ORIGINAL ARTICLE

n–3 Fatty Acids and Cardiovascular Events after Myocardial Infarction

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ABSTRACT

BACKGROUND

Results from prospective cohort studies and randomized, controlled trials have provided evidence of a protective effect of n–3 fatty acids against cardiovascular diseases. We examined the effect of the marine n–3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and of the plant-derived alpha-linolenic acid (ALA) on the rate of cardiovascular events among patients who have had a myocardial infarction.

METHODS

In a multicenter, double-blind, placebo-controlled trial, we randomly assigned 4837 patients, 60 through 80 years of age (78% men), who had had a myocardial infarction and were receiving state-of-the-art antihypertensive, antithrombotic, and lipid-modifying therapy to receive for 40 months one of four trial margarines: a margarine supplemented with a combination of EPA and DHA (with a targeted additional daily intake of 400 mg of EPA–DHA), a margarine supplemented with ALA (with a targeted additional daily intake of 2 g of ALA), a margarine supplemented with EPA–DHA and ALA, or a placebo margarine. The primary end point was the rate of major cardiovascular events, which comprised fatal and nonfatal cardiovascular events and cardiac interventions. Data were analyzed according to the intention-to-treat principle, with the use of Cox proportional-hazards models.

RESULTS

The patients consumed, on average, 18.8 g of margarine per day, which resulted in additional intakes of 226 mg of EPA combined with 150 mg of DHA, 1.9 g of ALA, or both, in the active-treatment groups. During the follow-up period, a major cardiovascular event occurred in 671 patients (13.9%). Neither EPA–DHA nor ALA reduced this primary end point (hazard ratio with EPA–DHA, 1.01; 95% confidence interval [CI], 0.87 to 1.17; P=0.93; hazard ratio with ALA, 0.91; 95% CI, 0.78 to 1.05; P=0.20). In the prespecified subgroup of women, ALA, as compared with placebo and EPA–DHA alone, was associated with a reduction in the rate of major cardiovascular events that approached significance (hazard ratio, 0.73; 95% CI, 0.51 to 1.03; P=0.07). The rate of adverse events did not differ significantly among the study groups.

CONCLUSIONS

Low-dose supplementation with EPA–DHA or ALA did not significantly reduce the rate of major cardiovascular events among patients who had had a myocardial infarction and who were receiving state-of-the-art antihypertensive, antithrombotic, and lipid-modifying therapy. (Funded by the Netherlands Heart Foundation and others; ClinicalTrials.gov number, NCT00127452.)

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This article (10.1056/NEJMoa1003603) was published on August 29, 2010, at NEJM.org.

N Engl J Med 2010.

A meta-analysis of randomized trials involving patients with cardiac disease showed that supplementation with the marine n–3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) reduced the rate of death from coronary heart disease by 20%.[1] Mozaffarian and Rimm concluded from their meta-analysis of cohort studies and clinical trials that a daily intake of 250 mg of EPA and DHA reduced the risk of fatal coronary heart disease by 36%.[2] There was no additional benefit from higher intakes. There is less evidence for a protective effect of the plant-derived n–3 fatty acid alpha-linolenic acid (ALA). A meta-analysis of five prospective cohort studies showed that the risk of fatal coronary heart disease was 21% lower among subjects who had a high intake of ALA than among subjects who had a low intake of ALA — a difference that was of borderline significance.[3] Data from randomized trials regarding the effect of ALA supplementation on the rate of cardiovascular disease are lacking.

n–3 fatty acids may prevent ventricular arrhythmias in patients who have had a myocardial infarction.[4] Basic research has shown that enrichment of myocardial membranes with these fatty acids reduces the vulnerability to cardiac arrhythmias.[5-7] These results corroborate the inverse associations that have been seen in case–control studies and cohort studies between fish in the diet, EPA and DHA content in the diet, or EPA and DHA concentration in the blood and the risk of sudden cardiac death.[8-11] However, in controlled trials involving patients with cardiac disease who had implantable cardioverter–defibrillators, high doses of EPA and DHA (ranging from 0.9 to 2.6 g per day) did not significantly reduce the rate of ventricular arrhythmias.[1] In the case of supplementation with ALA, an inverse relation with sudden death was observed in a cohort study of women.[12]

Cohort studies have suggested that low doses of n–3 fatty acids should be sufficient to reduce cardiovascular risk.[3,13,14] A dose–response relationship between the intake of EPA and DHA and the risk of cardiac death has not been shown in randomized trials.[1,15] We designed a trial to test the hypothesis that low doses of EPA–DHA (400 mg per day), ALA (2 g per day), or both, in margarines reduce the risk of cardiovascular events among patients who have had a myocardial infarction.

METHODS

STUDY DESIGN AND PATIENTS

The Alpha Omega Trial was a multicenter, double-blind, placebo-controlled trial with a 2-by-2 factorial design, which has been described in detail previously.[16] In brief, we recruited 4837 patients in collaboration with cardiologists at 32 hospitals in the Netherlands. Men and women, 60 to 80 years of age, who had had a clinically diagnosed myocardial infarction up to 10 years before randomization were eligible for participation. Major exclusion criteria were daily consumption of less than 10 g of margarine, use of n–3 fatty-acid supplements, unintended weight loss of more than 5 kg in the previous year, and a diagnosis of cancer with an estimated life expectancy of less than 1 year.

Patients were enrolled from April 2002 through December 2006 and were randomly assigned to receive trial margarines that provided low doses of n–3 fatty acids or placebo, according to a 2-by-2 factorial design, for 40 months. For logistic reasons, all the patients were given placebo margarine during the first 4 to 6 weeks after randomization. After this period, the patients received one of four trial margarines: a margarine with no additional n–3 fatty acids (placebo margarine) or a margarine with approximately 400 mg of EPA–DHA per day, 2 g of ALA per day, or a combination of EPA–DHA and ALA. The doses of the n–3 fatty acids corresponded to the recommended dietary allowances of those fatty acids.[17] In the trial margarines for the active-treatment groups, the various n–3 fatty acids replaced an equivalent amount of the oleic acid in the margarine (see Table 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The ratio of EPA to DHA in the margarines was 3:2. The margarines were similar to each other in taste, odor, texture, and color.

All patients provided written informed consent. 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. The steering committee monitored the progress of the trial, and the data and safety monitoring board monitored the safety of the patients. An interim analysis with the group assignments concealed was performed in February 2007. On the basis of the outcome of that analysis, the steer-

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ing committee decided to continue the trial as planned.

The Alpha Omega trial was initiated by the first author and carried out by the Alpha Omega Study Group. The first author wrote the first draft of the manuscript, and the other authors contributed to subsequent drafts. The margarines were developed by Unilever R&D (Vlaardingen, the Netherlands), which provided an unrestricted grant for the distribution of the trial margarines to the patients. The funding organizations had no role in the design of the study; the collection, analysis, or interpretation of the data; the writing of the manuscript; or the decision to submit the manuscript for publication. The authors vouch for the accuracy and completeness of the reported data as well as the fidelity of the report to the study protocol. The protocol, including the statistical analysis plan, is available at NEJM.org.

PROCEDURES

The study intervention in our trial was replacement of margarines that the patients usually used with study margarines, as opposed to supplementation with fish-oil capsules, which has been used in previous trials. After the patients underwent randomization, they received eight tubs, each of which contained 250 g of margarine, the specific composition of which could not be identified. The patients received a new set of tubs every 12 weeks. Unused margarine tubs were returned. The daily intakes of margarine and n–3 fatty acids were calculated on the basis of the amount of margarine that the patients were given and the amount that was returned unused. An objective measure of adherence was obtained by determining the levels of fatty acids in plasma cholesteryl esters in random subgroups of approximately 800 patients at baseline and after 20 and 40 months of intervention.[16]

At baseline, anthropometric measures were assessed, and blood pressure and heart rate were measured. In addition, nonfasting blood samples were obtained for the measurement of serum lipid and plasma glucose levels.[16] Demographic factors, lifestyle characteristics, and medication and medical histories were assessed with the use of questionnaires. Diabetes was considered to be present if a patient reported having received the diagnosis from a physician, was taking antidiabetic drugs, or had an elevated plasma glucose level (≥7.8 mmol per liter [140.5 mg per deciliter] in the case of patients who had fasted more than 4 hours or ≥11.1 mmol per liter [200.0 mg per deciliter] in the case of nonfasting patients). Baseline examinations were repeated after 20 months in a random sample of 810 patients and after 40 months in the 2531 patients (52.3%) who completed the trial before January 1, 2009. Owing to budget constraints, assessments of the remainder of the cohort were made with the use of questionnaires regarding demographic factors, lifestyle characteristics, and medication and medical histories that were mailed to the patients. Trained research staff performed structured telephone interviews with more than 90% of the cohort 12 and 24 months after the start of the intervention to collect data on adherence, cardiovascular events, adverse events, changes in medication, intake of fish, and use of n–3 fatty acid supplements.

END POINTS

We followed all patients, including those who discontinued the use of the trial margarine during the course of the trial, for the ascertainment of clinical events. We monitored the vital status of all the patients by means of a computerized link with municipal registries. In the case of patients who died, the death certificate was obtained from Statistics Netherlands, and the patient's primary physician filled out a standard form listing the primary and contributing causes of death. Additional information on fatal events was obtained from hospitals and family members. Events were coded by three members of the end-point adjudication committee, who were unaware of the identity of the patient, the identity of the treating physician, and the patient's assigned study group. During regular meetings, all information about the underlying causes of death was discussed by the committee members. In the case of disagreement, discussion among the three members took place until consensus was reached.

Patients were asked to record all hospitalizations in a structured diary. Follow-up to ascertain the occurrence of nonfatal cardiovascular events (myocardial infarction, cardiac arrest, and stroke) and cardiac interventions (percutaneous coronary intervention [PCI], coronary-artery bypass grafting [CABG], and placement of implantable cardioverter–defibrillators) was performed by research staff through annual telephone interviews. Self-reported nonfatal cardiovascular events and car-

diac interventions were verified against hospital records by trained research nurses or the research physician. Only events for which documentation of the clinical diagnosis (e.g., hospital discharge letters) could be retrieved were considered in the analysis. We also monitored incident prostate cancer, because a meta-analysis of epidemiologic studies suggested that ALA could be associated with an increased risk of prostate cancer.[3] Incident prostate cancer included fatal cases and verified hospital admissions for prostate cancer. Causes of death were coded according to the *International Classification of Diseases, 10th Revision*.[18]

The primary end point of this trial was major cardiovascular events, which comprised fatal and nonfatal cardiovascular disease and the cardiac interventions PCI and CABG.[16] Secondary end points were incident cardiovascular disease, fatal cardiovascular disease, fatal coronary heart disease, ventricular-arrhythmia–related events (sudden death, fatal and nonfatal cardiac arrest, and placement of implantable cardioverter–defibrillators), and death from any cause.

STATISTICAL ANALYSIS

Pretrial and post hoc power calculations for the study are provided in the Supplementary Appendix. Analysis of the data was performed before the treatment codes were broken, by an independent biostatistician who used a prespecified statistical analysis plan. Analyses were performed according to the intention-to-treat principle. Time-to-event data were analyzed with the use of the Kaplan–Meier method and the log-rank test. The two groups that received EPA–DHA were combined and compared with the two groups that did not receive EPA–DHA. Similarly, the two groups that received ALA were combined and compared with the two groups that did not receive ALA. Hazard ratios and 95% confidence intervals were calculated with the use of Cox proportional-hazards models.

Prespecified subgroup analyses were performed according to age, sex, time since the index myocardial infarction, baseline intake of fish and of EPA–DHA, and use of margarine during the trial. In addition, a post hoc analysis (i.e., after unblinding of the data) was performed according to the presence or absence of diabetes. No adjustments have been made for multiple comparisons. Two-sided P values of less than 0.05 were considered to indicate statistical significance. Data were analyzed with the use of SAS, version 9.2, and SPSS, version 17.0, statistical software.

RESULTS

PATIENTS

We enrolled 4837 patients — 3783 men (78.2%) and 1054 women (21.8%) (Fig. 1). The median period between the index myocardial infarction and entry into the study was 3.7 years (interquartile range, 1.7 to 6.3). In the case of 99.3% of the patients, the index myocardial infarction could be verified in hospital records. Diabetes was present in 1014 patients (21.0%). Antithrombotic agents were used by almost all the patients (97.5%), antihypertensive drugs by 89.7%, lipid-modifying treatment (mainly statins) by 86.0%, and antiarrhythmic drugs by 3.0%. Hormone-replacement therapy was reported by 2.2% of the women. A total of 16.9% of the study patients were current smokers, and 24.2% were obese (i.e., had a body-mass index [the weight in kilograms divided by the square of the height in meters] of 30 or more). At baseline, the median consumption of fish was 14.9 g per day (interquartile range, 6.1 to 18.7), and the median intake of EPA–DHA was 130 mg per day (interquartile range, 60 to 210). A total of 225 patients (4.7%) reported that they used commercially available n–3 fatty acid supplements at some point during the course of the trial. The four study groups did not differ significantly with respect to demographic factors, lifestyle characteristics, or cardiovascular risk factors (Table 1).

STUDY INTERVENTION

The mean (±SD) intake of trial margarine was 18.8±4.7 g per day; 90.5% of the patients adhered fully to the protocol and consumed a mean of 20.6±2.8 g of margarine per day. Patients in the two EPA–DHA groups received, on average, an additional 226 mg of EPA and 150 mg of DHA per day, and those in the two ALA groups received an additional 1.9 g of ALA per day. The median follow-up period was 40.8 months (interquartile range, 37.2 to 41.5), which included the first 4 to 6 weeks in which all the patients received placebo margarine. After 20 months, the additional intake of n–3 fatty acids was reflected in the fatty-acid composition of serum cholesteryl esters: ALA

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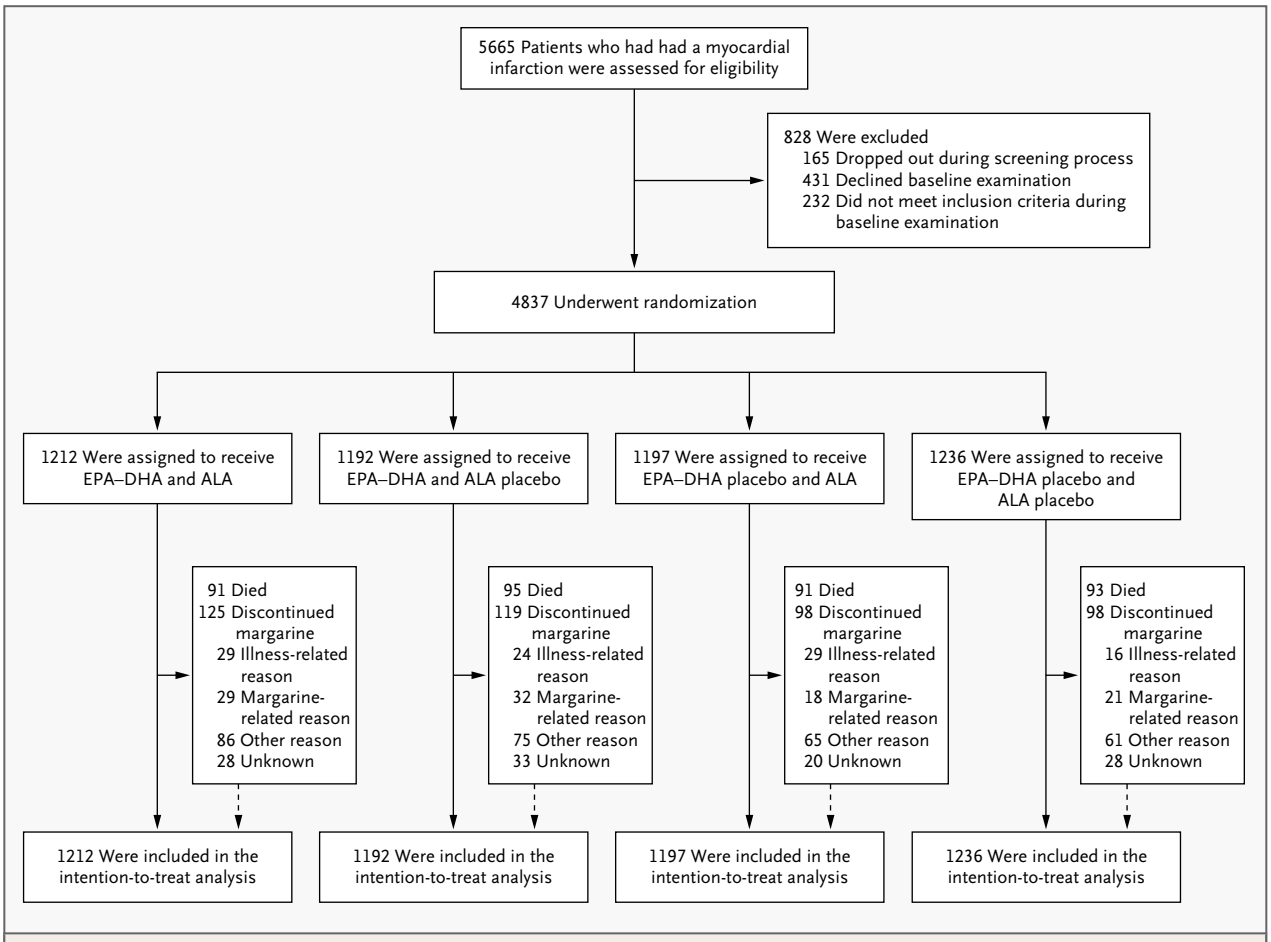

Figure 1. Screening, Randomization, and Follow-up.

Patients could have more than one reason for discontinuation of margarine use. ALA denotes alpha-linolenic acid, DHA docosahexaenoic acid, and EPA eicosapentaenoic acid.

supplementation in the margarine increased serum ALA by 69.6% as compared with placebo and EPA–DHA only, and EPA–DHA supplementation increased serum EPA by 53.3% and serum DHA by 28.6%, as compared with placebo and ALA only (Fig. 1 in the Supplementary Appendix). These changes were already apparent after 3 months in a pilot study of 76 patients, in which ALA increased by 49.0%, EPA by 41.3%, and DHA by 13.5%. The changes in the serum concentration of n–3 fatty acids from baseline to 20 months were maintained until 40 months. Serum triglyceride levels and other markers of risk did not change significantly in the groups that received supplemented margarine, as compared with the placebo group, during the course of the trial (Table 2 in the Supplementary Appendix).

EFFECT OF n–3 FATTY ACIDS ON STUDY END POINTS

No patients were lost to follow-up. We accrued 15,531 person-years of follow-up data, and 671 patients (13.9%) had a major cardiovascular event. The effects of n–3 fatty acids on end points are presented in Table 2. Kaplan–Meier curves showed that EPA–DHA (either alone or in combination with ALA), as compared with placebo and ALA only, had no effect on the rate of major cardiovascular events (Fig. 2). The two groups that received ALA had a rate of major cardiovascular events that was 9% lower than the rate in the groups that received placebo or EPA–DHA only, a difference that was not significant (hazard ratio, 0.91; 95% confidence interval [CI], 0.78 to 1.05; P=0.20). The Kaplan–Meier curve for fatal coronary heart disease showed that until approxi-

Table 1. Baseline Characteristics of the Patients, According to Study Group.*

Variable	EPA–DHA and ALA (N=1212)	EPA–DHA (N=1192)	ALA (N=1197)	Placebo (N=1236)
Age — yr	69.1±5.5	69.1±5.6	69.0±5.6	68.9±5.6
Male sex — no. (%)	946 (78.1)	931 (78.1)	933 (77.9)	973 (78.7)
Time since myocardial infarction — yr	4.2±3.1	4.3±3.2	4.4±3.3	4.3±3.3
Self-reported history of stroke — no. (%)	92 (7.6)	83 (7.0)	89 (7.4)	81 (6.6)
Diabetes mellitus — no. (%)				
Patients with diabetes	245 (20.2)	262 (22.0)	258 (21.6)	249 (20.1)
Patients taking antidiabetic drugs	180 (14.9)	184 (15.4)	192 (16.0)	184 (14.9)
Use of cardiovascular medication — no. (%)				
Antithrombotic agents	1166 (96.2)	1170 (98.2)	1172 (97.9)	1210 (97.9)
Blood-pressure–lowering drugs	1088 (89.8)	1090 (91.4)	1058 (88.4)	1104 (89.3)
Lipid-lowering drugs	1058 (87.3)	1017 (85.3)	1034 (86.4)	1052 (85.1)
Antiarrhythmic drugs	34 (2.8)	37 (3.1)	31 (2.6)	42 (3.4)
Systolic blood pressure — mm Hg	140.9±22.1	142.3±21.6	141.4±21.2	141.9±21.6
Plasma glucose — mmol/liter†	6.2±2.2	6.2±2.0	6.2±2.0	6.3±2.1
Serum lipids — mmol/liter‡				
Cholesterol				
Total	4.69±0.96	4.77±0.98	4.70±0.95	4.75±0.99
LDL	2.55±0.81	2.63±0.84	2.57±0.83	2.60±0.87
HDL	1.29±0.33	1.29±0.35	1.28±0.34	1.28±0.34
Triglycerides				
Median	1.64	1.63	1.65	1.69
Interquartile range	1.19–2.26	1.22–2.30	1.21–2.31	1.22–2.38
Body-mass index§				
Mean	27.8±4.0	27.7±3.7	27.8±3.8	27.8±3.9
≥30 — no. (%)	292 (24.1)	304 (25.5)	284 (23.7)	290 (23.5)
Current smoker — no. (%)	181 (14.9)	200 (16.8)	208 (17.4)	223 (18.0)
Consumption of ≥1 glass of alcohol/wk — no./total no. (%)	908/1209 (75.1)	864/1191 (72.5)	889/1195 (74.4)	910/1232 (73.9)
Consumption of fish — g/day				
Median	15.0	14.9	15.0	14.5
Interquartile range	5.9–18.7	6.5–18.4	7.4–20.9	5.9–18.4
Fish consumption ≥5 g/wk — no. (%)	976 (80.5)	971 (81.5)	996 (83.2)	998 (80.7)
Intake of EPA–DHA outside the study treatment — mg/day				
Median	130	120	130	120
Interquartile range	50–210	60–200	60–220	60–200

* Plus–minus values are means ±SD. ALA denotes alpha-linolenic acid, DHA docosahexaenoic acid, EPA eicosapentaenoic acid, HDL high-density lipoprotein, and LDL low-density lipoprotein.
† To convert the values for glucose to milligrams per deciliter, divide by 0.05551.
‡ To convert the values for cholesterol to milligrams per deciliter, divide by 0.02586. To convert the values for triglycerides to milligrams per deciliter, divide by 0.01129.
§ The body-mass index is the weight in kilograms divided by the square of the height in meters.

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Table 2. Primary and Secondary Outcomes, According to n–3 Fatty-Acid Supplementation.*

Outcome	EPA–DHA (N=2404)		Placebo or ALA Only (N=2433)		Hazard Ratio (95% CI)†	P Value
	no. (%)	*rate/1000 patient-yr*	*no. (%)*	*rate/1000 patient-yr*		
Primary outcome: major cardiovascular events‡	336 (14.0)	46.0	335 (13.8)	45.7	1.01 (0.87–1.17)	0.93
Secondary outcomes						
Incident cardiovascular disease	170 (7.1)	22.4	185 (7.6)	24.3	0.92 (0.75–1.13)	0.43
Death from cardiovascular disease	80 (3.3)	10.3	82 (3.4)	10.5	0.98 (0.72–1.33)	0.89
Death from coronary heart disease	67 (2.8)	8.7	71 (2.9)	9.1	0.95 (0.68–1.32)	0.75
Ventricular-arrhythmia–related events§	67 (2.8)	8.7	74 (3.0)	9.6	0.90 (0.65–1.26)	0.55
Death from any cause	186 (7.7)	24.0	184 (7.6)	23.7	1.01 (0.82–1.24)	0.92
	ALA (N=2409)		**Placebo or EPA–DHA Only (N=2428)**		**Hazard Ratio (95% CI)†**	**P Value**
	no. (%)	*rate/1000 patient-yr*	*no. (%)*	*rate/1000 patient-yr*		
Primary outcome: major cardiovascular events‡	319 (13.2)	43.6	352 (14.5)	48.1	0.91 (0.78–1.05)	0.20
Secondary outcomes						
Incident cardiovascular disease	168 (7.0)	22.1	187 (7.7)	24.5	0.90 (0.73–1.11)	0.34
Death from cardiovascular disease	78 (3.2)	10.1	84 (3.5)	10.8	0.94 (0.69–1.27)	0.67
Death from coronary heart disease	66 (2.7)	8.6	72 (3.0)	9.2	0.92 (0.66–1.29)	0.64
Ventricular-arrhythmia–related events§	62 (2.6)	8.1	79 (3.3)	10.2	0.79 (0.57–1.10)	0.16
Death from any cause	182 (7.6)	23.5	188 (7.7)	24.1	0.97 (0.79–1.19)	0.80

* For these analyses, the two groups that received eicosapentaenoic acid (EPA) with docosahexaenoic acid (DHA) were combined and compared with the two groups that did not receive EPA–DHA (i.e., the groups that received either placebo or only alpha-linolenic acid [ALA]). Similarly, the two groups that received ALA were combined and compared with the two groups that did not receive ALA (i.e., the groups that received either placebo or only EPA–DHA).
† The hazard ratios and 95% confidence intervals (CIs) were calculated with the use of Cox proportional-hazards models.
‡ Major cardiovascular events comprised fatal and nonfatal cardiovascular events and the cardiac interventions percutaneous coronary intervention and coronary-artery bypass grafting.
§ Ventricular-arrhythmia–related events comprised sudden death, fatal and nonfatal cardiac arrest, and placement of implantable cardioverter–defibrillators.

mately 30 months after the start of the intervention, the patients in the two groups that received EPA–DHA had a lower risk of fatal coronary heart disease than did those who received placebo or ALA only, but this effect disappeared toward the end of the trial (Fig. 2). There were nonsignificant reductions of 10% and of 21% in ventricular-arrhythmia–related events among patients who received EPA–DHA and ALA, respectively (Table 2, and Fig. 2 in the Supplementary Appendix).

SUBGROUP ANALYSES

Analyses of prespecified subgroups showed that the two groups that received EPA–DHA did not have significantly lower rates of major cardiovascular events than did the two groups that received no EPA–DHA, and the two groups that received ALA did not have significantly lower rates of major cardiovascular events than did the two groups that received no ALA. However, there was a 27% reduction in major cardiovascular events with ALA among women, which approached significance (hazard ratio, 0.73; 95% CI, 0.51 to 1.03; P=0.07) (Fig. 3). Patients with diabetes had a higher risk of all cardiovascular end points than did patients without diabetes (Table 3). A post hoc, exploratory analysis of data from these diabetic patients showed that the rates of fatal coronary heart disease and arrhythmia-related events were lower among patients in the EPA–DHA groups than among those in the groups that received no EPA–DHA (hazard ratio for fatal

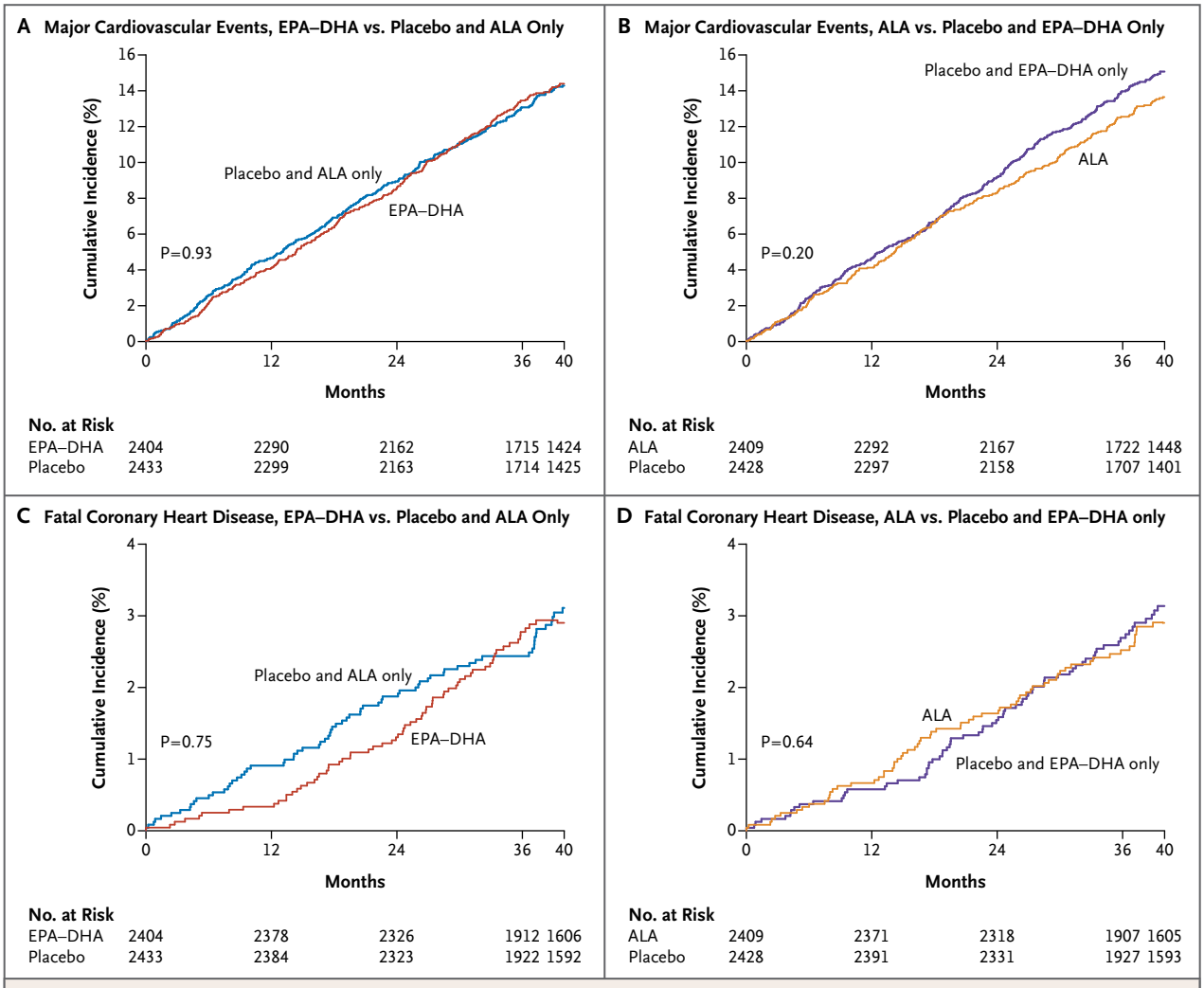

Figure 2. Kaplan–Meier Curves for Primary and Secondary End Points.

Kaplan–Meier curves are shown for the cumulative incidence of major cardiovascular events (the primary end point) and fatal coronary heart disease (a secondary end point) among 4837 patients who had had a myocardial infarction and were assigned to receive a study margarine containing supplemental eicosapentaenoic acid (EPA) combined with docosahexaenoic acid (DHA), a margarine containing alpha-linolenic acid (ALA), a margarine containing both EPA–DHA and ALA, or a placebo margarine.

coronary heart disease, 0.51; 95% CI, 0.27 to 0.97; hazard ratio for arrhythmia-related events, 0.51; 95% CI, 0.24 to 1.11) (Table 3, and Fig. 3 in the Supplementary Appendix). The rate of arrhythmia-related events was also reduced in the ALA groups, as compared with the groups that received no ALA (hazard ratio, 0.39; 95% CI, 0.17 to 0.88).

ADVERSE EVENTS

The rate of self-reported gastrointestinal symptoms did not differ significantly among the groups (Table 3 in the Supplementary Appendix). ALA supplementation and EPA–DHA supplementation

Figure 3 (facing page). Effect of EPA–DHA Supplementation and ALA Supplementation on the Primary End Point in Subgroups of Patients.

The primary end point of major cardiovascular events comprised fatal and nonfatal cardiovascular events and the cardiac interventions percutaneous coronary intervention and coronary-artery bypass grafting. Panel A shows the effects of supplementation with eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and Panel B the effects of supplementation with alpha-linolenic acid (ALA). Hazard ratios and 95% confidence intervals were calculated with the use of Cox proportional-hazards models. The size of each square is proportional to the number of patients; horizontal lines indicate 95% confidence intervals. P values are for the difference between active treatment and placebo.

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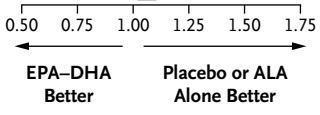
Subgroup	Primary End Point: EPA–DHA (no./total no.)	Primary End Point: Placebo or ALA alone (no./total no.)	Hazard Ratio (95% CI)	P Value
All patients	336/2404	335/2433	1.01 (0.87–1.17)	0.93
Age				
<70 yr	175/1351	172/1389	1.04 (0.84–1.29)	0.71
≥70 yr	161/1053	163/1044	0.97 (0.78–1.20)	0.76
Sex				
Male	277/1877	265/1906	1.06 (0.89–1.25)	0.51
Female	59/527	70/527	0.82 (0.58–1.16)	0.27
Time since myocardial infarction				
<3.7 yr	144/1197	154/1195	0.92 (0.73–1.16)	0.47
≥3.7 yr	188/1184	176/1208	1.10 (0.89–1.35)	0.39
Baseline fish intake				
<5 g/day	70/457	55/439	1.22 (0.86–1.74)	0.27
≥5 g/day	235/1722	244/1762	0.98 (0.82–1.17)	0.78
Baseline EPA–DHA intake				
<50 mg/day	73/470	59/435	1.15 (0.81–1.62)	0.43
≥50 mg/day	232/1709	240/1766	0.99 (0.83–1.18)	0.89
Intake of trial margarine				
<10 g/day	41/241	30/188	1.02 (0.64–1.63)	0.95
10 to <20 g/day	139/965	145/944	0.92 (0.73–1.16)	0.49
≥20 g/day	156/1198	160/1301	1.06 (0.85–1.32)	0.60



B

Subgroup	Primary End Point: ALA (no./total no.)	Primary End Point: Placebo or EPA–DHA alone (no./total no.)	Hazard Ratio (95% CI)	P Value
All patients	319/2409	352/2428	0.91 (0.78–1.05)	0.20
Age				
<70 yr	158/1366	189/1374	0.83 (0.67–1.03)	0.08
≥70 yr	161/1043	163/1054	1.00 (0.80–1.24)	0.98
Sex				
Male	264/1879	278/1904	0.96 (0.81–1.13)	0.60
Female	55/530	74/524	0.73 (0.51–1.03)	0.07
Time since myocardial infarction				
<3.7 yr	142/1183	156/1209	0.92 (0.73–1.15)	0.45
≥3.7 yr	174/1202	190/1190	0.91 (0.74–1.12)	0.36
Baseline fish intake				
<5 g/day	56/437	69/459	0.84 (0.59–1.20)	0.34
≥5 g/day	234/1756	245/1728	0.93 (0.78–1.12)	0.45
Baseline EPA–DHA intake				
<50 mg/day	63/446	69/459	0.94 (0.67–1.33)	0.73
≥50 mg/day	227/1747	245/1728	0.91 (0.76–1.09)	0.29
Intake of trial margarine				
<10 g/day	33/211	38/218	0.88 (0.55–1.40)	0.59
10 to <20 g/day	144/991	140/918	0.95 (0.75–1.20)	0.65
≥20 g/day	142/1207	174/1292	0.87 (0.69–1.08)	0.20

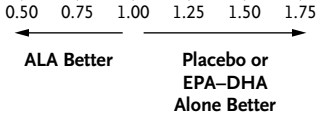


Table 3. Cardiovascular Outcomes in Patients, According to the Presence or Absence of Diabetes and n–3 Fatty-Acid Supplementation.*

Outcome	EPA–DHA (N=2404)		Placebo or ALA Only (N=2433)		Hazard Ratio (95% CI)†	P Value
	no./total no. (%)	*rate/1000 patient-yr*	*no./total no. (%)*	*rate/1000 patient-yr*		
Patients with diabetes						
Major cardiovascular events‡	78/507 (15.4)	51.9	98/507 (19.3)	66.4	0.78 (0.58–1.05)	0.11
Incident cardiovascular disease	39/507 (7.7)	24.8	59/507 (11.6)	38.2	0.65 (0.43–0.97)	0.04
Death from cardiovascular disease	19/507 (3.7)	11.8	31/507 (6.1)	19.6	0.60 (0.34–1.07)	0.08
Death from coronary heart disease	14/507 (2.8)	8.7	27/507 (5.3)	17.1	0.51 (0.27–0.97)	0.04
Ventricular-arrhythmia–related events§	10/507 (2.0)	6.2	19/507 (3.7)	12.2	0.51 (0.24–1.11)	0.09
Patients without diabetes						
Major cardiovascular events‡	258/1897 (13.6)	44.5	237/1926 (12.3)	40.5	1.10 (0.92–1.31)	0.30
Incident cardiovascular disease	131/1897 (6.9)	21.7	126/1926 (6.5)	20.8	1.05 (0.82–1.34)	0.72
Death from cardiovascular disease	61/1897 (3.2)	9.9	51/1926 (2.6)	8.2	1.21 (0.83–1.75)	0.32
Death from coronary heart disease	53/1897 (2.8)	8.7	44/1926 (2.3)	7.1	1.21 (0.81–1.81)	0.34
Ventricular-arrhythmia–related events§	57/1897 (3.0)	9.3	55/1926 (2.9)	9.0	1.04 (0.72–1.51)	0.83
	ALA (N=2409)		**Placebo or EPA–DHA Only (N=2428)**		**Hazard Ratio (95% CI)†**	**P Value**
	no./total no. (%)	*rate/1000 patient-yr*	*no./total no. (%)*	*rate/1000 patient-yr*		
Patients with diabetes						
Major cardiovascular events‡	83/503 (16.5)	56.2	93/511 (18.2)	61.8	0.91 (0.68–1.22)	0.53
Incident cardiovascular disease	48/503 (9.5)	31.2	50/511 (9.8)	31.7	0.98 (0.66–1.46)	0.94
Death from cardiovascular disease	23/503 (4.6)	14.6	27/511 (5.3)	16.7	0.87 (0.50–1.52)	0.63
Death from coronary heart disease	18/503 (3.6)	11.5	23/511 (4.5)	14.2	0.80 (0.43–1.48)	0.48
Ventricular-arrhythmia–related events§	8/503 (1.6)	5.1	21/511 (4.1)	13.1	0.39 (0.17–0.88)	0.02
Patients without diabetes						
Major cardiovascular events‡	236/1906 (12.4)	40.4	259/1917 (13.5)	44.6	0.91 (0.76–1.08)	0.28
Incident cardiovascular disease	120/1906 (6.3)	19.8	137/1917 (7.1)	22.7	0.88 (0.69–1.12)	0.29
Death from cardiovascular disease	55/1906 (2.9)	8.9	57/1917 (3.0)	9.2	0.97 (0.67–1.40)	0.87
Death from coronary heart disease	48/1906 (2.5)	7.9	49/1917 (2.6)	7.9	0.98 (0.66–1.46)	0.93
Ventricular-arrhythmia–related events§	54/1906 (2.8)	8.8	58/1917 (3.0)	9.5	0.93 (0.64–1.35)	0.71

* Diabetes was considered to be present if a patient reported having received the diagnosis from a physician, was taking antidiabetic drugs, or had an elevated plasma glucose level (≥7.8 mmol per liter [140.5 mg per deciliter] in the case of patients who had fasted more than 4 hours or ≥11.1 mmol per liter [200.0 mg per deciliter] in the case of nonfasting patients). A total of 1014 patients had diabetes, and 3823 did not have diabetes. For these analyses, the two groups that received eicosapentaenoic acid (EPA) with docosahexaenoic acid (DHA) were combined and compared with the two groups that did not receive EPA–DHA (i.e., the groups that received either placebo or only alpha-linolenic acid [ALA]) . Similarly, the two groups that received ALA were combined and compared with the two groups that did not receive ALA (i.e., the groups that received placebo or only EPA–DHA).

† The hazard ratios and 95% confidence intervals were calculated with the use of Cox proportional-hazards models.

‡ Major cardiovascular events comprised fatal and nonfatal cardiovascular events and the cardiac interventions percutaneous coronary intervention and coronary-artery bypass grafting.

§ Ventricular-arrhythmia–related events comprised sudden death, fatal and nonfatal cardiac arrest, and placement of implantable cardioverter–defibrillators.

were not related to the incidence of prostate cancer or to death from cancer. Four patients specifically attributed their adverse events to the use of trial margarines, but the members of the data and safety monitoring board evaluated these cases and judged that there were no causal relationships.

10.1056/NEJMoa1003603 NEJM.ORG

DISCUSSION

An additional daily intake of an average of 376 mg of EPA–DHA or 1.9 g of ALA did not significantly reduce the rate of major cardiovascular events in patients who had had a myocardial infarction and who were receiving state-of-the-art antihypertensive, antithrombotic, and lipid-modifying therapy. A prespecified analysis according to sex showed that there were fewer major cardiovascular events among women who received ALA than among women who received placebo, a reduction that approached significance. The number of adverse events did not differ significantly among the groups during the course of the intervention.

In this study, a low dose of EPA–DHA had no effect on the rate of major cardiovascular events in patients who had had a myocardial infarction. However, previous randomized, controlled trials involving patients with cardiac disease did show protective effects of EPA, either with or without DHA, on various composite cardiovascular end points.[19-21] This discrepancy may be related to differences between patient populations in age, sex distribution, and presence or absence of a history of coronary artery disease. The patient population in our trial consisted mainly of men, the average age of the patients was 69 years, and the index myocardial infarction had occurred an average of 4 years before enrollment. In contrast, the participants in the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI) trials were patients who had had a recent myocardial infarction (<3 months before enrollment)[19] or patients with heart failure (GISSI-HF; ClinicalTrials.gov number, NCT00336336),[20] and the patients in the Japan Eicosapentaenoic Acid (EPA) Lipid Intervention Study (JELIS; NCT00231738) were mostly women.[21] These populations were also about 10 years younger than were the patients in our study.

The lack of an effect of EPA–DHA in our trial could be due to an improvement in cardioprotective drug treatment, such as that seen in the time between the 1995–1996 and the 2006–2007 European Action on Secondary Prevention through Intervention to Reduce Events (EUROASPIRE) surveys.[22] The introduction of statins represented a major change in the treatment of patients with cardiovascular disease in the early 1990s, as shown in the GISSI-Prevenzione trial,[19] in which only 5% of the patients received statins at baseline (1993–1995), whereas 46% were receiving them after 42 months of intervention. In our trial, 85% of the patients were receiving statins. The survival rates in the GISSI-Prevenzione trial were lower than those in our study (Table 2). In recent years, not only has there been improvement in survival but the causes of death have shifted from cardiovascular to noncardiovascular causes.[23] Consequently, among patients who have had a myocardial infarction but who are receiving good clinical care and are at relatively low risk for future cardiovascular events, such as the patients in the Alpha Omega Trial, a beneficial effect of low doses of EPA–DHA is difficult to prove.[24] Finally, we cannot exclude the possibility that EPA and DHA had no therapeutic effect in patients who had had a myocardial infarction but whose condition was stable and who were at relatively low risk for future cardiovascular events.

We observed a nonsignificant 9% reduction in the primary end point with ALA supplementation, as compared with placebo and EPA–DHA only, in the total patient population and a 27% reduction, which approached significance, among women. The Kaplan–Meier curves started to diverge after approximately 20 months, especially among women (Fig. 4 in the Supplementary Appendix), suggesting that there was a cumulative effect over time. ALA may slow the formation and calcification of atherosclerotic plaque, as suggested by the results of cross-sectional analyses in the National Heart, Lung, and Blood Institute Family Heart Study.[25,26] Other possible mechanisms of a beneficial effect of ALA on cardiovascular disease are plaque stabilization[27] and antiarrhythmic effects,[7] either directly or through desaturation and elongation of ALA into EPA. It is also possible that this apparent effect was due to the play of chance. Additional trials involving high-risk patients, however, are needed to prove a cardioprotective effect of ALA.

Patients with diabetes who have had a myocardial infarction are particularly prone to ventricular arrhythmias and sudden death.[4,28] In a post hoc, exploratory analysis of data from these diabetic patients, we found reductions in cardiovascular end points with EPA–DHA, as compared with placebo, that were in line with those shown in the GISSI Prevenzione trial.[19] The strongest effects — reductions of approximately 50% —

were the effects on the rates of fatal coronary heart disease and arrhythmia-related events. The rate of arrhythmia-related events was also reduced with ALA as compared with placebo or EPA–DHA only. This finding is supported by the results of a cohort study involving women, in which ALA intake was inversely associated with the risk of sudden death.[12] However, it is important to note that our results with respect to patients with diabetes are only hypothesis-generating and do not permit definitive conclusions to be drawn.

In conclusion, in this trial involving patients who had had a myocardial infarction and who were receiving good clinical care, low doses of n–3 fatty acids did not significantly reduce the rates of cardiovascular end points.

Supported by the Netherlands Heart Foundation, the National Institutes of Health, and Unilever R&D, the Netherlands. Unilever provided an unrestricted grant for the distribution of trial margarines to the patients.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org

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