

ORIGINAL ARTICLE

n-3 Fatty Acids in Patients with Multiple Cardiovascular Risk Factors

The Risk and Prevention Study Collaborative Group*

ABSTRACT

BACKGROUND

Trials have shown a beneficial effect of n-3 polyunsaturated fatty acids in patients with a previous myocardial infarction or heart failure. We evaluated the potential benefit of such therapy in patients with multiple cardiovascular risk factors or atherosclerotic vascular disease who had not had a myocardial infarction.

METHODS

In this double-blind, placebo-controlled clinical trial, we enrolled a cohort of patients who were followed by a network of 860 general practitioners in Italy. Eligible patients were men and women with multiple cardiovascular risk factors or atherosclerotic vascular disease but not myocardial infarction. Patients were randomly assigned to n-3 fatty acids (1 g daily) or placebo (olive oil). The initially specified primary end point was the cumulative rate of death, nonfatal myocardial infarction, and nonfatal stroke. At 1 year, after the event rate was found to be lower than anticipated, the primary end point was revised as time to death from cardiovascular causes or admission to the hospital for cardiovascular causes.

RESULTS

Of the 12,513 patients enrolled, 6244 were randomly assigned to n-3 fatty acids and 6269 to placebo. With a median of 5 years of follow-up, the primary end point occurred in 1478 of 12,505 patients included in the analysis (11.8%), of whom 733 of 6239 (11.7%) had received n-3 fatty acids and 745 of 6266 (11.9%) had received placebo (adjusted hazard ratio with n-3 fatty acids, 0.97; 95% confidence interval, 0.88 to 1.08; $P=0.58$). The same null results were observed for all the secondary end points.

CONCLUSIONS

In a large general-practice cohort of patients with multiple cardiovascular risk factors, daily treatment with n-3 fatty acids did not reduce cardiovascular mortality and morbidity. (Funded by Società Prodotti Antibiotici and others; ClinicalTrials.gov number, NCT00317707.)

The members of the writing group, who are listed in the Appendix, assume responsibility for the content and integrity of this article. Address reprint requests to the Risk and Prevention Study Office, IRCCS—Istituto di Ricerche Farmacologiche Mario Negri, Via Giuseppe La Masa 19, 20156 Milan, Italy, or to rep@marionegri.it.

*The investigators of the Risk and Prevention Study Collaborative Group are listed in the Supplementary Appendix, available at NEJM.org.

This article was updated on May 9, 2013, at NEJM.org.

N Engl J Med 2013;368:1800-8.

DOI: 10.1056/NEJMoa1205409

Copyright © 2013 Massachusetts Medical Society.

IT HAS BEEN SUGGESTED THAT THE USE OF n-3 polyunsaturated fatty acids derived from fish may reduce the risk of cardiovascular disease by means of beneficial effects on arrhythmic, atherosclerotic, inflammatory, and thrombotic processes.¹ A benefit of n-3 fatty acids in reducing cardiovascular mortality and morbidity has been documented in patients surviving a myocardial infarction² and in patients with heart failure.³

The Risk and Prevention Study, conceived after completion of the Primary Prevention Project⁴ and a pilot study,⁵⁻⁷ was a double-blind, placebo-controlled trial assessing the efficacy of n-3 fatty acids in patients at high cardiovascular risk, as judged by a nationwide network of general practitioners in Italy. These studies reflect the view that general practice is the most representative setting for testing primary prevention strategies.

METHODS

STUDY DESIGN AND OVERSIGHT

The background and design of the Risk and Prevention Study have been described in detail elsewhere.⁸ For this community-based trial, 860 general practitioners were selected because of their involvement in previous research projects^{4,9} or from general practitioner-investigator registries in local health units. The trial was designed by the steering committee (for a list of members, see the Supplementary Appendix, available with the full text of this article at NEJM.org) and approved by the ethics committees of the local health units. Standard operating procedures complied with the Harmonized Tripartite Guideline for Good Clinical Practice from the International Conference on Harmonisation.¹⁰ An independent data and safety monitoring board oversaw the study and monitored patient safety, with a planned blind interim analysis when the investigators had reported half the expected number of end-point events.

The steering committee had the full and sole responsibility for planning and coordinating the study, analyzing and interpreting the data, and preparing the manuscript and submitting it for publication. Società Prodotti Antibiotici, Pfizer, and Sigma Tau funded the trial but had no role in the study design, planning, conduct, or analysis or in the interpretation or reporting of the results. All the authors vouch for the accuracy

and completeness of the data and analyses and for the fidelity of this report to the trial protocol, which is available at NEJM.org.

STUDY PARTICIPANTS

Eligible patients were men and women who met at least one of the following criteria: multiple cardiovascular risk factors, clinical evidence of atherosclerotic vascular disease, or any other condition putting the patient at high cardiovascular risk in the opinion of the patient's general practitioner. The criterion of multiple cardiovascular risk factors was defined as at least four of the following (or, for patients with diabetes, at least one of the following): an age of 65 years or older, male sex, hypertension (clinical history of hypertension or use of antihypertensive treatment), hypercholesterolemia (clinical history of hypercholesterolemia or use of lipid-lowering treatment), status as a current smoker, obesity (a body-mass index [the weight in kilograms divided by the square of the height in meters] of 30 or more), or a family history of premature cardiovascular disease (defined as cardiovascular disease at <55 years of age in the patient's father or a brother or at <65 years of age in the patient's mother or a sister). Clinical evidence of atherosclerotic vascular disease was defined as angina pectoris, peripheral artery disease, a history of ischemic stroke or transient ischemic attack, or previous treatment with an arterial revascularization procedure.

Exclusion criteria were previous myocardial infarction, hypersensitivity to n-3 fatty acids, pregnancy, clinical conditions with poor short-term prognosis, and conditions that would affect the ability to provide informed consent or comply with the protocol. All patients coming to the attention of one of the participating general practitioners and meeting the criteria for inclusion in the study were consecutively enrolled over a period of time that was prespecified by each general practitioner. All patients provided written informed consent before enrollment.

STUDY PROCEDURES

Study patients were randomly assigned to receive one capsule daily containing 1 g of n-3 fatty acids (polyunsaturated fatty acid ethyl esters with eicosapentaenoic acid and docosahexaenoic acid content not <85%, in a ratio that could range from

0.9:1 to 1.5:1) or placebo (olive oil). Treatment was centrally assigned by means of telephone on the basis of a concealed, computer-generated randomization list, stratified according to general practitioner. Patients, general practitioners, coordination and statistical staff, and outcome assessors were unaware of the study assignments until the final analyses were completed.

At baseline and at the scheduled yearly follow-up visits, the patient's general practitioner collected prespecified study information, including anthropometric measures, blood pressure, heart rate, lifestyle habits, current clinical conditions, any new diagnosis of cardiovascular disease, essential laboratory tests, current medical therapies, treatment compliance (according to patient self-report), and clinical outcomes. During these visits, the general practitioner also evaluated the patient for the presence and treatment of cardiovascular risk factors and considered, in light of current guidelines, how to reduce the patient's overall cardiovascular risk. Patients whose treatment was stopped for any reason were followed until the end of the study.

END POINTS

At the beginning of the trial, the primary efficacy end point was defined as the cumulative rate of death, nonfatal myocardial infarction, and nonfatal stroke.⁸ However, after a blinded assessment at 1 year showed an event rate that was lower than expected, the primary efficacy end point was revised as the composite of time to death from cardiovascular causes or hospital admission for cardiovascular causes.

Secondary efficacy measures included the composite of time to death, nonfatal myocardial infarction, or nonfatal stroke (the original primary end point); the composite of time to death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke; death from coronary heart disease; and sudden death from cardiac causes (see the Supplementary Appendix for definitions). Fatal and nonfatal coronary events and major ventricular arrhythmic events were included in preplanned exploratory analyses. All events included in the primary efficacy end point were documented with the use of a narrative summary and supporting documentation and were adjudicated on the basis of prespecified criteria by an ad hoc committee consisting of a cardiologist, an internist, and a neurologist who were

unaware of the study assignments. All serious adverse events, including those that were not necessarily related to the study drugs, were reported.

STATISTICAL ANALYSIS

The primary efficacy end point was initially defined as the cumulative rate of death, nonfatal myocardial infarction, and nonfatal stroke; the event rate was expected to be 2% per year. However, on blinded assessment at 1 year, the event rate was lower than expected, at 1.4% per year.⁸ Therefore, the primary end point was redefined as the time to death from cardiovascular causes or first hospital admission for cardiovascular causes. For this revised primary end point, we assumed an event rate in the placebo group of 15% at 5 years and a relative risk reduction of 15%, with a withdrawal rate of 10%. We adopted an event-driven design; to achieve a power of 90% at an alpha level of 0.05, a total of 1383 events were necessary to close the trial, which required an enrollment of approximately 11,200 patients. However, we decided that randomization could continue until all the participating general practitioners had had the opportunity to recruit patients.

Baseline characteristics of the patients who underwent randomization were compared by means of the chi-square test for categorical variables and the t-test or nonparametric test for continuous variables. Changes from baseline to 5 years in systolic and diastolic blood pressure; heart rate; total, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol levels; triglyceride levels; and blood glucose and glycated hemoglobin levels were assessed by means of analysis of variance, with adjustment for baseline values, and were reported as least-square means ($\pm$ SE).

Analyses were performed in the intention-to-treat population, except for a prespecified per-protocol analysis of the primary end point in patients with no major protocol violations who did not permanently stop treatment. Treatment effect on the study end points was analyzed by fitting Cox proportional-hazards models. Unadjusted hazard ratios and 95% confidence intervals were calculated for analyses of the primary and secondary end points and for the prespecified subgroup analyses. For the primary end point, results are also reported as hazard ratios adjusted for baseline variables that were unbalanced ($P < 0.05$) between the study groups. The

assumption of proportional hazards for the randomly assigned treatments was assessed by estimating the log(-log[survival distribution]) plotted against the log(failure time) and by the time-dependent covariate test. Kaplan-Meier estimates of survival curves were based on the results of the log-rank test.

The effect of the study treatment on the primary end point was assessed in subgroups defined by risk level or coexisting condition, age (<65 years vs. ≥65 years), sex, and inclusion criteria. We performed Cox analyses of the primary outcome in subgroups by fitting a Cox model with one term representing the study group, one representing the covariate of interest, and an interaction term to test for heterogeneity of the effect of n-3 fatty acids. All reported P values are two-sided. All analyses were performed with the use of SAS software, version 9.2 (SAS Institute).

RESULTS

TRIAL PARTICIPANTS

Between February 2004 and March 2007, a total of 12,513 patients were enrolled in the trial, of whom 6244 were randomly assigned to n-3 fatty acids and 6269 to placebo. A total of 12,505 patients were included in the intention-to-treat analyses, of whom 6239 received n-3 fatty acids and 6266 received placebo (see Fig. S1 in the Supplementary Appendix for the flow diagram).

Baseline characteristics are reported in Table 1, and in Table S1 in the Supplementary Appendix. The mean age was 64.0 years, and 61.5% of the patients were men. The most common inclusion criterion was diabetes mellitus plus one or more cardiovascular risk factors, present in 5986 patients (47.9%); 3691 patients (29.5%) had a history of atherosclerotic disease, 2602 (20.8%) had at least four cardiovascular risk factors excluding diabetes, and 226 (1.8%) had an increased cardiovascular risk according to the judgment of the general practitioner.

CARDIOVASCULAR RISK FACTORS AND MEDICATIONS

By the end of the trial, the overall cardiovascular-risk profile had improved in both groups (Table S2 in the Supplementary Appendix). The plasma triglyceride level fell significantly more in patients given n-3 fatty acids than in those who received placebo (-28.2 ± 1.3 mg per deciliter vs. -20.1 ± 1.3 mg per deciliter, $P < 0.001$). There was a

slight increase in the HDL level in patients who received n-3 fatty acids. There were no significant differences in blood pressure, heart rate, total and LDL cholesterol levels, or blood glucose or glycated hemoglobin levels between the two groups. Prescriptions of recommended cardiovascular drugs increased during follow-up to a similar degree in the two study groups (Table S3 in the Supplementary Appendix).

EFFICACY END POINTS

The follow-up period ended on October 31, 2011, after a median duration of 5.0 years (interquartile range, 4.0 to 5.5). The primary end point occurred in 1478 patients (11.8%), including 733 of 6239 who received n-3 fatty acids (11.7%) and 745 of 6266 who received placebo (11.9%). The incidence of the primary end point was not significantly reduced by n-3 fatty acids (adjusted hazard ratio, 0.97; 95% confidence interval [CI], 0.88 to 1.08; $P = 0.58$) (Table 2 and Fig. 1).

By the end of the study, 1115 patients who received n-3 fatty acids (17.9%) had stopped treatment, as had 1218 of those who received placebo (19.4%) (Table 3). In the per-protocol analysis, which included the remaining 10,172 patients, there were 527 primary end-point events among patients who received n-3 fatty acids (10.3% of patients) and 510 among those who received placebo (10.1%) (hazard ratio, 1.01; 95% CI, 0.89 to 1.14; $P = 0.89$).

The rates of secondary end points were also similar in the two study groups (Table 2). Death from cardiovascular causes occurred in 142 patients who received n-3 fatty acids (2.3%), as compared with 137 patients who received placebo (2.2%; hazard ratio, 1.03; 95% CI, 0.82 to 1.30; $P = 0.80$). Sudden death from cardiac causes occurred in 49 patients who received n-3 fatty acids (0.8%) and in 40 who received placebo (0.6%; hazard ratio, 1.22; 95% CI, 0.80 to 1.85; $P = 0.36$). There was no significant difference between the two groups in the proportion of patients who died from any of the other identified causes (Table S4 in the Supplementary Appendix). There was no significant difference in the number of hospital admissions for cardiovascular causes (620 in the group of patients who received n-3 fatty acids [9.9%] and 630 in the placebo group [10.1%]; hazard ratio, 0.98; 95% CI, 0.87 to 1.09; $P = 0.68$), but there were significantly fewer admissions for heart failure among patients who

Table 1. Baseline Characteristics of the Intention-to-Treat Population, According to Study Group.*

Characteristic	n-3 Fatty Acids (N=6239)	Placebo (N=6266)	P Value
Age — yr	63.9±9.3	64.0±9.6	0.54
Male sex — no. (%)	3890 (62.3)	3797 (60.6)	0.04
History of cardiovascular disease or risk factors — no. (%)			
Angina	778 (12.5)	730 (11.7)	0.16
Revascularization intervention	555 (8.9)	551 (8.8)	0.84
Stroke	296 (4.7)	298 (4.8)	0.98
Transient ischemic attack	521 (8.4)	501 (8.0)	0.47
Peripheral artery disease	499 (8.0)	487 (7.8)	0.63
Heart failure	180 (2.9)	219 (3.5)	0.05
Hypertension	5280 (84.6)	5297 (84.5)	0.87
Hypercholesterolemia	4402 (70.6)	4486 (71.6)	0.21
Diabetes mellitus	3721 (59.6)	3773 (60.2)	0.53
Obesity	3046 (48.8)	3036 (48.5)	0.69
Family history of premature cardiovascular disease	1964 (31.5)	1922 (30.7)	0.33
Current smoking	1377 (22.1)	1339 (21.4)	0.16
Medical treatment — no. (%)			
ACE inhibitor	2831 (45.4)	2807 (44.8)	0.52
ARB	1366 (21.9)	1371 (21.9)	0.98
Diuretic agent	2608 (41.8)	2576 (41.1)	0.43
Calcium-channel blocker	1812 (29.0)	1710 (27.3)	0.03
Beta-blocker	1316 (21.1)	1258 (20.1)	0.16
Oral hypoglycemic drug	2745 (44.0)	2771 (44.2)	0.80
Insulin	419 (6.7)	403 (6.4)	0.52
Statin	2544 (40.8)	2594 (41.4)	0.48
Antiplatelet agent	2569 (41.2)	2601 (41.5)	0.71
Fish consumption — no./total no. (%)			0.76
Never or very seldom	1444/6066 (23.8)	1467/6092 (24.1)	
1 time/wk	2625/6066 (43.3)	2620/6092 (43.0)	
2 times/wk	1635/6066 (27.0)	1666/6092 (27.3)	
≥3 times/wk	362/6066 (6.0)	339/6092 (5.6)	

* Plus-minus values are means ±SD. ACE denotes angiotensin-converting enzyme, and ARB angiotensin-receptor blocker.

received n-3 fatty acids than among those who received placebo (96 patients [1.5%] vs. 142 patients [2.3%], $P=0.002$) (Table S5 in the Supplementary Appendix).

In the prespecified subgroup analyses, there was a significant interaction between the efficacy of n-3 fatty acids and sex ($P=0.04$ for interaction). The event rate for the primary end point was lower among women than among men, with

a significantly lower rate of events among those who received n-3 fatty acids than among those who received placebo (hazard ratio, 0.82; 95% CI, 0.67 to 0.99; $P=0.04$) (Fig. 2).

A post hoc analysis of the efficacy of n-3 fatty acids in relation to baseline fish consumption (Table S6 in the Supplementary Appendix) showed no significant heterogeneity ($P=0.46$ for interaction). Post hoc subgroup analyses of the

Table 2. Primary and Secondary Outcomes.

Outcome	n-3 Fatty Acids (N=6239) <i>number (percent)</i>	Placebo (N=6266) <i>number (percent)</i>	Unadjusted Hazard Ratio (95% CI)	P Value
Primary end point	733 (11.7)	745 (11.9)	0.98 (0.88–1.08)	0.64
Components of primary end point				
Death from cardiovascular cause	142 (2.3)	137 (2.2)	1.03 (0.82–1.30)	0.80
Hospitalization for cardiovascular cause	620 (9.9)	630 (10.1)	0.98 (0.87–1.09)	0.68
Death or nonfatal myocardial infarction or stroke	484 (7.8)	467 (7.5)	1.03 (0.91–1.17)	0.64
Death from cardiovascular cause or nonfatal myocardial infarction or stroke	290 (4.6)	276 (4.4)	1.05 (0.89–1.23)	0.59
Fatal or nonfatal coronary event	310 (5.0)	324 (5.2)	0.95 (0.81–1.11)	0.51
Death from coronary cause	82 (1.3)	76 (1.2)	1.07 (0.78–1.46)	0.66
Sudden death from cardiac cause or major ventricular arrhythmia	60 (1.0)	47 (0.8)	1.27 (0.87–1.86)	0.22
Sudden death from cardiac cause	49 (0.8)	40 (0.6)	1.22 (0.80–1.85)	0.36

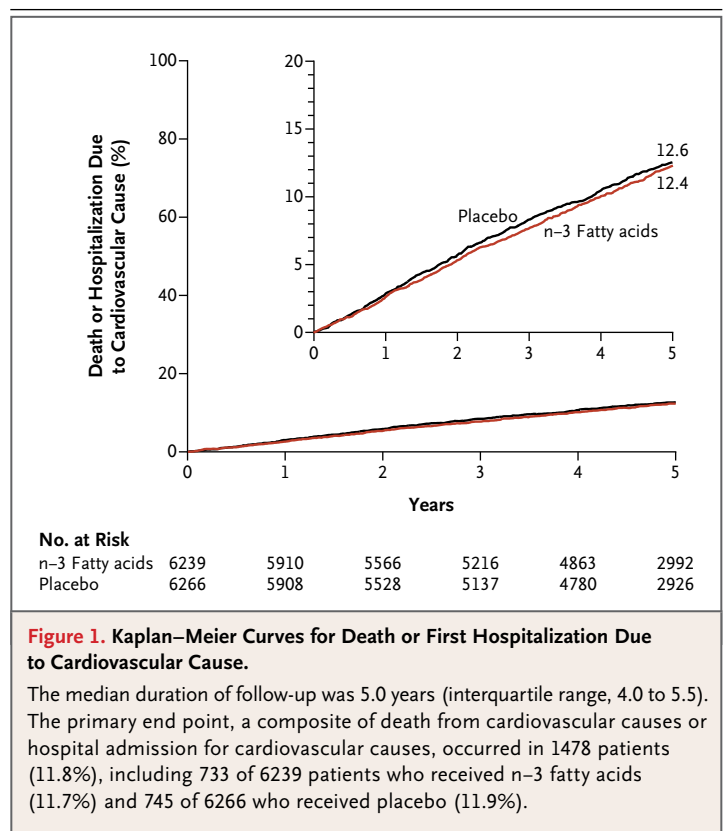
interaction of treatment with n-3 fatty acids in relation to aspirin use and statin use at baseline showed no evidence of interaction with these drugs ($P=0.34$ and $P=0.28$ for interaction, respectively).

ADVERSE EVENTS

Gastrointestinal side effects (abdominal pain, nausea, diarrhea, and other symptoms) were the most frequently reported adverse drug reactions, but the incidence did not differ significantly between the two groups (Table 3). The investigators attributed two cases of severe epistaxis, both in patients who were also receiving anticoagulant or antiplatelet therapy, to the experimental treatment. Among the serious adverse events, there were 490 diagnoses of cancer among patients who received n-3 fatty acids (7.9% of patients) and 453 among those who received placebo (7.2%, $P=0.19$); bleeding occurred in 16 patients who received n-3 fatty acids (0.3%) and in 12 who received placebo (0.2%, $P=0.44$).

DISCUSSION

The Risk and Prevention Study tested the hypothesis that n-3 fatty acids, which have been shown to be beneficial in patients who have had a myocardial infarction (in the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocar-



dico [GISSI]-Prevenzione study²) or heart failure (in the GISSI Heart Failure [GISSI-HF] study³), would be effective in reducing cardiovascular

Table 3. Permanent Discontinuation of Study Treatment and Reasons for Discontinuation.*

Variable	n-3 Fatty Acids (N = 6239)	Placebo (N = 6266)	P Value
	number (percent)		
Permanent discontinuation of treatment	1115 (17.9)	1218 (19.4)	0.03
Reason for discontinuation			
Adverse drug reaction	240 (3.8)	218 (3.5)	0.27
Gastrointestinal disorder	200 (3.2)	186 (3.0)	0.44
Skin disorder	8 (0.1)	17 (0.3)	0.07
Other	34 (0.5)	21 (0.3)	0.08
Severe epistaxis	2 (<0.1)	0	0.16
Patient's decision	514 (8.2)	601 (9.6)	0.01
Clinical reason	255 (4.1)	280 (4.5)	0.29
Open-label treatment with n-3 fatty acids	53 (0.8)	63 (1.0)	0.36
Other	54 (0.9)	45 (0.7)	0.35

* Each patient could have more than one reason for discontinuation. The reason for stopping treatment was missing for 22 patients.

risk among patients who were treated according to the standard of care and who had multiple cardiovascular risk factors or atherosclerotic disease but no previous myocardial infarction. Our findings provide no evidence of the usefulness of n-3 fatty acids for preventing cardiovascular death or disease in this population.

The consistently null effect across the various end points and subgroups does not suggest alternative interpretations, but a few epidemiologic observations are useful. The overall frequency of hard end points (particularly the rates of sudden death from cardiac causes and death from coronary causes), on which n-3 fatty acids showed a clear benefit in the GISSI-Prevenzione study,² was substantially lower than expected,⁸ possibly reflecting a country-specific low cardiovascular-risk profile (particularly with regard to dietary habits) and the rather intensive exposure of our study population to preventive treatments with further improvement during the 5-year follow-up period. Death from cardiovascular causes at 5 years made up only 18.7% of the primary composite end point. In addition, hospital admissions for cardiovascular causes were concentrated among patients 65 years of age or older and were rarely predictive of death: only 7.7% of patients admitted to the hospital for a cardiovascular cause died from cardiovascular causes during the trial.

The only two significant results (a reduction in hospital admissions for heart failure with n-3 fatty acids and their preventive effect in women) must be considered conservatively. Both may be due to chance, although they are consistent with two findings from other studies: the beneficial effect of n-3 fatty acids in patients with heart failure in the GISSI-HF study³ and the decrease in nonfatal coronary events in patients with hypercholesterolemia, the majority of whom were women, in the Japan Eicosapentaenoic Acid Lipid Intervention Study (JELIS).¹¹ Our results are more consistent with the null findings of the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial, which tested supplementation with n-3 fatty acids in patients with dysglycemia.¹²

Although the reasons for the discrepancy between the null results of our study and the results of the GISSI-Prevenzione and GISSI-HF trials^{2,3} remains to be determined, a possible explanation can be hypothesized. The beneficial effect of n-3 fatty acids in those two trials was due to a reduction in sudden deaths from cardiac causes. It is conceivable that the effects of n-3 fatty acids become manifest primarily in patients who are particularly prone to ventricular arrhythmic events (e.g., those with a myocardial scar or left ventricular dysfunction). Our trial had extremely limited power to detect a reduction in sudden deaths from cardiac causes or arrhythmic events. The safety

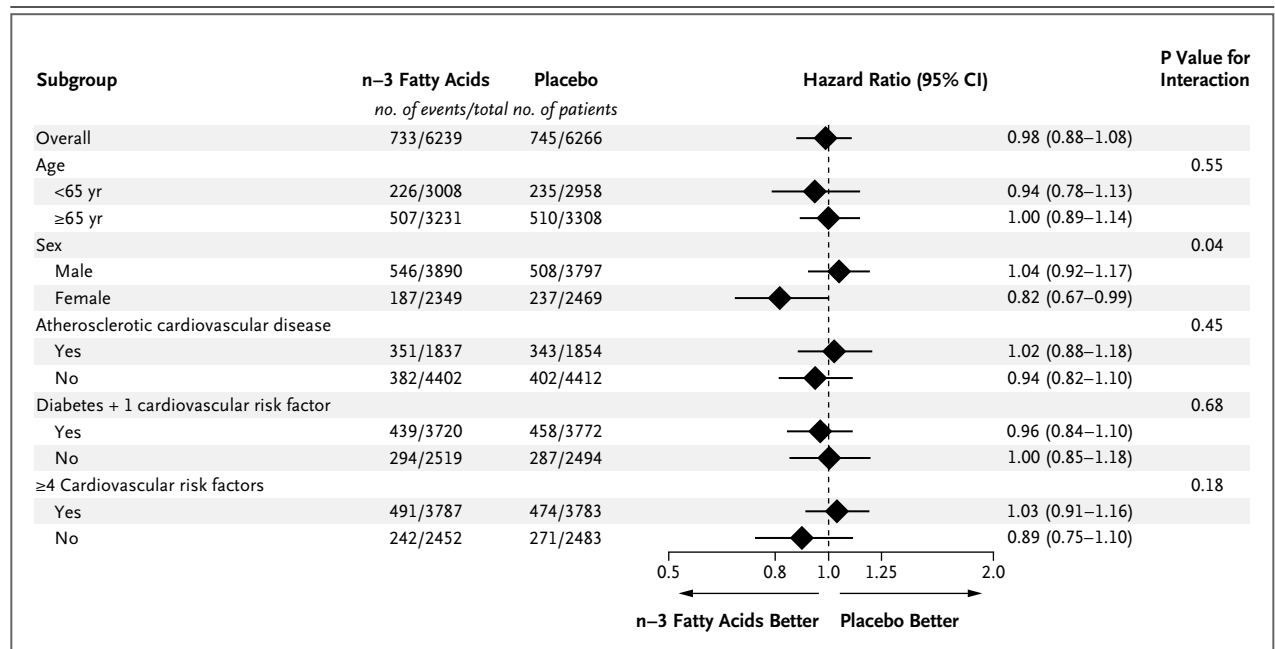


Figure 2. Effect of n-3 Polyunsaturated Fatty Acids on the Risk of Death or First Hospitalization Due to Cardiovascular Cause, According to Prespecified Subgroups.

In the prespecified subgroup analyses, the only significant interaction was between the efficacy of n-3 fatty acids and sex. The event rate for the primary outcome was lower among women than among men, with a significantly lower rate of events among those who received n-3 fatty acids than among those who received placebo. Horizontal lines indicate 95% confidence intervals, which were calculated by means of a Cox proportional-hazards model.

profile of n-3 fatty acids in this population of older persons who are already receiving many treatments for chronic disease could be of interest for their use in patient populations that are more prone to fatal and nonfatal arrhythmic events.^{2,3,13}

In summary, we conducted a randomized trial of n-3 fatty acids in a large population of patients with multiple cardiovascular risk factors but no history of myocardial infarction. The trial incorporated systematic efforts to optimize medical therapies and control cardiovascular risk factors.

On the basis of the results, we conclude that there was no significant benefit of n-3 fatty acids in reducing the risk of death from cardiovascular causes or hospital admission for cardiovascular causes.

Supported by Società Prodotti Antibiotici, Pfizer, and Sigma-Tau. Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the women and men who agreed to participate in the study; F. Clerici, B. Ferri, A. Flamminio, A. Palumbo, C. Pera, A. Polidoro, and G. Sgaroni for help in the conduct of the study; and J.D. Baggott for editing an earlier draft of the manuscript.

APPENDIX

The members of the writing group are as follows: Maria Carla Roncaglioni, M.Sc., Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS)—Istituto di Ricerche Farmacologiche Mario Negri, Milan; Massimo Tombesi, M.D., Centro Studi e Ricerche in Medicina Generale, Monza; Fausto Avanzini, M.D., IRCCS—Istituto di Ricerche Farmacologiche Mario Negri, Milan; Simona Barlera, M.Sc., IRCCS—Istituto di Ricerche Farmacologiche Mario Negri, Milan; Vittorio Caimi, M.D., Centro Studi e Ricerche in Medicina Generale, Monza; Paolo Longoni, M.D., Centro Studi e Ricerche in Medicina Generale, Monza; Irene Marzona, M.Sc., IRCCS—Istituto di Ricerche Farmacologiche Mario Negri, Milan; Valentina Milani, M.Sc., IRCCS—Istituto di Ricerche Farmacologiche Mario Negri, Milan; Maria Giuseppina Silletta, M.Sc., Consorzio Mario Negri Sud, Santa Maria Imbaro, Chieti; Gianni Tognoni, M.D., Consorzio Mario Negri Sud, Santa Maria Imbaro, Chieti; and Roberto Marchioli, M.D., Consorzio Mario Negri Sud, Santa Maria Imbaro, Chieti — all in Italy.

REFERENCES

1. De Caterina R. n-3 Fatty acids in cardiovascular disease. *N Engl J Med* 2011; 364:2439-50.
2. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. 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.

[Errata, Lancet 2001;357:642, 2007;369:106.]

3. GISSI-HF Investigators. 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.

4. Collaborative Group of the Primary Prevention Project. Low dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice. *Lancet* 2001;357:89-95.

5. Roncaglioni MC, Avanzini F, Roccatagliata D, et al. How general practitioners perceive and grade the cardiovascular risk of their patients. *Eur J Cardiovasc Prev Rehabil* 2004;11:233-8.

6. Roccatagliata D, Avanzini F, Monesi L, et al. Is global cardiovascular risk considered in current practice? Treatment

and control of hypertension, hyperlipidemia, and diabetes according to patients' risk level. *Vasc Health Risk Manag* 2006;2:507-14.

7. Monesi L, Avanzini F, Barlera S, et al. Appropriate use of antiplatelets: is prescription in daily practice influenced by the global cardiovascular risk? *Eur J Clin Pharmacol* 2005;61:595-601.

8. Rischio and Prevenzione Investigators. Efficacy of n-3 polyunsaturated fatty acids and feasibility of optimizing preventive strategies in patients at high cardiovascular risk: rationale, design and baseline characteristics of the Rischio and Prevenzione study, a large randomized trial in general practice. *Trials* 2010;11:68.

9. Avanzini F, Alli C, Bettelli G, et al. Feasibility of a large prospective study in general practice: an Italian experience. *BMJ* 1987;294:157-60.

10. International Conference on Harmonisation home page (<http://www.ich.org>).

11. 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.

12. The ORIGIN Trial Investigators. n-3 Fatty acids and cardiovascular outcomes in patients with dysglycemia. *N Engl J Med* 2012;367:309-18.

13. Marchioli R, Barzi F, Bomba E, et al. Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione. *Circulation* 2002;105:1897-903.

Copyright © 2013 Massachusetts Medical Society.

AN NEJM APP FOR IPHONE

The NEJM Image Challenge app brings a popular online feature to the smartphone. Optimized for viewing on the iPhone and iPod Touch, the Image Challenge app lets you test your diagnostic skills anytime, anywhere. The Image Challenge app randomly selects from 300 challenging clinical photos published in NEJM, with a new image added each week. View an image, choose your answer, get immediate feedback, and see how others answered. The Image Challenge app is available at the iTunes App Store.