

ORIGINAL ARTICLE

n–3 Fatty Acids and Cardiovascular Outcomes in Patients with Dysglycemia

The ORIGIN Trial Investigators*

ABSTRACT

BACKGROUND

The use of n–3 fatty acids may prevent cardiovascular events in patients with recent myocardial infarction or heart failure. Their effects in patients with (or at risk for) type 2 diabetes mellitus are unknown.

METHODS

In this double-blind study with a 2-by-2 factorial design, we randomly assigned 12,536 patients who were at high risk for cardiovascular events and had impaired fasting glucose, impaired glucose tolerance, or diabetes to receive a 1-g capsule containing at least 900 mg (90% or more) of ethyl esters of n–3 fatty acids or placebo daily and to receive either insulin glargine or standard care. The primary outcome was death from cardiovascular causes. The results of the comparison between n–3 fatty acids and placebo are reported here.

RESULTS

During a median follow up of 6.2 years, the incidence of the primary outcome was not significantly decreased among patients receiving n–3 fatty acids, as compared with those receiving placebo (574 patients [9.1%] vs. 581 patients [9.3%]; hazard ratio, 0.98; 95% confidence interval [CI], 0.87 to 1.10; $P=0.72$). The use of n–3 fatty acids also had no significant effect on the rates of major vascular events (1034 patients [16.5%] vs. 1017 patients [16.3%]; hazard ratio, 1.01; 95% CI, 0.93 to 1.10; $P=0.81$), death from any cause (951 [15.1%] vs. 964 [15.4%]; hazard ratio, 0.98; 95% CI, 0.89 to 1.07; $P=0.63$), or death from arrhythmia (288 [4.6%] vs. 259 [4.1%]; hazard ratio, 1.10; 95% CI, 0.93 to 1.30; $P=0.26$). Triglyceride levels were reduced by 14.5 mg per deciliter (0.16 mmol per liter) more among patients receiving n–3 fatty acids than among those receiving placebo ($P<0.001$), without a significant effect on other lipids. Adverse effects were similar in the two groups.

CONCLUSIONS

Daily supplementation with 1 g of n–3 fatty acids did not reduce the rate of cardiovascular events in patients at high risk for cardiovascular events. (Funded by Sanofi; ORIGIN ClinicalTrials.gov number, NCT00069784.)

The members of the writing committee, who are listed in the Appendix, assume responsibility for the overall content and integrity of this article. Address reprint requests to the ORIGIN Project Office, Population Health Research Institute, Hamilton General Hospital, DBCVSRI, 237 Barton St. E., 2nd Fl., Hamilton, ON L8L 2X2, Canada, or to origin@phri.ca.

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THE USE OF N-3 FATTY ACIDS MAY HAVE beneficial effects on arrhythmias, elevated triglyceride levels, atherosclerotic plaque, impaired endothelial function, platelet aggregation, and inflammation. Epidemiologic studies have shown a reduced risk of cardiovascular events among persons who consume fish regularly or who take supplements containing n-3 fatty acids.¹⁻⁴ These data have provided the impetus for clinical trials evaluating the effect of such supplements on cardiovascular events and death. These studies included participants with a variety of cardiovascular risk factors, were either open-label or placebo-controlled, and tested either dietary regimens or pharmaceutical preparations containing n-3 fatty acids. Previous meta-analyses of such trials of n-3 fatty acids have shown modest reductions in the rates of fatal and nonfatal cardiovascular events.⁵⁻⁷ However, a recent meta-analysis that was limited to blinded, randomized, placebo-controlled trials of such supplementation showed no effect on cardiovascular outcomes.⁸

Patients with type 2 diabetes, impaired fasting glucose, or impaired glucose tolerance are at increased risk for cardiovascular events,⁹ but no large trials have focused on the effect of n-3 fatty acids in such patients. In the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial,¹⁰ we tested the hypothesis that long-term supplementation with n-3 fatty acids would reduce the rate of cardiovascular events in this population of patients.

METHODS

STUDY DESIGN

In a randomized trial with a 2-by-2 factorial design, we sought to determine the effect of a 1-g capsule containing at least 900 mg (90% or more) of ethyl esters of n-3 fatty acids (Omacor, Pronova BioPharma Norge) as compared with placebo and of insulin glargine as compared with standard care on cardiovascular outcomes in patients with (or at risk for) diabetes. Details regarding the design of this study were published in 2008,¹⁰ and the results of the insulin glargine intervention are reported separately in the *Journal* by Gerstein et al.¹¹ The study protocol is provided with the full text of this article at NEJM.org. The ethics committee at each participating site approved the

trial, and all participants provided written informed consent.

PARTICIPANTS

Eligibility criteria were an age of at least 50 years; a diagnosis of diabetes with receipt of no more than one oral glucose-lowering drug, impaired glucose tolerance (plasma glucose level at 2 hours, ≥ 7.8 mM [140 mg per deciliter] and < 11.1 mM [200 mg per deciliter] after a 75-g oral glucose load), or impaired fasting glucose (range, ≥ 6.1 mM [110 mg per deciliter] to < 7.0 mM [126 mg per deciliter]); a history of myocardial infarction, stroke, or revascularization; angina with documented ischemia; a ratio of urinary albumin to creatinine of more than 30 mg per gram; left ventricular hypertrophy; 50% or more stenosis of a coronary, carotid, or lower-limb artery on angiography; or an ankle-brachial index of less than 0.9.

Participants were excluded if they were unwilling to discontinue use of a nonstudy preparation of n-3 fatty acids, had a locally measured glycated hemoglobin level of 9% or more, had undergone coronary-artery bypass grafting within the previous 4 years with no intervening cardiovascular event, had severe heart failure, or had a cancer that might affect survival.

RANDOMIZATION, STUDY INTERVENTION, AND FOLLOW-UP

Participants underwent randomization, after a 10-day run-in period, to receive either 1 g of n-3 fatty acids (containing 465 mg of eicosapentaenoic acid [EPA] and 375 mg of docosahexaenoic acid [DHA]) or placebo containing approximately 1 g of olive oil.

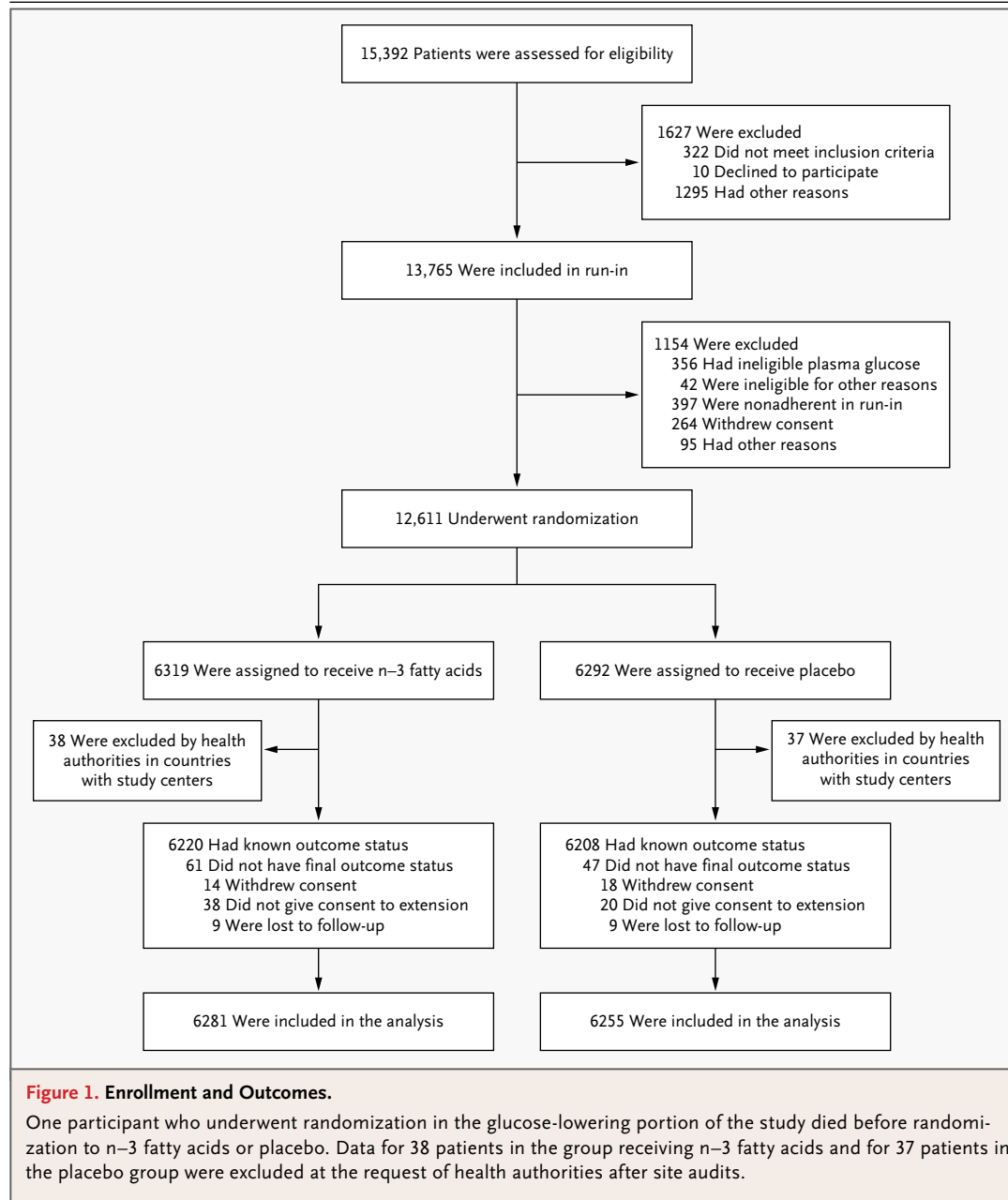
We evaluated clinical outcomes occurring after randomization, adherence to the study-drug regimen, and adverse events associated with a change in the dose of a study drug during follow-up visits at 0.5, 1, 2, and 4 months after randomization and every 4 months thereafter. We made no study-specific dietary recommendations pertaining to consumption of fish or other marine products. However, the use of nonstudy supplements containing n-3 fatty acids was discouraged. A food-frequency questionnaire was administered at randomization, at 2 years, and at the end of the study. We calculated the dietary intake of EPA and DHA at baseline, at 2 years, and at the end of the study, using data from the food-frequency questionnaire

and the Department of Agriculture National Nutrient Database for Standard Reference, release 23 (USDA Food Search for Windows, version 1.0).

STUDY OUTCOMES

The primary outcome was death from cardiovascular causes. Secondary outcomes included the composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke; death from any cause; and death from

arrhythmia (which included sudden unexpected death, death from documented arrhythmia, unwitnessed death, and resuscitated cardiac arrest). Other outcomes included all myocardial infarctions, all strokes, revascularizations, heart failure, angina, limb amputation for ischemia, and hospitalization for cardiovascular causes. All primary and secondary outcomes were adjudicated with the use of prespecified definitions by a committee whose members were unaware of



study-group assignments. Detailed definitions of key study outcomes are in the Supplementary Appendix, available at NEJM.org.

STUDY OVERSIGHT

The trial was designed and conducted by the steering committee, which included the two principal investigators, national leaders from each participating country, one representative from the manufacturer of n-3 fatty acids (Pronova BioPharma Norge), and one representative from the trial sponsor (Sanofi, which manufactures insulin glargine). Project management, data management, support for the adjudication committee, and statistical analyses were all independently provided by the trial's project office, based at the Population Health Research Institute in Hamilton, Ontario, Canada. An independent data and

safety monitoring committee reviewed efficacy and safety outcomes on a regular basis. Two planned interim analyses were conducted when 50% and 75% of the expected number of events had occurred. Funding and regulatory support were provided by Sanofi. Capsules containing n-3 fatty acids and placebo were provided by Pronova BioPharma Norge. The steering committee prepared the manuscript, made the decision to submit it for publication, and vouches for the completeness and accuracy of the data and the fidelity of the study to the protocol.

STATISTICAL ANALYSIS

We calculated that the enrollment of 12,500 participants during a 2-year period, with follow-up for at least 6 years, would provide a power of 90% to detect an 18.6% reduction (and a power of 80%

Table 1. Baseline Characteristics of the Patients.*

Characteristic	n-3 Fatty Acids (N=6281)	Placebo (N=6255)
Age — yr	63.5±7.8	63.6±7.9
Female sex — no. (%)	2176 (34.6)	2210 (35.3)
Cardiovascular history or risk factors — no. (%)		
Myocardial infarction, stroke, or revascularization	3713 (59.1)	3664 (58.6)
Hypertension	4941 (78.7)	5021 (80.3)
Current smoking	762 (12.1)	790 (12.6)
Other risk factors — no. (%)		
Microalbuminuria or macroalbuminuria	980 (15.6)	944 (15.1)
History of cancer	279 (4.4)	274 (4.4)
Body-mass index†	29.8±5.3	29.9±5.2
Heart rate — beats per minute	69.9±12.2	69.8±12.1
Blood pressure — mm Hg		
Systolic	145.6±21.8	146.0±21.8
Diastolic	84.1±12.1	84.2±12.1
Ankle-brachial index	1.16±0.21	1.16±0.20
Cholesterol — mg/dl		
Total	189±46	190±47
Low-density lipoprotein	112±40	112±40
High-density lipoprotein	46±12	46±12
Serum creatinine — mg/dl	1.0±0.3	1.0±0.2
Estimated glomerular filtration rate — ml/min/1.73 m ²	77.1±21.5	77.5±21.1
Fasting plasma glucose — mg/dl		
Median	125	124
Interquartile range	110–148	108–148
Glycated hemoglobin — %		
Median	6.4	6.4
Interquartile range	5.8–7.2	5.8–7.2

Table 1. (Continued.)

Characteristic	n-3 Fatty Acids (N=6281)	Placebo (N=6255)
Albumin:creatinine ratio [‡]		
Median	5.2	5.1
Interquartile range	2.5–19.3	2.5–18.1
Triglycerides — mg/dl		
Median	142	140
Interquartile range	99–196	97–195
Dietary EPA–DHA intake — mg/day		
Median	210.0	209.3
Interquartile range	39.7–577.4	39.6–563.1
Cardiovascular medication — no. (%)		
ACE inhibitor or ARB	4320 (68.8)	4360 (69.7)
Thiazide diuretics	1180 (18.8)	1191 (19.0)
Aspirin or other antiplatelet agent	4374 (69.6)	4291 (68.6)
Anticoagulant	438 (7.0)	432 (6.9)
Beta-blocker	3314 (52.8)	3284 (52.5)
Calcium-channel blocker	1708 (27.2)	1751 (28.0)
Statin	3331 (53.0)	3408 (54.5)

* Plus–minus values are means \pm SD. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, DHA docosahexaenoic acid, and EPA eicosapentaenoic acid.

[†] The body-mass index is the weight in kilograms divided by the square of the height in meters.

[‡] Urinary albumin was measured in milligrams, and creatinine was measured in grams.

to detect a 16.4% reduction) in the risk of death from cardiovascular causes in the group receiving supplementation with n-3 fatty acids, assuming an event rate of 1.5% per year in the placebo group and a two-sided type I error rate of 5%.

To compare the time-to-first-event curves, we used an intention-to-treat approach for all efficacy analyses and a log-rank test stratified according to the assignment to receive either insulin glargine or standard care, baseline metabolic status (impaired fasting glucose, impaired glucose tolerance, newly diagnosed diabetes, or established diabetes), and status with respect to a history of cardiovascular disease. Estimates of the hazard ratios and two-sided 95% confidence intervals were calculated overall and for subgroups with the use of a Cox regression model stratified according to use of insulin glargine versus standard care, baseline metabolic status (impaired fasting glucose, impaired glucose tolerance, newly diagnosed diabetes, or established diabetes), and status with respect to a history of cardiovascular disease. Cox regression models

with adjustment for these three factors were used if there were fewer than five events in any stratum. For all outcomes and interaction terms, a P value of less than 0.05 was considered to indicate statistical significance.

We used the Kaplan–Meier method to create survival curves for up to 7 years. We used the Peto–Yusuf method to calculate odds ratios and confidence intervals for the addition of the ORIGIN results to a meta-analysis of the efficacy of n-3 fatty acid supplementation in the secondary prevention of cardiovascular disease (see the Discussion section).

RESULTS

PATIENTS

From September 2003 through December 2005, we randomly assigned 12,611 patients to a study group. We subsequently excluded data for 75 patients at the request of national regulatory agencies after local audits. We followed the remaining 12,536 patients (mean age, 64 years; 35% wom-

en) from 573 centers (cardiology, diabetes, and general practice clinics) in 40 countries for a median of 6.2 years, until November 2011 (Fig. 1). At baseline, 59% of the patients had had a myocardial infarction or stroke or had undergone revascularization. The median dietary intake of EPA or DHA was 210 mg per day (interquartile range, 40 to 568) (Table 1). Information regarding the primary outcome was available for 12,428 patients (99.1%) at the end of the study (Fig. 1).

Rates of adherence to the study-drug regimen were similar in the two groups, with 96% of patients continuing to receive a study drug at 1 year, 92% at 4 years, and 88% at the end of the study. Other than participant preference, the most commonly reported reasons for permanently stopping a study drug among patients receiving n-3 fatty acids and those receiving placebo were abdominal discomfort (in 32 patients and 18 patients, respectively) and lower gastrointestinal symptoms (in 14 and 24 patients, respectively). Bleeding was reported in 57 patients receiving n-3 fatty acids, as compared with 65 patients in the placebo group, with intracranial bleeding reported in 42 patients and 51 patients, respectively.

EFFICACY OUTCOMES

Supplementation with n-3 fatty acids did not significantly reduce deaths from cardiovascular causes, which occurred in 574 patients (9.1%), as compared with 581 patients (9.3%) receiving placebo (hazard ratio, 0.98; 95% confidence interval [CI], 0.87 to 1.10; $P=0.72$) (Table 2 and Fig. 2). There was no significant between-group difference in the primary outcome in key subgroups, including groups defined by baseline consumption of n-3 fatty acids, baseline triglyceride level, baseline glycemic status, and assignment to insulin glargine versus standard glycemic treatment (Fig. S3 in the Supplementary Appendix). In addition, the receipt of n-3 fatty acids did not have a significant influence on major vascular events, which occurred in 1034 patients (16.5%) receiving n-3 fatty acids, as compared with 1017 patients (16.3%) receiving placebo (hazard ratio, 1.01; 95% CI, 0.93 to 1.10; $P=0.81$), or on death from any cause (951 patients [15.1%] vs. 964 patients [15.4%]; hazard ratio, 0.98; 95% CI, 0.89 to 1.07; $P=0.63$), death from arrhythmia (288 [4.6%] vs. 259 [4.1%]; hazard ratio, 1.10; 95% CI, 0.93 to 1.30; $P=0.26$), and all other predefined study outcomes (Table 2). There was no significant

Table 2. Primary and Other Outcomes.

Outcome	n-3 Fatty Acids (N=6281)		Placebo (N=6255)		Adjusted Hazard Ratio (95% CI)	P Value
	no. (%)	rate/100 patient-yr	no. (%)	rate/100 patient-yr		
Primary outcome: death from cardiovascular causes	574 (9.1)	1.55	581 (9.3)	1.58	0.98 (0.87–1.10)	0.72
Secondary outcomes						
Myocardial infarction, stroke, or death from cardiovascular causes	1034 (16.5)	2.92	1017 (16.3)	2.88	1.01 (0.93–1.10)	0.81
Death from any cause	951 (15.1)	2.57	964 (15.4)	2.62	0.98 (0.89–1.07)	0.63
Death from arrhythmia*	288 (4.6)	0.78	259 (4.1)	0.70	1.10 (0.93–1.30)	0.26
Other outcomes						
Fatal and nonfatal myocardial infarction	344 (5.5)	0.95	316 (5.1)	0.88	1.09 (0.93–1.27)	0.28
Fatal and nonfatal stroke	314 (5.0)	0.86	336 (5.4)	0.93	0.92 (0.79–1.08)	0.32
Hospitalization for heart failure	331 (5.3)	0.91	320 (5.1)	0.88	1.02 (0.88–1.19)	0.76
Revascularization procedure	866 (13.8)	2.54	896 (14.3)	2.65	0.96 (0.87–1.05)	0.39
Angina†	724 (11.5)	2.11	725 (11.6)	2.12	1.00 (0.90–1.10)	0.94
Limb or digit amputation for ischemia	52 (0.8)	0.14	47 (0.8)	0.13	1.09 (0.74–1.62)	0.67
Hospitalization for any cardiovascular cause	2055 (32.7)	6.87	2087 (33.4)	7.00	0.98 (0.92–1.04)	0.50

* Death from arrhythmia was a composite of sudden unexpected death, nonsudden death, unwitnessed death, or resuscitation after cardiac arrest.

† Angina included new, worsening, or unstable disease.

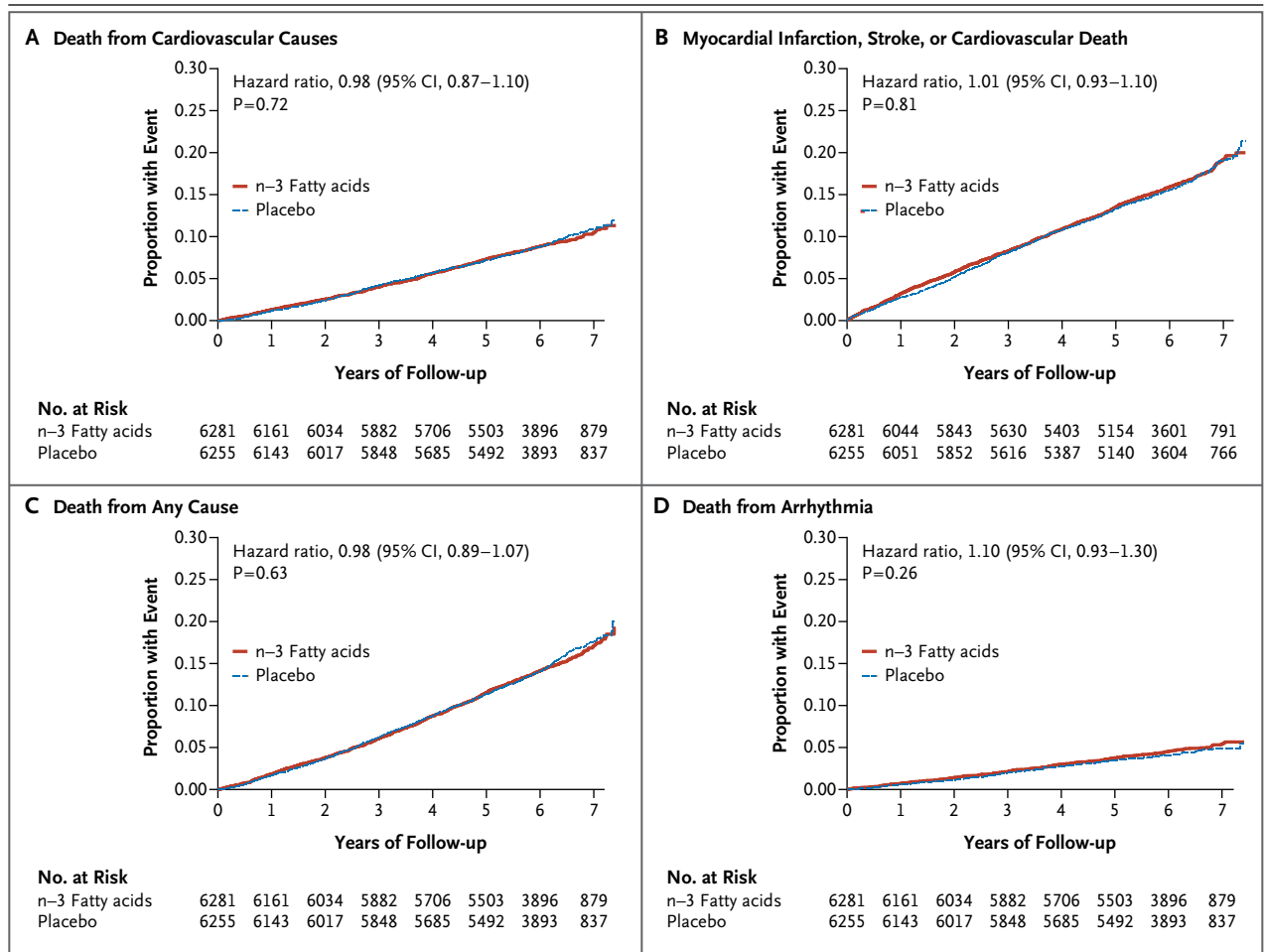


Figure 2. Primary and Secondary Outcomes.

Shown are the proportions of participants with primary or secondary outcome events. The primary outcome was death from cardiovascular causes (Panel A), and the secondary outcomes were a composite of myocardial infarction, stroke, or death from cardiovascular causes (Panel B), death from any cause (Panel C), and fatal arrhythmia (Panel D).

between-group difference in the rate of cancer diagnoses, and there were no significant interactions with the study-group assignments in the glucose-lowering portion of the study, indicating that the effect was similar for patients in the insulin glargine group and the standard-care group (Fig. S3 in the Supplementary Appendix).

By the end of the trial, patients in the group receiving n-3 fatty acids had a mean reduction in the triglyceride level of 14.5 mg per deciliter (0.16 mmol per liter), as compared with the placebo group (P<0.001) (Table 3). There were no other significant between-group differences in the levels of other lipid fractions, plasma glucose levels, glycated hemoglobin levels, blood pressure, or heart rate (Table 3).

DISCUSSION

In this study, we found that a daily 1-g dose of n-3 fatty acids, as compared with placebo, did not prevent death or any cardiovascular outcomes in patients who had (or were at high risk for) diabetes and were at increased risk for cardiovascular events. Several possibilities may account for differences between our findings and the reports of benefit from some previous trials of supplements containing n-3 fatty acids.

First, two of the largest trials recruited patients who had had a myocardial infarction within the past 3 months or who had heart failure.^{12,13} Such participants might have been more likely to benefit from any possible antiarrhythmic

Table 3. Changes in Key Risk Factors.*

Risk Factor	n-3 Fatty Acids (N=6281)	Placebo (N=6255)	P Value
Blood pressure (mm Hg)			
Systolic	-4.37±22.5	-4.51±22.5	0.75
Diastolic	-4.93±12.8	-4.96±13.1	0.91
Heart rate (beats/min)	-0.13±12.3	0.25±12.2	0.13
Cholesterol (mg/dl)			
Total	-15.7±1.0	-14.6±1.0	0.17
Low-density lipoprotein	-11.8±0.8	-12.4±0.8	0.44
High-density lipoprotein	-0.1±0.3	-0.2±0.3	0.78
Triglycerides (mg/dl)	-23.5±3.0	-9.0±3.0	<0.001

* Plus-minus values are means ±SD for blood pressure and heart rate and means ±SE for cholesterol and triglycerides.

mic effect of n-3 fatty acids than were participants in our study.

Second, participants in our trial were taking more concomitant cardioprotective therapies than were those in many previously published trials. These therapies may have reduced the incidence of death from cardiovascular causes, thereby reducing the statistical power to detect any effect of n-3 fatty acids. These two possibilities are supported by the results of a recent trial,¹⁴ which did not show a beneficial effect of n-3 fatty acids in patients who had had a myocardial infarction and were receiving concomitant therapies at proportions similar to those in our study.

Third, participants in some of the other trials may have had a daily dietary intake of n-3 fatty acids that differed from the intake in our study population (median, 210 mg per day) and thus might have derived greater benefit from supplementation. Our study did not detect a difference in effect on the basis of the dietary intake of n-3 fatty acids at baseline. However, it should be noted that the reported dietary intake of participants in our study was well below the 1 g per day recommended in various guidelines.^{15,16}

Fourth, our study was restricted to patients with impaired fasting glucose, impaired glucose tolerance, or diabetes, and n-3 fatty acids may not be effective in such patients. However, in other trials, analyses of data from participants with similar glycemic conditions suggest benefits of supplementation with n-3 fatty acids in these subgroups.^{17,18} Despite these differences, the fact that the confidence intervals that were

observed in our trial clearly overlapped with those observed in meta-analyses of the previous trials^{6,8} suggests that our findings are consistent with the small or neutral effect reported in these meta-analyses. When the results of our study are added to the most recent meta-analysis,⁸ the risk estimate for death from cardiovascular causes changes minimally, from 0.91 (95% CI, 0.84 to 0.99) to 0.94 (95% CI, 0.87 to 1.10).

In our study, the dose of n-3 fatty acids was not chosen on the basis of any estimate of its effect on triglyceride levels. Nevertheless, a significant between-group difference in triglyceride levels was shown for patients receiving n-3 fatty acids (a reduction of 0.16 mmol per liter), which was in keeping with the triglyceride reduction shown in a similar study involving patients with diabetes, in which those receiving 2 g of n-3 fatty acids per day had a reduction in the triglyceride level of 0.09 mmol per liter.¹⁹ Although in our study other lipid values changed between baseline and the end of the study, the changes were similar in the two groups.

Among the strengths of our study are its large size, the large number of events, the long follow-up period, high adherence to study medication, ascertainment of the final outcome status in 99% of participants, and a focus on patients with diabetes or a glycemic status indicating a high risk of diabetes, a population in which n-3 fatty acid supplementation has not been extensively studied. Limitations of the study include the possibility that a daily dose of 1 g of n-3 fatty acids may have been too low. However, this dose was chosen on the basis of previous trials that showed a reduction in cardiovascular events.¹² Although the cardiovascular effect of daily doses ranging from 0.4 g to 4.8 g have been tested during the past 15 years, a recent meta-analysis⁸ did not show a relationship between results and dose. Nevertheless, whether larger doses of n-3 fatty acids can reduce cardiovascular events is unknown. Furthermore, assessment of whether the effect of n-3 fatty acids on death from cardiovascular causes varied according to dietary intake of n-3 fatty acids was based on the use of a dietary questionnaire rather than measurement of serum levels.

At least three other large trials, currently under way, are assessing the use of n-3 fatty acids to prevent cardiovascular disease in low-risk participants. In the *Rischio* and *Prevenzione* study,

among 12,513 participants who underwent randomization between February 2004 and March 2007, investigators are evaluating whether 5 years of daily supplementation with 1 g of n-3 fatty acids can prevent death or hospitalization for cardiovascular events in participants without previous myocardial infarction.²⁰ Follow-up was completed in October 2011, and results are awaited. A Study of Cardiovascular Events in Diabetes (ASCEND, NCT00135226), involving 15,480 participants with diabetes but no previous cardiovascular disease, is assessing whether daily supplementation with 1 g of n-3 fatty acids, as compared with placebo, will prevent cardiovascular events. Follow-up of participants will continue until 2017. The third large study, the Vitamin D and Omega-3 Trial (VITAL, NCT01169259), is currently recruiting 20,000 participants in the United States who have no history of heart disease, stroke, or cancer to determine whether daily supplementation with 1 g of n-3 fatty acids will prevent these diseases. These studies will provide further evidence re-

garding the value of supplementation with n-3 fatty acids. In addition, the three studies include both high- and low-risk participants and will therefore provide important information about the effect of supplementation with n-3 fatty acids in persons at various risk levels.

In conclusion, the administration of 1 g of n-3 fatty acids did not reduce the rate of death from cardiovascular causes or other outcomes during a period of 6 years in patients with dysglycemia and additional cardiovascular risk factors. Whether similar results would have been observed at higher doses is unknown. Furthermore, these findings may not be relevant to dietary recommendations to consume more fish, because dietary change not only increases the intake of foods containing n-3 fatty acids but is also associated with a reduction in the consumption of foods such as red meats, which may be harmful.²¹

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

APPENDIX

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