ORIGINAL ARTICLE

Effects of n–3 Fatty Acid Supplements in Diabetes Mellitus

The ASCEND Study Collaborative Group*

ABSTRACT

BACKGROUND

Increased intake of n–3 fatty acids has been associated with a reduced risk of cardiovascular disease in observational studies, but this finding has not been confirmed in randomized trials. It remains unclear whether n–3 (also called omega-3) fatty acid supplementation has cardiovascular benefit in patients with diabetes mellitus.

METHODS

We randomly assigned 15,480 patients with diabetes but without evidence of atherosclerotic cardiovascular disease to receive 1-g capsules containing either n–3 fatty acids (fatty acid group) or matching placebo (olive oil) daily. The primary outcome was a first serious vascular event (i.e., nonfatal myocardial infarction or stroke, transient ischemic attack, or vascular death, excluding confirmed intracranial hemorrhage). The secondary outcome was a first serious vascular event or any arterial revascularization.

RESULTS

During a mean follow-up of 7.4 years (adherence rate, 76%), a serious vascular event occurred in 689 patients (8.9%) in the fatty acid group and in 712 (9.2%) in the placebo group (rate ratio, 0.97; 95% confidence interval [CI], 0.87 to 1.08; P=0.55). The composite outcome of a serious vascular event or revascularization occurred in 882 patients (11.4%) and 887 patients (11.5%), respectively (rate ratio, 1.00; 95% CI, 0.91 to 1.09). Death from any cause occurred in 752 patients (9.7%) in the fatty acid group and in 788 (10.2%) in the placebo group (rate ratio, 0.95; 95% CI, 0.86 to 1.05). There were no significant between-group differences in the rates of nonfatal serious adverse events.

CONCLUSIONS

Among patients with diabetes without evidence of cardiovascular disease, there was no significant difference in the risk of serious vascular events between those who were assigned to receive n–3 fatty acid supplementation and those who were assigned to receive placebo. (Funded by the British Heart Foundation and others; Current Controlled Trials number, ISRCTN60635500; ClinicalTrials.gov number, NCT00135226.)

The members of the writing committee (Louise Bowman, M.D., Marion Mafham, M.D., Karl Wallendszus, M.Sc., Will Stevens, Ph.D., Georgina Buck, M.Sc., Jill Barton, Kevin Murphy, Theingi Aung, M.D., Richard Haynes, D.M., Jolyon Cox, D.Phil., Aleksandra Murawska, M.Sc., Allen Young, Ph.D., Michael Lay, D.Phil., Fang Chen, M.D., Ph.D., Emily Sammons, M.B., Ch.B., Emma Waters, M.B., B.S., Amanda Adler, M.D., Ph.D., Jonathan Bodansky, M.D., Andrew Farmer, D.M., Roger McPherson, B.M., F.R.C.Ophth., Andrew Neil, D.Sc., F.R.C.P., David Simpson, Richard Peto, F.R.S., F.Med.Sci., Colin Baigent, F.F.P.H., F.R.C.P., Rory Collins, F.R.S., F.Med.Sci., Sarah Parish, D.Phil., and Jane Armitage, F.R.C.P., F.F.P.H.) assume responsibility for the overall content and integrity of this article. The affiliations of the members of the writing committee are listed in the Appendix. Address reprint requests to Dr. Bowman at the Medical Research Council, Population Health Research Unit, Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health, Richard Doll Bldg., Old Road Campus, Roosevelt Dr., Oxford OX3 7LF, United Kingdom, or at ascend@ndph.ox.ac.uk or louise.bowman@ndph.ox.ac.uk.

*A complete list of the members of the ASCEND Study Collaborative Group is provided in Supplementary Appendix 1, available at NEJM.org.

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Observational studies in different populations have suggested that fish consumption once or twice a week is associated with a reduced risk of heart disease.[1,2] In 2002, a systematic review concluded that eating the equivalent of 40 to 60 g of fish daily (providing about 0.2 to 1.0 g of n–3 fatty acids) was associated with nearly a 50% reduction in cardiovascular mortality.[3] However, randomized trials of supplementation with n–3 (also called omega-3) fatty acids have shown conflicting results regarding the effects on fatal or nonfatal outcomes.[4-8] Meta-analyses of these trials have generally not identified significant beneficial effects of n–3 fatty acid supplementation on major vascular events.[9,10]

However, interest has persisted about possible benefits with respect to particular types of vascular events (including arrhythmias, heart failure, and death from coronary heart disease) on the basis, at least in part, of selected results in open-label trials.[4,11,12] A recent meta-analysis[10] was conducted of 10 long-term, randomized trials of n–3 fatty acids as either primary or secondary prevention in a total of 78,000 participants, including approximately one third with diabetes or dysglycemia who were enrolled mainly in two large trials.[8,13] During a mean follow-up of 4.4 years, the meta-analysis did not show significantly lower rates of coronary heart disease or major vascular events among the patients who had received n–3 fatty acids than among those in the control groups.

The American Heart Association guidelines currently recommend n–3 fatty acid supplements for secondary prevention of coronary heart disease,[14] and fish consumption for primary prevention is recommended in cardiovascular disease prevention guidelines.[15] Since patients with diabetes have two to three times the risk of cardiovascular disease as the general population,[16] a safe dietary supplement with even a modest protective effect could have a major public health benefit.

We performed the randomized ASCEND (A Study of Cardiovascular Events in Diabetes) to assess the efficacy and safety of daily supplementation with n–3 fatty acids, as compared with placebo, in patients with diabetes without evidence of cardiovascular disease at trial entry. Using a factorial design in the same trial, we also randomly assigned the patients to receive a daily regimen of either 100 mg of aspirin or placebo, findings that are now reported elsewhere in the *Journal*.[17]

Methods

Trial Oversight

ASCEND was designed and conducted by independent investigators in the Clinical Trial Service Unit at the University of Oxford (the regulatory trial sponsor). The trial methods, patient characteristics, and data analysis plan (including outcome definitions) have been reported previously.[18,19] The protocol (available with the full text of this article at NEJM.org) was approved by the North West Multicenter Research Ethics Committee. The trial was funded by the British Heart Foundation. Capsules containing the n–3 fatty acids and matching placebo (along with funding for packaging) were provided by Mylan (and formerly by Solvay and Abbott), and Bayer provided the aspirin and placebo. Mylan, Solvay, and Abbott had nonvoting representation at meetings of the steering committee and provided comments regarding the trial design and draft manuscript but otherwise had no role in data collection or analysis or in the decision to submit the manuscript for publication.

The manuscript was prepared by the writing committee and was reviewed and approved for submission by the steering committee. The first and last members of the writing committee vouch for the completeness and accuracy of the data and analyses, and for the fidelity of the trial to the study protocol and data analysis plan. Requests for data sharing will be handled in line with the data access and sharing policy of the Nuffield Department of Population Health, University of Oxford (available at www.ndph.ox.ac.uk/about/data-access-policy).

Patients

Men and women who were at least 40 years of age (without an upper age limit) were considered eligible if they had received a diagnosis of diabetes mellitus (any type) but did not have evidence of cardiovascular disease. Key exclusion criteria were a clear indication or contraindication for the receipt of n–3 fatty acids or (with respect to the factorial design, reported separately) aspirin or other condition that might limit adherence to at

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least 5 years of participation in the trial. Patients who reported the over-the-counter receipt of fish oil or n–3 fatty acid supplements were asked to stop them wherever possible, but they remained eligible to participate in the trial, provided that the daily dose was less than 1 g. All the patients provided written informed consent.

PROCEDURES

Using regional diabetes registers or general practice data from around the United Kingdom, we identified potential patients and mailed them a screening questionnaire. Those who returned the questionnaire indicating that they were willing and eligible to participate in the trial entered a prerandomization run-in phase, during which we supplied capsules containing placebo n–3 fatty acid (and placebo aspirin in the separate portion of the trial), informed their family doctor of their potential participation, and sent them a kit to return nonfasting blood and urine samples and to record measures of blood pressure, height, and weight. After this run-in period of 8 to 10 weeks, patients remained eligible if they returned a randomization questionnaire that confirmed their willingness to continue, they still met the eligibility criteria, and they had adhered to the trial regimen.

Using minimized randomization,[19] we then assigned eligible patients to receive 1-g capsules containing either 840 mg of marine n–3 fatty acids (460 mg of eicosapentaenoic acid [EPA] and 380 mg of docosahexaenoic acid [DHA]) (fatty acid group) or a matching placebo capsule (olive oil) to be taken once daily. (In the separate portion of the trial, patients were also assigned to receive 100 mg of aspirin or matching placebo once daily.) The patients then were mailed a 6-month supply of the appropriate active or placebo capsules and tablets until the end of the scheduled treatment period or until the patient chose to discontinue taking either the capsules or tablets.

After randomization, we sent follow-up questionnaires to patients every 6 months until the end of the trial. In these questionnaires, we sought information regarding all serious adverse events (including potential trial outcomes), adherence to trial regimens, use of nontrial antiplatelet or anticoagulant therapy, nonserious adverse events resulting in the discontinuation of a trial agent, and any symptomatic bleeding episodes for which the patients sought medical assistance. After a mean follow-up of 2.5 years, we requested blood and urine samples, along with measures of blood pressure and weight, from 1800 randomly selected patients. (Details are provided in the Methods section of Supplementary Appendix 1, available at NEJM.org.)

OUTCOMES

While recruitment was still ongoing, we modified the original primary outcome to include transient ischemic attack (TIA) in the definition of serious vascular events, a change that was made to increase the statistical power of the trial. Thus, the prespecified primary efficacy outcome was the first serious vascular event, which was defined as a composite of nonfatal myocardial infarction or stroke (excluding confirmed intracranial hemorrhage), TIA, or vascular death excluding intracranial hemorrhage. The secondary efficacy outcome was a composite of any serious vascular event or any arterial revascularization procedure. All reports of possible primary or secondary outcomes were adjudicated centrally by clinicians who were unaware of trial-group assignments in accordance with prespecified definitions. It was prespecified that analyses would be based on all confirmed plus unrefuted reported events (see the Methods section of Supplementary Appendix 1).

STATISTICAL ANALYSIS

The data analysis plan was finalized by the steering committee and published while all the members were still unaware of the trial results according to group assignment (except for a statistician who was aware of trial-group assignments but was not involved in the development of the analysis plan). In addition to revising the definition of serious vascular events to include TIA, the sample size was increased to at least 15,000 patients and the duration of follow-up was extended to at least 7 years to increase the power of the trial.[19] (Details are provided in Supplementary Appendix 1.)

On the basis of a rate of serious vascular events of 1.2 to 1.3% per year, as observed in both groups combined after recruitment was complete, we determined that 7.5 years of scheduled treatment and follow-up would provide a power of 90% at an alpha value of less than 0.05 to detect a relative between-group difference of 15%. We used log-rank methods to conduct intention-to-treat comparisons in time-to-event analyses of the first occurrence of each type of event of interest among

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patients in the two trial groups. A two-tailed P value of less than 0.05 was considered to indicate statistical significance for the primary efficacy outcome.

For secondary and exploratory outcomes, it was prespecified that the combined secondary outcome of a serious vascular event or revascularization would be used for any subgroup analyses. We made allowance for multiple hypothesis testing in the interpretation of secondary and exploratory outcomes, with no formal adjustment to P values. Consequently, the results are reported as point estimates and 95% confidence intervals that have not been adjusted for multiple comparisons, so the intervals should not be used to infer definitive treatment effects within subgroups or for secondary outcomes. Details regarding other secondary and exploratory assessments are provided in the data analysis plan,[19] with further details regarding statistical analysis methods provided in Supplementary Appendix 1.

Results

Patients

From June 2005 through July 2011, a total of 15,480 patients underwent randomization. The characteristics of the patients were well balanced between the groups (Table 1, and Tables S1 and S2 in Supplementary Appendix 1). At the end of the scheduled follow-up period, complete follow-up data were available for 15,341 patients (99.1%) (Fig. 1, and Table S3 in Supplementary Appendix 1). At a mean follow-up of 7.4 years, data were available for 57,022 person-years in the fatty acid group and 56,924 person-years in the placebo group. Adjudication was complete for more than 90% of the primary and secondary outcomes.

Adherence and Effects on Cardiovascular Measures

The mean adherence to the assigned regimen (weighted according to person-years at risk) was 77% in the fatty acid group and 76% in the placebo group. Reasons for discontinuation of a trial intervention did not differ between groups (Tables S4 and S5 in Supplementary Appendix 1). The use of over-the-counter fish oil supplement was reported by 10% of the patients at baseline and by 7% after 6.7 years of follow-up, with no significant difference between the groups. In addition, there was no significant between-group difference in the use of nontrial medications at randomization or after 6.7 years of follow-up (Table S6 in Supplementary Appendix 1).

In exploratory analyses, various vascular markers were measured in a subgroup of patients at a mean of 2.5 years after randomization and did not clearly differ according to trial group (Table S7 in Supplementary Appendix 1). The Omega-3 Index (a measure of the EPA and DHA content of red cells expressed as a percentage of fatty acids)[20] was measured in a randomly selected subgroup of 152 patients who provided blood samples at both baseline and during follow-up. There was little change in the percentage among patients in the placebo group (6.6% at baseline and 6.5% at follow-up), whereas the percentage increased from 7.1% to 9.1% in the fatty acid group, a relative increase of 32.5% (95% confidence interval [CI], 26.3 to 39.1), as compared with placebo, after allowance for the baseline Omega-3 Index.

Primary and Secondary Outcomes

Serious vascular events occurred in 689 patients (8.9%) in the fatty acid group and in 712 patients (9.2%) in the placebo group (rate ratio, 0.97; 95% CI, 0.87 to 1.08; P=0.55) (Fig. 2A), with no evidence of effects emerging with longer follow-up (Fig. 2B). There was also no significant between-group difference in the secondary outcome of serious vascular events or revascularization, which occurred in 882 patients (11.4%) in the fatty acid group and in 887 (11.5%) in the placebo group (rate ratio, 1.00; 95% CI, 0.91 to 1.09) (Fig. 3).

There were similar rates of deaths from any cause in the fatty acid group and the placebo group, with deaths reported in 752 patients (9.7%) and 788 patients (10.2%), respectively (rate ratio, 0.95; 95% CI, 0.86 to 1.05). We could not reliably ascertain specific arrhythmic causes of death, so sudden deaths that were believed to be from coronary disease were combined with other deaths attributed to coronary disease. In exploratory analyses, there were fewer vascular deaths (which represented 28% of all deaths) in the fatty acid group than in the placebo group, regardless of whether deaths from intracranial hemorrhage were excluded (186 patients [2.4%] vs. 228 [2.9%]) (Fig. 3) or included (196 patients [2.5%] vs. 240 [3.1%]) (Fig. 4).

Subgroup Analyses

In subgroup analyses of serious vascular events or revascularization, there was no evidence that

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Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Fatty Acid Group (N=7740)	Placebo Group (N=7740)
Age		
Mean — yr	63.3±9.2	63.3±9.2
<60 yr — no. (%)	2791 (36.1)	2799 (36.2)
60 to <70 yr — no. (%)	3127 (40.4)	3120 (40.3)
≥70 yr — no. (%)	1822 (23.5)	1821 (23.5)
Male sex — no. (%)	4842 (62.6)	4842 (62.6)
White race — no. (%)†	7467 (96.5)	7468 (96.5)
Body-mass index‡		
Mean	30.7±6.3	30.8±6.2
<25 — no. (%)	1129 (14.6)	1120 (14.5)
25 to <30 — no. (%)	2771 (35.8)	2758 (35.6)
≥30 — no. (%)	3584 (46.3)	3617 (46.7)
Unknown — no. (%)	256 (3.3)	245 (3.2)
Smoking status — no. (%)		
Current smoker	639 (8.3)	640 (8.3)
Former smoker	3527 (45.6)	3524 (45.5)
Never smoker	3489 (45.1)	3488 (45.1)
Unknown	85 (1.1)	88 (1.1)
Patient-reported hypertension — no. (%)	4768 (61.6)	4765 (61.6)
Medication use — no. (%)		
Aspirin	2744 (35.5)	2764 (35.7)
Statin	5791 (74.8)	5862 (75.7)
Type 2 diabetes — no. (%)§	7280 (94.1)	7289 (94.2)
Duration		
Median (IQR) — yr	7 (3–12)	7 (3–13)
<9 yr — no. (%)	4332 (56.0)	4327 (55.9)
≥9 yr — no. (%)	2980 (38.5)	2985 (38.6)
Unknown — no. (%)	428 (5.5)	428 (5.5)
Systolic blood pressure¶		
Mean — mm Hg	136.2±15.4	136.2±15.1
<130 mm Hg — no. (%)	1695 (21.9)	1699 (22.0)
130 to <140 mm Hg — no. (%)	1547 (20.0)	1544 (19.9)
≥140 mm Hg — no. (%)	2279 (29.4)	2276 (29.4)
Unknown — no. (%)	2219 (28.7)	2221 (28.7)
Vascular risk score‖		
Low	3144 (40.6)	3120 (40.3)
Moderate	3269 (42.2)	3279 (42.4)
High	1327 (17.1)	1341 (17.3)

* Plus–minus values are means ±SD. There were no significant differences between the assigned groups. Percentages may not total 100 because of rounding. IQR denotes interquartile range.
† Race and ethnic group were reported by the patients. Other groups were Indian, Pakistani, or Bangladeshi (1%), African or Caribbean (1%), and other or unknown (1%).
‡ The body-mass index (the weight in kilograms divided by the square of the height in meters) was based on values for height and weight reported by the patients.
§ The presence of type 2 diabetes was based on a broad clinical definition that included the age at the time of diagnosis, use of insulin within 1 year after diagnosis, and body-mass index.
¶ Blood pressure was measured at the time that a blood sample was obtained, generally before randomization.
‖ The vascular risk score was the predicted 5-year risk of a serious vascular event (including transient ischemic attack) without the receipt of aspirin or n–3 fatty acids. The risk was categorized as low (<5%), moderate (5% to <10%), and high (≥10%). Details about how this score was calculated are provided in Supplementary Appendix 1.

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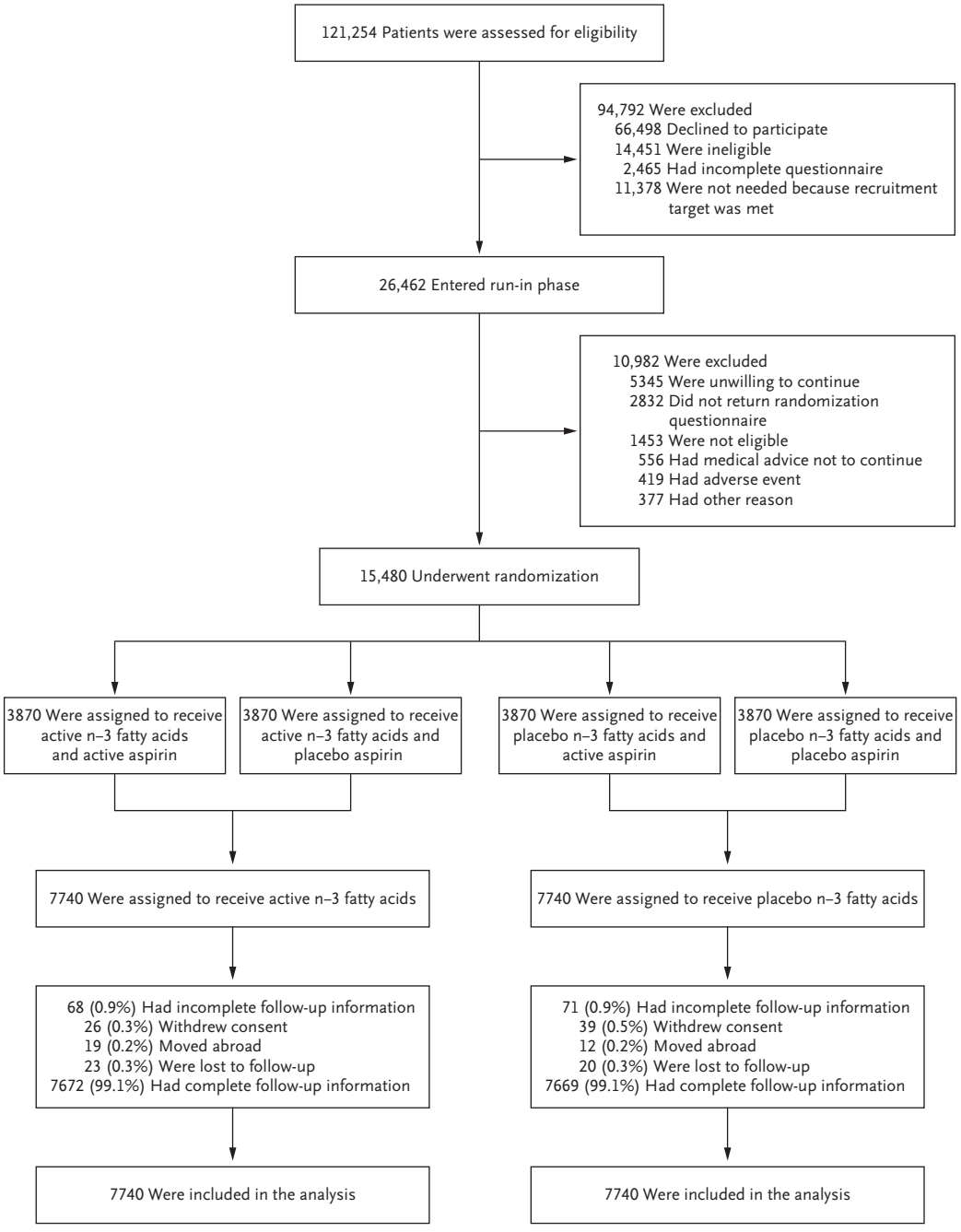

Figure 1. Enrollment and Completeness of Data.

the proportional effects of n–3 fatty acids varied according to prespecified baseline characteristics or according to aspirin or placebo assignment (P=0.71 for interaction) (Fig. S1 in Supplementary Appendix 1). Exploratory assessments of the effects on other vascular and microvascular outcomes are shown in Table S8 and Figure S2 in Supplementary Appendix 1, with similar results in the two groups.

Effects on Cancer and Other Nonvascular Outcomes

There were no significant between-group differences in the incidence of fatal or nonfatal cancer

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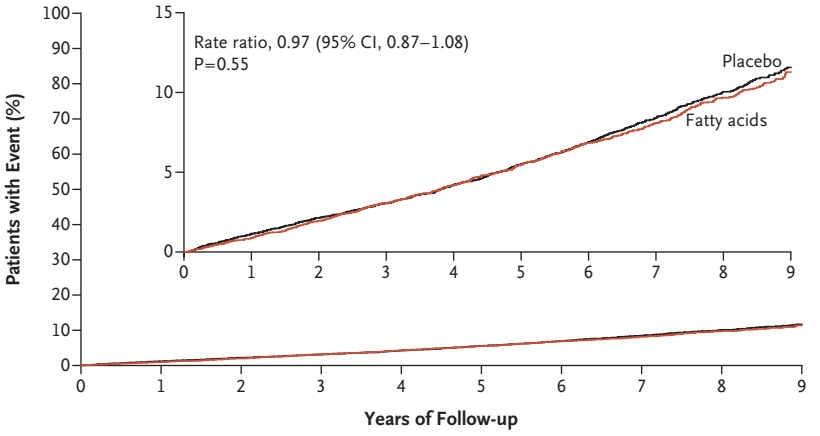
A First Serious Vascular Event



No. at Risk										
Placebo	7740	7627	7503	7377	7222	7047	5792	3934	2224	1428
Fatty acids	7740	7646	7519	7369	7218	7050	5804	3922	2198	1430
Cumulative benefit per 1000 patients in fatty acid group		3±2	2±2	0±3	0±3	0±4	1±4	3±5	4±6	3±7

B First Serious Vascular Event, According to Year of Follow-up

Year of First Event	Fatty Acids (N=7740)	Placebo (N=7740)	Rate Ratio (95% CI)	P Value
	no. of patients with event (%)			
<3	236 (3.0)	234 (3.0)	1.01 (0.84–1.21)	
3 to <5	181 (2.5)	186 (2.5)	0.97 (0.79–1.20)	
5 to <7	167 (2.4)	184 (2.6)	0.91 (0.74–1.12)	
≥7	105 (2.7)	108 (2.7)	0.98 (0.75–1.28)	
All	**689 (8.9)**	**712 (9.2)**	**0.97 (0.87–1.08)**	**0.55**

Test for trend across years χ^2=0.22 (P=0.64)

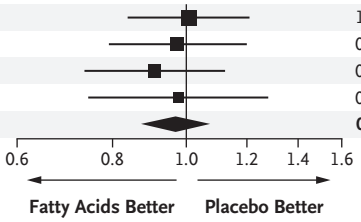


Figure 2. First Serious Vascular Events during Follow-up.

Panel A shows a Kaplan–Meier plot of the first serious vascular event (a composite of nonfatal myocardial infarction or ischemic stroke, transient ischemic attack, or vascular death excluding confirmed intracranial hemorrhage) during follow-up. The numbers of patients at risk at the start of each year of follow-up are shown, along with the cumulative number (±SE) of patients in whom a serious vascular event was avoided per 1000 patients in the fatty acid group, as compared with the placebo group. The inset graph shows the same data on an expanded y axis. Panel B shows rate ratios for the first serious vascular event among the patients in the fatty acid group, as compared with the placebo group, according to follow-up period. The numbers at risk declined with each period of follow-up because of data censoring, so the percentages are the number of events as a proportion of the number of patients at risk at the start of the period. For each period of follow-up, rate ratios are plotted as squares, with the size of each square proportional to the amount of statistical information that was available. The horizontal lines represent 95% confidence intervals, which have not been adjusted for multiple comparisons.

either overall or at any particular body site (Figs. S3 and S4 in Supplementary Appendix 1). Rates of death from nonvascular causes were also similar in the two groups (Fig. 4). Searchable tabulations of all recorded fatal or nonfatal serious adverse events, as classified according to the definitions in the *Medical Dictionary for Regulatory Activities*, version 14.0, are provided in Supplementary Appendix 2, available at NEJM.org. After allowance for multiple comparisons, no significant differences at the system organ class level or lower levels were observed between the two trial groups.

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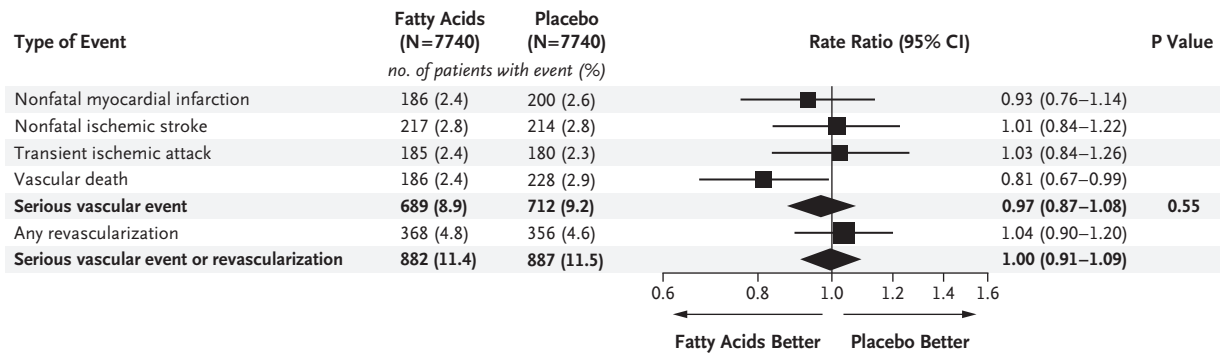

Figure 3. Components of Serious Vascular Events and Revascularization.

Shown are rate ratios for the components of the primary outcome and for the secondary outcome (serious vascular events or any revascularization procedure) in the fatty acid group and the placebo group. Patients could have more than one component event. The data for vascular death do not include patients who had intracranial hemorrhage. The size of the square for each rate ratio is proportional to the amount of statistical information that was available. For composite outcomes, the rate ratio and corresponding 95% confidence interval are represented by diamonds. The horizontal lines represent 95% confidence intervals, which have not been adjusted for multiple comparisons.

Discussion

Patients with diabetes and no evidence of cardiovascular disease who received a daily regimen of 1-g capsules of n–3 fatty acids did not have a significantly lower incidence of serious vascular events than those who received placebo after a follow-up of 7.4 years. There also was no significant between-group difference in the incidence of a secondary composite outcome of serious vascular events or revascularization. This lack of effect is consistent with the results for coronary heart disease and for major vascular events in a recent meta-analysis of 10 randomized trials involving 78,000 patients, including more than one third who had diabetes or dysglycemia,[10] and with the findings in a recent Cochrane review.[21] Similarly, there were no apparent significant benefits of supplementation in a meta-analysis that was restricted to placebo-controlled trials[9] or in a meta-analysis that also included trials involving patients with an implantable cardioverter–defibrillator, who would be at elevated risk for sudden death.[22]

In some reviews, investigators have suggested that n–3 fatty acid supplementation may reduce the risk of fatal coronary heart disease or cardiac death, but such reviews have typically included observational studies (which are prone to various biases) along with randomized trials (including unblinded ones in which biased outcome ascertainment cannot be ruled out).[23,24] The recent meta-analysis[10] suggested a possible modest benefit for n–3 fatty acid supplementation with respect to fatal coronary heart disease (rate ratio, 0.93; 95% CI, 0.85 to 1.00), but this finding was partially driven by the results of two open-label trials. If the results of ASCEND for this outcome had been included in the meta-analysis, there is a possibility of a small benefit with respect to fatal coronary heart disease. However, the rate ratio for major vascular events (including stroke and revascularization) in the meta-analysis[10] was 0.97 (95% CI, 0.93 to 1.01) and the rate ratio for serious vascular events or revascularization in our trial was 1.00 (95% CI, 0.91 to 1.09), which suggests little or no benefit when all vascular events are considered. Additional data from the ongoing placebo-controlled VITAL (Vitamin D and Omega-3 Trial) of n–3 fatty acids in the primary prevention of cancer and cardiovascular disease involving 25,875 adults will provide more information about any potential effects of such supplementation.[25]

Previous trials have not suggested any differences in the effects of n–3 fatty acid supplementation in primary prevention, as compared with secondary prevention or in participants with diabetes, as compared with those without diabetes.

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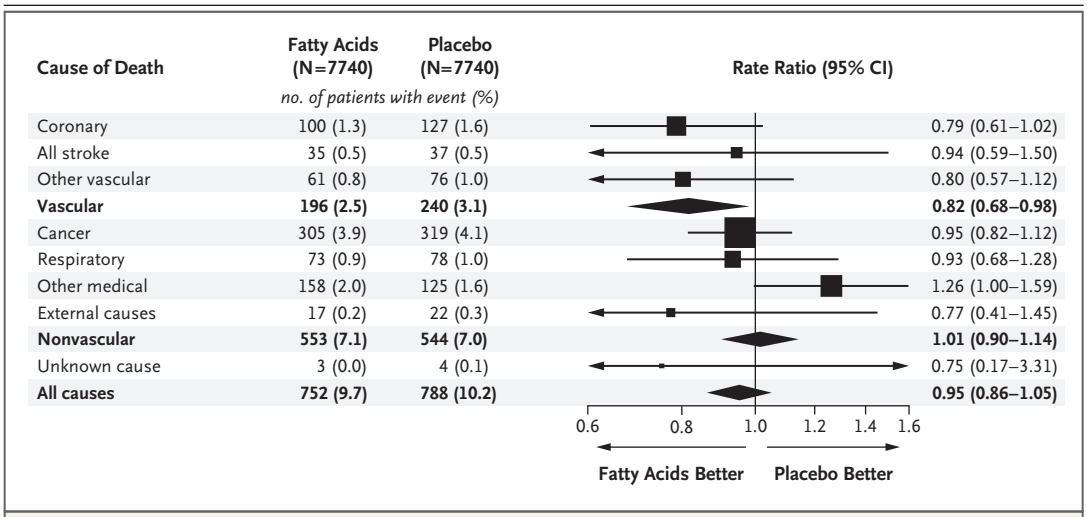

Figure 4. Death from Vascular or Other Causes.

Shown are rate ratios for death, according to the cause, in the fatty acid group and the placebo group. For the composite of all deaths, the rate ratio and its corresponding 95% confidence interval are represented by a diamond.

Seven of the 10 randomized trials (mean duration, 4.4 years) that were included in the recent meta-analysis assessed a daily regimen of 1-g capsules of n–3 fatty acids (as in our trial), whereas one assessed a lower dose using fortified margarine,[7] one small trial assessed 2.4 g daily, and the large, open-label JELIS (Japan EPA Lipid Intervention Study) assessed 1.8 g of EPA alone daily.[12] The relative reduction in the rate of coronary heart disease among the patients who received n–3 fatty acid supplementation, as compared with controls (19%; 95% CI, 5 to 31), in JELIS has prompted the initiation of two additional trials — STRENGTH (Statin Residual Risk Reduction with EpaNova in High Cardiovascular Risk Patients with Hypertriglyceridemia; ClinicalTrials.gov number, NCT02104817), involving 13,000 patients, and REDUCE-IT (Reduction of Cardiovascular Events with EPA-Intervention Trial, NCT01492361), involving 8000 patients — which are assessing the effects of 3 to 4 g of EPA daily.

The dose of n–3 fatty acids that we tested in our trial was associated with no excesses of symptoms leading to discontinuation, and there was no suggestion of major adverse effects on any type of serious adverse event (including cancer at any site). Triglyceride levels can be reduced by the administration of higher doses of n–3 fatty acid supplements (typically, 2 to 4 g daily) than were used in our trial (in which triglyceride levels were not measured), and it is possible that a reduction in the triglyceride level may produce benefits in some patients with diabetes.[26]

Some clinical guidelines still recommend the use of n–3 fatty acid supplements for the secondary prevention of coronary heart disease[27] and advocate the consumption of fish once or twice a week to reduce the risk of congestive heart failure, coronary heart disease, ischemic stroke, and sudden cardiac death,[15,28] despite the accumulating evidence from randomized trials that such supplements have little or no effect on cardiovascular outcomes. In some earlier trials, investigators evaluated the results of either increased fish consumption or n–3 fatty acid supplementation,[4,5] a study design that has made it difficult to assess the effects of either intervention alone. Fish clearly contain other nutrients, and consumption of one food alters the consumption of others. The recommendations to increase fish intake are based on observational evidence, but the randomized trials of supplements have largely not shown cardiovascular benefit.

In conclusion, among patients with diabetes but without evidence of cardiovascular disease at baseline, there was no significant difference in the incidence of serious vascular events between those who received n–3 fatty acids and those who received placebo. These findings, together with results of earlier randomized trials involving patients with and those without diabetes, do not support the current recommendations for routine

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dietary supplementation with n–3 fatty acids to prevent vascular events.

The members of the writing committee (Louise Bowman, M.D., Marion Mafham, M.D., Karl Wallendszus, M.Sc., Will Stevens, Ph.D., Georgina Buck, M.Sc., Jill Barton, Kevin Murphy, Theingi Aung, M.D., Richard Haynes, D.M., Jolyon Cox, D.Phil., Aleksandra Murawska, M.Sc., Allen Young, Ph.D., Michael Lay, D.Phil., Fang Chen, M.D., Ph.D., Emily Sammons, M.B., Ch.B., Emma Waters, M.B., B.S., Amanda Adler, M.D., Ph.D., Jonathan Bodansky, M.D., Andrew Farmer, D.M., Roger McPherson, B.M., F.R.C.Ophth., Andrew Neil, D.Sc., F.R.C.P., David Simpson, Richard Peto, F.R.S., F.Med.Sci., Colin Baigent, F.F.P.H., F.R.C.P., Rory Collins, F.R.S., F.Med.Sci., Sarah Parish, D.Phil., and Jane Armitage, F.R.C.P., F.F.P.H.) assume responsibility for the overall content and integrity of this article. The affiliations of the members of the writing committee are listed in the Appendix.

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Appendix

The affiliations of the members of the writing committee are as follows: Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health (L.B., M.M., K.W., W.S., G.B., J. Barton, K.M., R.H., J.C., A.M., A.Y., M.L., F.C., E.S., E.W., D.S., R.P., C.B., R.C., S.P., J.A.), Nuffield Department of Primary Care Health Sciences (A.F.), and Wolfson College (A.N.), University of Oxford, Oxford, the Royal Berkshire NHS Foundation Trust, Reading (T.A.), Addenbrooke's Hospital, Cambridge (A.A.), Leeds General Infirmary, Leeds (J. Bodansky), and University Hospital of Wales, Cardiff (R.M.) — all in the United Kingdom.

References

1. Kromhout D, Bosschieter EB, de Lezenne Coulander C. The inverse relation between fish consumption and 20-year mortality from coronary heart disease. N Engl J Med 1985;312:1205-9.
2. Shekelle RB, Missell L, MacMillan Shyrock A, et al. Fish consumption and mortality from coronary heart disease. N Engl J Med 1985;313:820-4.
3. Kris-Etherton PM, Harris WS, Appel LJ. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. Circulation 2002;106:2747-57.
4. Burr ML, Fehily AM, Gilbert JF, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: Diet and Reinfarction Trial (DART). Lancet 1989;2:757-61.
5. Burr ML, Ashfield-Watt PA, Dunstan FD, et al. Lack of benefit of dietary advice to men with angina: results of a controlled trial. Eur J Clin Nutr 2003;57:193-200.
6. Tavazzi L, Maggioni AP, Marchioli R, et al. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet 2008;372:1223-30.
7. Kromhout D, Giltay EJ, Geleijnse JM. n–3 Fatty acids and cardiovascular events after myocardial infarction. N Engl J Med 2010;363:2015-26.
8. The ORIGIN Trial Investigators. n–3 Fatty acids and cardiovascular outcomes in patients with dysglycemia. N Engl J Med 2012;367:309-18.
9. Kwak SM, Myung SK, Lee YJ, Seo HG. Efficacy of omega-3 fatty acid supplements (eicosapentaenoic acid and docosahexaenoic acid) in the secondary prevention of cardiovascular disease: a meta-analysis of randomized, double-blind, placebo-controlled trials. Arch Intern Med 2012;172:686-94.
10. Aung T, Halsey J, Kromhout D, et al. Associations of omega-3 fatty acid supplement use with cardiovascular disease risks: meta-analysis of 10 trials involving 77 917 individuals. JAMA Cardiol 2018;3:225-34.
11. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Lancet 1999;354:447-55.
12. Yokoyama M, Origasa H, Matsuzaki M, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet 2007;369:1090-8.
13. The Risk and Prevention Study Collaborative Group. n–3 Fatty acids in patients with multiple cardiovascular risk factors. N Engl J Med 2013;368:1800-8.
14. Siscovick DS, Barringer TA, Fretts AM, et al. Omega-3 polyunsaturated fatty acid (fish oil) supplementation and the prevention of clinical cardiovascular disease: a science advisory from the American Heart Association. Circulation 2017;135(15):e867-e884.
15. Rimm EB, Appel LJ, Chiuve SE, et al. Seafood long-chain n-3 polyunsaturated fatty acids and cardiovascular disease: a science advisory from the American Heart Association. Circulation 2018;138(1):e35-e47.
16. The Emerging Risk Factors Collaboration. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet 2010;375:2215-22.
17. The ASCEND Study Collaborative Group. Effects of aspirin for primary prevention in persons with diabetes mellitus. N Engl J Med. DOI: 10.1056/NEJMoa1804988.
18. The ASCEND Study Collaborative Group. Cost-effective recruitment methods for a large randomised trial in people with diabetes: A Study of Cardiovascular Events in Diabetes (ASCEND). Trials 2016;17:286.
19. The ASCEND Study Collaborative Group. ASCEND: A Study of Cardiovascular Events in Diabetes: characteristics of a randomized trial of aspirin and of omega-3 fatty acid supplementation in 15,480 people with diabetes. Am Heart J 2018;198:135-44.
20. Harris WS, Von Schacky C. The Omega-3 Index: a new risk factor for death from coronary heart disease? Prev Med 2004;39:212-20.
21. Abdelhamid AS, Brown TJ, Brainard JS, et al. Omega-3 fatty acids for the primary and secondary prevention of cardio-

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vascular disease. Cochrane Database Syst Rev 2018;7:CD003177.
22. Rizos EC, Ntzani EE, Bika E, Kostapanos MS, Elisaf MS. Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: a systematic review and meta-analysis. JAMA 2012;308:1024-33.
23. Kotwal S, Jun M, Sullivan D, Perkovic V, Neal B. Omega 3 fatty acids and cardiovascular outcomes: systematic review and meta-analysis. Circ Cardiovasc Qual Outcomes 2012;5:808-18.
24. Wang C, Harris WS, Chung M, et al. n-3 Fatty acids from fish or fish-oil supplements, but not alpha-linolenic acid, benefit cardiovascular disease outcomes in primary- and secondary-prevention studies: a systematic review. Am J Clin Nutr 2006; 84:5-17.
25. Pradhan AD, Manson JE. Update on the Vitamin D and OmegA-3 trial (VITAL). J Steroid Biochem Mol Biol 2016;155:Pt B: 252-6.
26. Hartweg J, Farmer AJ, Holman RR, Neil A. Potential impact of omega-3 treatment on cardiovascular disease in type 2 diabetes. Curr Opin Lipidol 2009; 20:30-8.
27. Smith SC Jr, Benjamin EJ, Bonow RO, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. Circulation 2011;124:2458-73.
28. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts): developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J 2016; 37:2315-81.

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