grafting) was monitored by annual telephone interviews conducted by research staff and verified against hospital records. The primary endpoint of this study was the rate of major cardiovascular events, which comprised fatal CVDs, non-fatal MI, non-fatal cardiac arrest, non-fatal stroke, and cardiac interventions (percutaneous coronary intervention and coronary artery bypass grafting).

Statistical analysis

Demographic and health characteristics of the participants who received the different margarines, stratified for statin users and non-users, were compared by using Student’s t-test or the Mann–Whitney U-test for continuous variables and the x2-test for nominal variables.

Uni- and multivariable general linear regression models were used to assess differences in changes in lipid levels over time among statin users and non-users randomized to n-3 fatty acid supplementation or placebo. Uni- and multivariable Cox’s proportional hazard models were used to estimate hazard rate ratios (HR) for major cardiovascular events with the placebo group as reference. Fixed effects in the models were the n-3 fatty acids and the use of statins. To test whether the effect of EPA–DHA and/or ALA differed between patients with and without statins, the product term of n-3 fatty acids and statins was added to the models.

In the multivariable models, we adjusted for age, gender, and diabetes mellitus. In addition, we checked whether inclusion one by one of other potential confounding variables altered the relationship of EPA–DHA and/or ALA with major cardiovascular events by ≥10%. We selected the following potential confounders: baseline levels of body mass index, current smoking (yes/no), physical activity level (≥5 or <5 days/week engaged in physical activity with a Metabolic Equivalent TASK score >3), self-reported history of stroke, dietary EPA–DHA intake, alcohol consumption (≥1 or <1 glass/week), ratio of total to HDL cholesterol, serum triglyceride levels, systolic blood pressure, current use of blood pressure-lowering...
medication (ATC codes C02, C03, C07, C08, and C09), antithrombotic agents (B01), and hormone replacement therapy (G03).

**Results**

**Demographic and health characteristics of the patients**

Of the 4837 patients who were enrolled in the Alpha Omega Trial, 3740 (77%) patients were consistent statin users and 413 (9%) patients were consistent statin non-users. The remainder of the patients (n = 684, 14%) were starters, stoppers, or inconsistent users of statins and were for this reason excluded from the study. The mean age of all participants was 68.9 ± 5.6 years and 78% were males. The median time since last MI before study entry was 3.7 years (inter-quartile range: 1.7–6.3). For statin users as well as for statin non-users, the four study groups receiving placebo, EPA–DHA only, ALA only, or EPA–DHA plus ALA were similar for most characteristics (Table 1). Among statin users, significant differences between study groups were observed for the use of blood pressure-lowering drugs, triglyceride levels, and consumption of fish. Among statin non-users, significant differences between study groups were observed for the percentage of patients with diabetes mellitus, self-reported stroke, the use of antithrombotic drugs, physical activity, and plasma glucose and serum triglyceride levels.

**Effects of n-3 fatty acids on lipid levels**

Table 2 presents the average changes in lipid levels between baseline and 41-month follow-up among statin users and statin non-users, respectively. No significant effects were observed in the groups receiving EPA–DHA only and ALA only. Yet, the combination of EPA–DHA and ALA reduced triglycerides significantly by 0.17 mmol/L in statin users.

**Effects of n-3 fatty acids on major cardiovascular events**

No patient was lost to follow-up and hence all patients’ data were included in the Cox proportional hazard analysis. During 12 048 persons-years of follow-up, 495 (13%) statin users had a major cardiovascular event. For statin non-users, 1234 persons-years of follow-up were accumulated and 62 (15%) major cardiovascular events occurred. Among statin users, there was no significant difference in the rate of major cardiovascular events between the four groups (Table 3). Supplementation with EPA–DHA only or with ALA only did not reduce major cardiovascular events in statin non-users. However, 9% of the statin non-users who received EPA–DHA plus ALA had a major cardiovascular event during the 41-month follow-up period compared with 18% of the patients in the placebo group. Statin non-users receiving EPA–DHA plus ALA had a 54% lower incidence of major cardiovascular events compared with the placebo group, which was borderline statistically significant (HRadj 0.46; 95% confidence interval: 0.21, 1.01; P = 0.051). The effect of the combination of EPA–DHA plus ALA on major cardiovascular events was borderline statistically significantly different between statin users and non-users (P = 0.057).

**Discussion**

The present study suggests that statin treatment modifies the effects of n-3 fatty acids on the incidence of major cardiovascular events. In statin users, additional n-3 fatty acids had no effect on major cardiovascular events, despite a significant reduction in triglycerides. In statin non-users, reductions in major cardiovascular events due to EPA–DHA alone or ALA alone were 18 and 10%, respectively, and not statistically significant. However, combined effects of EPA–DHA plus ALA accumulated to 54% (P = 0.051). This is consistent with the hypothesis that the effects of EPA–DHA and ALA alone are additive and independent, although this has been disputed in a recent review.

The Alpha Omega Trial is the first double-blind placebo-controlled trial in which the effect of adding 400 mg EPA–DHA and/or 2 g ALA/day on major cardiovascular events was investigated. Other large randomized controlled trials have concentrated on the effect of consuming EPA–DHA alone. Apart from the Alpha Omega Trial, also the recently published OMEGA trial and the SU.FOL.OM3 trial, both carried out in cardiac patients, failed to show a reduction in major cardiovascular events after a moderate additional intake of, respectively, 840 and 600 mg EPA–DHA per day. In all three trials, at least 85% of the patients were treated with statins. However, in the 11 years earlier published GISSI-Prevenzione (GISSI-P) trial, treatment with 850–882 mg daily of EPA–DHA decreased major cardiovascular events defined as fatal CVD plus non-fatal MI and non-fatal stroke by 20% in patients after a recent MI. In this trial, the percentage of statin users increased from 5% at baseline to 29% after 6 months and to 46% at the end of the trial. Baseline total to HDL cholesterol ratio was 5.1 and clinically important changes in total and HDL cholesterol were not observed during the course of the trial. In the Alpha Omega Trial, supplementation with 400 mg daily of EPA–DHA did not reduce major cardiovascular events. Eighty-five per cent of the participants in this trial were on statin treatment and baseline ratio of total to HDL cholesterol ratio was 3.9, i.e. 1.2 unit lower than in GISSI-P, treatment with 850–882 mg daily of EPA–DHA did not reduce major cardiovascular events. In statin users, additional amount of 400 mg EPA–DHA, 2 g ALA, or both did not reduce the number of major cardiovascular events (Table 3). These results suggest that in cardiac patients with
Table 1  Baseline characteristics of users and non-users of statins randomized to placebo or n-3 fatty acid supplementation in the Alpha Omega Trial

<table>
<thead>
<tr>
<th></th>
<th>Statin users (n = 3740)</th>
<th>Statin non-users (n = 413)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n = 943)</td>
<td>EPA–DHA (n = 920)</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td>68.7 ± 5.6</td>
<td>68.7 ± 5.5</td>
</tr>
<tr>
<td><strong>Male gender, n (%)</strong></td>
<td>745 (79)</td>
<td>718 (78)</td>
</tr>
<tr>
<td><strong>Median time since MI, years</strong></td>
<td>3.4 (15–6.2)</td>
<td>3.6 (1.7–6.3)</td>
</tr>
<tr>
<td><strong>Self-reported history of stroke, n (%)</strong></td>
<td>58 (6)</td>
<td>61 (7)</td>
</tr>
</tbody>
</table>

Use of cardiovascular medication, n (%) (n = 943)

- **Antithrombotic agents**
  - 930 (99) Placebo
  - 909 (99) EPA–DHA
  - 919 (99) ALA
  - 925 (98) EPA–DHA + ALA
- **Antihypertensive agents**
  - 856 (90) Placebo
  - 853 (93) EPA–DHA
  - 835 (90) ALA
  - 856 (90) EPA–DHA + ALA

**Blood pressure, mmHg**

- **Systolic**
  - 141.6 (142.3–141.2) Placebo
  - 142.3 (142.3–141.2) EPA–DHA
  - 141.2 (141.2–140.8) ALA
  - 140.8 (140.8–140.8) EPA–DHA + ALA
- **Diastolic**
  - 80.0 (80.5–80.0) Placebo
  - 80.5 (80.5–80.3) EPA–DHA
  - 80.3 (80.3–80.2) ALA
  - 80.2 (80.2–80.2) EPA–DHA + ALA

**Plasma glucose, mmol/L**

- 6.25 (6.21–6.17) Placebo
- 6.61 (6.21–6.17) EPA–DHA
- 6.59 (6.21–6.17) ALA
- 6.58 (6.21–6.17) EPA–DHA + ALA

**Serum lipids, mmol/L**

- **Total cholesterol**
  - 4.59 (4.61–4.56) Placebo
  - 4.61 (4.61–4.56) EPA–DHA
  - 4.56 (4.56–4.56) ALA
  - 4.55 (4.55–4.55) EPA–DHA + ALA
- **LDL cholesterol**
  - 2.44 (2.48–2.43) Placebo
  - 2.48 (2.48–2.43) EPA–DHA
  - 2.43 (2.43–2.43) ALA
  - 2.44 (2.44–2.44) EPA–DHA + ALA
- **HDL cholesterol**
  - 1.29 (1.29–1.29) Placebo
  - 1.29 (1.29–1.29) EPA–DHA
  - 1.29 (1.29–1.29) ALA
  - 1.29 (1.29–1.29) EPA–DHA + ALA
- **TC/HDL cholesterol ratio**
  - 3.76 (3.76–3.76) Placebo
  - 3.76 (3.76–3.76) EPA–DHA
  - 3.76 (3.76–3.76) ALA
  - 3.76 (3.76–3.76) EPA–DHA + ALA

**Median triglycerides, mmol/L (range)**

- 1.68 (1.22–2.38) Placebo
- 1.62 (1.24–2.28) EPA–DHA
- 1.61 (1.19–2.28) ALA
- 1.59 (1.18–2.20) EPA–DHA + ALA

**BMI, kg/m²**

- 27.9 (27.7–27.8) Placebo
- 27.7 (27.7–27.8) EPA–DHA
- 27.8 (27.8–27.9) ALA
- 27.6 (27.6–27.9) EPA–DHA + ALA

**Diabetes mellitus, n (%)**

- 190 (20) Placebo
- 204 (22) EPA–DHA
- 201 (22) ALA
- 180 (19) EPA–DHA + ALA

**Physical activityc, 5 days/week, n (%)**

- 197 (21) Placebo
- 188 (20) EPA–DHA
- 194 (21) ALA
- 217 (23) EPA–DHA + ALA

**Alcohol use ≥ 1 glass/week, n (%)**

- 169 (18) Placebo
- 153 (17) EPA–DHA
- 165 (18) ALA
- 142 (15) EPA–DHA + ALA

**Median fish consumption, g/day (range)**

- 14.3 (5.9–18.4) Placebo
- 15.0 (7.5–19.8) EPA–DHA
- 15.3 (7.8–22.4) ALA
- 15.1 (6.4–19.4) EPA–DHA + ALA

**Intake of fish ≥ 20 g/day, n (%)**

- 288 (31) Placebo
- 286 (31) EPA–DHA
- 296 (32) ALA
- 292 (31) EPA–DHA + ALA

**Median intake of EPA–DHA, mg/day (range)**

- 120 (50–210) Placebo
- 130 (60–205) EPA–DHA
- 130 (60–220) ALA
- 130 (50–210) EPA–DHA + ALA

**BMI, kg/m²**

- 27.9 (27.7–27.8) Placebo
- 27.7 (27.7–27.8) EPA–DHA
- 27.8 (27.8–27.9) ALA
- 27.6 (27.6–27.9) EPA–DHA + ALA

**Diabetes mellitus, n (%)**

- 190 (20) Placebo
- 204 (22) EPA–DHA
- 201 (22) ALA
- 180 (19) EPA–DHA + ALA

**Physical activityc, 5 days/week, n (%)**

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- 188 (20) EPA–DHA
- 194 (21) ALA
- 217 (23) EPA–DHA + ALA

**Alcohol use ≥ 1 glass/week, n (%)**

- 169 (18) Placebo
- 153 (17) EPA–DHA
- 165 (18) ALA
- 142 (15) EPA–DHA + ALA

**Median fish consumption, g/day (range)**

- 14.3 (5.9–18.4) Placebo
- 15.0 (7.5–19.8) EPA–DHA
- 15.3 (7.8–22.4) ALA
- 15.1 (6.4–19.4) EPA–DHA + ALA

**Intake of fish ≥ 20 g/day, n (%)**

- 288 (31) Placebo
- 286 (31) EPA–DHA
- 296 (32) ALA
- 292 (31) EPA–DHA + ALA

**Median intake of EPA–DHA, mg/day (range)**

- 120 (50–210) Placebo
- 130 (60–205) EPA–DHA
- 130 (60–220) ALA
- 130 (50–210) EPA–DHA + ALA

**Plus–minus values are means ± SD; range is the inter-quartile range. ALA, α-linolenic acid; BMI, body mass index; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; MI, myocardial infarction; TC/HDL cholesterol ratio, total to HDL cholesterol ratio.**

**Values within a row with different superscripts were significantly different (P < 0.05).**

**Physical activity with a Metabolic Equivalent Task score ≥ 3.**

**Intake of EPA–DHA outside the study treatment.**

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Table 2  Unadjusted and adjusted changes in total cholesterol, low-density lipoprotein cholesterol, total to high-density lipoprotein cholesterol ratio, and triglycerides between baseline and 41-month follow-up among statin users and statin non-users randomized to n-3 fatty acid supplementation in the Alpha Omega Trial with the placebo group as reference

<table>
<thead>
<tr>
<th></th>
<th>Total cholesterol, mmol/L</th>
<th>LDL cholesterol, mmol/L</th>
<th>TC/HDL cholesterol ratio</th>
<th>Triglycerides, mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β (95% CI)</td>
<td>Adj β (95% CI)</td>
<td>β (95% CI)</td>
<td>Adj β (95% CI)</td>
</tr>
<tr>
<td>Statin users (n = 1893)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>EPA–DHA</td>
<td>0.032 (–0.099, 0.11)</td>
<td>0.028 (–0.052, 0.11)</td>
<td>–0.0081 (–0.077, 0.061)</td>
<td>–0.0085 (–0.077, 0.060)</td>
</tr>
<tr>
<td>ALA</td>
<td>–0.034 (–0.11, 0.0047)</td>
<td>–0.036 (–0.12, 0.043)</td>
<td>0.0026 (–0.066, 0.071)</td>
<td>0.0033 (–0.065, 0.071)</td>
</tr>
<tr>
<td>EPA–DHA + ALA</td>
<td>–0.069 (–0.15, 0.0112)</td>
<td>–0.071 (–0.15, 0.0092)</td>
<td>–0.025 (–0.093, 0.044)</td>
<td>–0.025 (–0.093, 0.043)</td>
</tr>
<tr>
<td>Statin non-users (n = 178)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPA–DHA</td>
<td>0.0082 (–0.24, 0.26)</td>
<td>–0.0012 (–0.25, 0.25)</td>
<td>0.076 (–0.14, 0.29)</td>
<td>0.071 (–0.14, 0.29)</td>
</tr>
<tr>
<td>ALA</td>
<td>–0.12 (–0.38, 0.14)</td>
<td>–0.094 (–0.35, 0.16)</td>
<td>0.11 (–0.11, 0.33)</td>
<td>0.12 (–0.099, 0.34)</td>
</tr>
<tr>
<td>EPA–DHA + ALA</td>
<td>–0.26 (–0.53, 0.0059)</td>
<td>–0.24 (–0.51, 0.020)</td>
<td>0.017 (–0.21, 0.25)</td>
<td>0.025 (–0.20, 0.25)</td>
</tr>
</tbody>
</table>

*Adjusted for age, gender and diabetes mellitus types I and II.

1β < 0.05 when compared with the baseline value.

ALA, α-linolenic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; TC/HDL cholesterol ratio, total to HDL cholesterol ratio.
should be regarded as preliminary until these have been confirmed in larger patient populations.

In conclusion, the present study indicates that low-dose supplementation with n-3 fatty acids might reduce the risk of major cardiovascular events in statin non-users with a history of MI. These results contribute to the explanation of the inconsistent results on the effects of n-3 fatty acids in secondary prevention trials.

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Table 3  Unadjusted and adjusted hazard rate ratios for major cardiovascular events among statin users and statin non-users randomized to n-3 fatty acid supplementation in the Alpha Omega Trial with the placebo group as reference

<table>
<thead>
<tr>
<th>Statin users (n = 3740)</th>
<th>Statin non-users (n = 413)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No./total (%)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Placebo (reference)</td>
<td>123/943 (13)</td>
</tr>
<tr>
<td>EPA – DHA</td>
<td>127/920 (14)</td>
</tr>
<tr>
<td>ALA</td>
<td>119/930 (13)</td>
</tr>
<tr>
<td>EPA – DHA + ALA</td>
<td>126/947 (13)</td>
</tr>
</tbody>
</table>

ALA, α-linolenic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid.

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Table 4  Effect of EPA–DHA and/or ALA on major cardiovascular events in post-myocardial patients in the GISSI-Prevenzione Trial13 and the Alpha Omega Trial16

<table>
<thead>
<tr>
<th>GISSI-Prevenzione</th>
<th>All patients in Alpha Omega</th>
<th>Statin non-users in Alpha Omega</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>11 324</td>
<td>4837</td>
</tr>
<tr>
<td>Intake of fish</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 1 serving/week or ≥ 20 g/daya (%)</td>
<td>86</td>
<td>31</td>
</tr>
<tr>
<td>Dose EPA (mg)</td>
<td>289</td>
<td>226</td>
</tr>
<tr>
<td>Dose DHA (mg)</td>
<td>577</td>
<td>150</td>
</tr>
<tr>
<td>Dose ALA (mg)</td>
<td>0</td>
<td>1882</td>
</tr>
<tr>
<td>Medication use (%)b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-platelet drug</td>
<td>88</td>
<td>84</td>
</tr>
<tr>
<td>ACE-inhibitors</td>
<td>41</td>
<td>42</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>41</td>
<td>69</td>
</tr>
<tr>
<td>Statins</td>
<td>29</td>
<td>85</td>
</tr>
<tr>
<td>Serum lipids, mmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>5.45 ± 1.10</td>
<td>4.73 ± 0.97</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>3.55 ± 0.98</td>
<td>2.59 ± 0.84</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>1.07 ± 0.29</td>
<td>1.29 ± 0.34</td>
</tr>
<tr>
<td>TC/HDL cholesterol ratioc</td>
<td>5.08</td>
<td>3.87 ± 1.13</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.83 ± 0.97</td>
<td>1.92 ± 1.04</td>
</tr>
<tr>
<td>RR reduction in MCEd</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPA – DHA</td>
<td>0.80 (0.68, 0.95)</td>
<td>1.05 (0.85, 1.29)</td>
</tr>
<tr>
<td>ALA</td>
<td>0.94 (0.76, 1.17)</td>
<td>0.90 (0.47, 1.72)</td>
</tr>
<tr>
<td>EPA – DHA plus ALA</td>
<td>0.91 (0.74, 1.13)</td>
<td>0.46 (0.21, 1.01)</td>
</tr>
</tbody>
</table>

ACE, angiotensin-converting enzyme; ALA, α-linolenic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; MCE, major cardiovascular events; RR, relative risk; TC/HDL cholesterol ratio, total to HDL cholesterol ratio.

aFish intake was categorized into ≥ 1 or < 1 serving/week in GISSI-Prevenzione and as ≥ 20 or < 20 g/day in Alpha Omega.
bMedication use in GISSI-Prevenzione at 6 months.
cTotal to HDL cholesterol ratio was not presented in GISSI-Prevenzione but was derived by dividing the total cholesterol level by the HDL cholesterol level.
dMCE comprised fatal cardiovascular disease, non-fatal myocardial infarction, and non-fatal stroke in GISSI-Prevenzione. In Alpha Omega, MCE comprised fatal cardiovascular disease, non-fatal myocardial infarction, non-fatal stroke, non-fatal cardiac arrest, and cardiac interventions (percutaneous coronary intervention and coronary artery bypass grafting).
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References