ORIGINAL ARTICLE

Marine n−3 Fatty Acids and Prevention of Cardiovascular Disease and Cancer

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ABSTRACT

BACKGROUND

Higher intake of marine n−3 (also called omega-3) fatty acids has been associated with reduced risks of cardiovascular disease and cancer in several observational studies. Whether supplementation with n−3 fatty acids has such effects in general populations at usual risk for these end points is unclear.

METHODS

We conducted a randomized, placebo-controlled trial, with a two-by-two factorial design, of vitamin D_3 (at a dose of 2000 IU per day) and marine n−3 fatty acids (at a dose of 1 g per day) in the primary prevention of cardiovascular disease and cancer among men 50 years of age or older and women 55 years of age or older in the United States. Primary end points were major cardiovascular events (a composite of myocardial infarction, stroke, or death from cardiovascular causes) and invasive cancer of any type. Secondary end points included individual components of the composite cardiovascular end point, the composite end point plus coronary revascularization (expanded composite of cardiovascular events), site-specific cancers, and death from cancer. Safety was also assessed. This article reports the results of the comparison of n−3 fatty acids with placebo.

RESULTS

A total of 25,871 participants, including 5106 black participants, underwent randomization. During a median follow-up of 5.3 years, a major cardiovascular event occurred in 386 participants in the n−3 group and in 419 in the placebo group (hazard ratio, 0.92; 95% confidence interval [CI], 0.80 to 1.06; P=0.24). Invasive cancer was diagnosed in 820 participants in the n−3 group and in 797 in the placebo group (hazard ratio, 1.03; 95% CI, 0.93 to 1.13; P=0.56). In the analyses of key secondary end points, the hazard ratios were as follows: for the expanded composite end point of cardiovascular events, 0.93 (95% CI, 0.82 to 1.04); for total myocardial infarction, 0.72 (95% CI, 0.59 to 0.90); for total stroke, 1.04 (95% CI, 0.83 to 1.31); for death from cardiovascular causes, 0.96 (95% CI, 0.76 to 1.21); and for death from cancer (341 deaths from cancer), 0.97 (95% CI, 0.79 to 1.20). In the analysis of death from any cause (978 deaths overall), the hazard ratio was 1.02 (95% CI, 0.90 to 1.15). No excess risks of bleeding or other serious adverse events were observed.

CONCLUSIONS

Supplementation with n−3 fatty acids did not result in a lower incidence of major cardiovascular events or cancer than placebo. (Funded by the National Institutes of Health and others; VITAL ClinicalTrials.gov number, NCT01169259.)

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ARINE-DERIVED LONG-CHAIN N−3 (also called omega-3) fatty acids have shown promise for the primary prevention of cardiovascular disease in studies in animals; in small, randomized trials designed with intermediate cardiovascular end points; and in observational epidemiologic investigations.[1] However, midsize-to-large trials testing the effect of n−3 fatty acid supplements on clinical cardiovascular outcomes in the context of secondary prevention or high-risk populations have shown inconsistent results.[1,2] There is a paucity of data from large trials of n−3 supplements for the primary prevention of cardiovascular disease in a general population selected only on the basis of age and not on the basis of cardiovascular risk factors such as diabetes or dyslipidemia. Data from studies of n−3 fatty acids and cancer risk have also been inconsistent.[3] Given the popularity of fish oil as a strategy to reduce the incidence of chronic disease,[4] clarifying the relation between supplemental n−3 fatty acids and risks of cardiovascular disease and cancer and obtaining more-definitive data on the benefit–risk balance of these supplements is a high priority. The Vitamin D and Omega-3 Trial (VITAL) was conducted to address these knowledge gaps in a diverse U.S. cohort.

METHODS

TRIAL DESIGN AND OVERSIGHT

We conducted this randomized, double-blind, placebo-controlled trial, with a two-by-two factorial design, to test the benefits and risks of supplementation with vitamin D_3 (at a dose of 2000 IU per day) and n−3 fatty acids (1 g per day as a fish-oil capsule containing 840 mg of n−3 fatty acids, including 460 mg of eicosapentaenoic acid [EPA] and 380 mg of docosahexaenoic acid [DHA]) in the primary prevention of cardiovascular disease and cancer among men 50 years of age or older and women 55 years of age or older in the United States. The dose of n−3 fatty acids chosen was the one recommended by the American Heart Association for cardioprotection[5] and shown to be beneficial in a secondary prevention population.[6] The results are presented in two articles, with details of the full trial design provided in the accompanying article containing the vitamin D data,[7] in the Supplementary Appendix (available with the full text of this article

at NEJM.org), and in articles that have been published previously.[8,9] The protocol is available at NEJM.org.

Questionnaires were used at baseline to collect data on clinical and lifestyle risk factors and included a dietary questionnaire that ascertained participant-reported intake of fish and other foods. Annual questionnaires assessed adherence to and potential side effects of the randomized trial interventions, the development of major illnesses, and risk-factor updates. Blood samples were obtained at baseline from all willing participants and were assayed for the plasma n−3 index (EPA plus DHA as a percentage of total fatty acids[10]) by Quest Diagnostics with the use of liquid chromatography–tandem mass spectrometry.

The National Institutes of Health, the sponsors of the trial, had a collaborative role in the design and conduct of the trial. Final decisions regarding the data collection, management, and analysis, the review and approval of the manuscript, and the decision to submit the manuscript for publication resided with trial investigators and the trial research group. The trial was approved by the institutional review board of Partners HealthCare–Brigham and Women's Hospital, and the trial agents have received Investigational New Drug approval from the Food and Drug Administration. Pharmavite donated vitamin D and Pronova Bio-Pharma and BASF donated fish oil (Omacor); the companies also donated matching placebos and packaging in the form of calendar packs. Quest Diagnostics measured the plasma n−3 index at no cost to the trial. None of the donating companies had any role in the trial design or conduct, the data collection or analysis, or the manuscript preparation or review. The first three authors and the last author had full access to all the trial data and vouch for the completeness and accuracy of the data, for the accuracy of the data analyses, and for the fidelity of the trial to the protocol. All the participants provided written informed consent before enrollment in the trial.

TRIAL END POINTS

The primary end points were major cardiovascular events (composite of myocardial infarction, stroke, and death from cardiovascular causes) and invasive cancer of any type. Secondary cardiovascular end points were major cardiovascular events plus coronary revascularization (percutaneous coronary intervention [PCI] or coronary-artery bypass

grafting [CABG]) and individual components of the primary end point. Secondary cancer end points were colorectal, breast, and prostate cancers during the trial period and death from cancer. Medical records of the participants who had any of the end points were reviewed by an end-points committee of physicians who were unaware of the trial-group assignments. Myocardial infarction and stroke were confirmed with the use of established criteria.[11,12] Cancer was confirmed by histologic or cytologic data.[13] Additional details regarding end-point confirmation are provided in the accompanying article[7] and in the Supplementary Appendix.

STATISTICAL ANALYSIS

Analyses of the effects of the n−3 fatty acid intervention were based on the intention-to-treat principle, as described in the accompanying article on vitamin D supplementation.[7] Primary analyses were based on Cox proportional-hazards models that were controlled for age, sex, and randomization group in the vitamin D portion of the trial (vitamin D group or placebo group).

Possible variations in n−3 treatment effects according to age, sex, baseline cardiovascular risk factors, baseline dietary fish intake and plasma n−3 index, and concurrent randomization to the vitamin D group were specified a priori. Because vitamin D was also studied, the effects in racial or ethnic groups were of interest. Aspirin use and statin use were additional stratification variables. There was no control for multiple hypothesis testing, and no formal adjustment was made to the P values or confidence intervals. Thus, the results regarding exploratory end points and subgroups should be interpreted with caution. Additional details regarding the statistical analyses are provided in the Supplementary Appendix.

RESULTS

TRIAL PARTICIPANTS

Randomization to receive n−3 fatty acids, vitamin D, both active agents, or both placebos took place from November 2011 through March 2014. The trial intervention ceased as planned on December 31, 2017, which yielded a median follow-up of 5.3 years (range, 3.8 to 6.1). Figure S1 in the Supplementary Appendix shows the enrollment, randomization, and follow-up of the participants.

The characteristics of the trial participants at baseline are shown in Table 1, and in Table S1 in the Supplementary Appendix. Of the 25,871 participants, 51% were women. The mean age of the participants was 67.1 years. The cohort was racially diverse and included 5106 black participants (20.2% of the 25,304 participants with data on race and ethnic group). The characteristics were balanced between the two groups. The rate of response to the questionnaire averaged 93.1%, and rates of adherence to the trial regimen that were reported by the participants (percentage of participants who took at least two thirds of the trial capsules) in the n−3 group averaged 81.6% and in the placebo group averaged 81.5% over 5 years of follow-up (Table S2 in the Supplementary Appendix). The prevalence of outside use of fish-oil supplements was below 3.5% in each group throughout follow-up.

Blood samples were obtained at baseline from 16,956 of 25,871 participants (65.5%). Among the 15,535 participants (60.0%) who had blood samples at baseline that could be analyzed, the mean (±SD) plasma n−3 index was 2.7±0.9% in each group. Among the 1583 participants who also provided a blood sample at 1 year that could be analyzed, the mean n−3 index rose to 4.1% (increase of 54.7%) in the n−3 group and changed by less than 2% in the placebo group. There was no interaction between the two active treatments in the two-by-two factorial trial design. The outcomes regarding vitamin D supplementation are presented in the accompanying article.[7]

CARDIOVASCULAR DISEASE

During follow-up, there were 805 major cardiovascular events, with events in 386 participants in the n−3 group and in 419 in the placebo group (hazard ratio, 0.92; 95% confidence interval [CI], 0.80 to 1.06; P=0.24) (Table 2). In the analyses of prespecified secondary cardiovascular end points, the hazard ratios were as follows: for total myocardial infarction, 0.72 (95% CI, 0.59 to 0.90); for death from cardiovascular causes, 0.96 (95% CI, 0.76 to 1.21); for total stroke, 1.04 (95% CI, 0.83 to 1.31); and for the expanded composite end point of cardiovascular events, 0.93 (95% CI, 0.82 to 1.04). Additional cardiovascular end points included PCI (hazard ratio, 0.78; 95% CI, 0.63 to 0.95), CABG (hazard ratio, 0.99; 95% CI, 0.73 to 1.33), fatal myocardial infarction (hazard ratio, 0.50; 95% CI, 0.26 to 0.97), and total coronary heart disease (hazard ratio, 0.83; 95% CI, 0.71 to 0.97) (Ta-

Table 1. Characteristics of the Participants at Baseline, According to Randomized Assignment to Marine n–3 Fatty Acids or Placebo.*

Characteristic	Total (N=25,871)	n–3 Group (N=12,933)	Placebo Group (N=12,938)
Age — yr	67.1±7.1	67.2±7.1	67.1±7.1
Female sex — no. (%)	13,085 (50.6)	6547 (50.6)	6538 (50.5)
Race or ethnic group — no./total no. (%)†			
Non-Hispanic white	18,046/25,304 (71.3)	9044/12,653 (71.5)	9002/12,651 (71.2)
Black	5106/25,304 (20.2)	2549/12,653 (20.1)	2557/12,651 (20.2)
Nonblack Hispanic	1013/25,304 (4.0)	491/12,653 (3.9)	522/12,651 (4.1)
Asian or Pacific Islander	388/25,304 (1.5)	200/12,653 (1.6)	188/12,651 (1.5)
Native American	228/25,304 (0.9)	120/12,653 (0.9)	108/12,651 (0.9)
Other or unknown	523/25,304 (2.1)	249/12,653 (2.0)	274/12,651 (2.2)
Body-mass index‡	28.1±5.7	28.1±5.7	28.1±5.8
Current smoking — no./total no. (%)	1836/25,485 (7.2)	920/12,739 (7.2)	916/12,746 (7.2)
Hypertension treated with medication — no./total no. (%)	12,791/25,698 (49.8)	6338/12,853 (49.3)	6453/12,845 (50.2)
Current use of cholesterol-lowering medication — no./total no. (%)	9524/25,428 (37.5)	4788/12,707 (37.7)	4736/12,721 (37.2)
Diabetes — no./total no. (%)	3549/25,828 (13.7)	1799/12,912 (13.9)	1750/12,916 (13.5)

* Plus–minus values are means ±SD. There were no significant differences between the two groups with regard to the baseline characteristics. Percentages may not total 100 because of rounding.
† Race and ethnic group were reported by the participant.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters. Data were available for 12,615 participants in the n–3 group and for 12,639 in the placebo group.

ble 2). The results regarding stroke subtypes and death from stroke are shown in Table 2.

Cumulative incidence rates of major cardiovascular events are shown in Figure 1A. For major cardiovascular events, the curves did not differ significantly between the two groups. In an analysis that excluded the first 2 years of follow-up, the hazard ratio for major cardiovascular events in the n–3 group, as compared with the placebo group, was 0.89 (95% CI, 0.76 to 1.05), and the lower incidence of myocardial infarction in the n–3 group persisted (Table 2). The cumulative incidence rates of the prespecified secondary end points are shown in Figure S2 in the Supplementary Appendix.

Subgroup analyses showed a possible lower incidence of the primary cardiovascular end point with n–3 supplementation than with placebo among participants with low fish consumption (Fig. 2). Additional subgroup analyses are presented in Tables S3 and S4 and Figure S3 in the Supplementary Appendix, with a focus on exploring differences according to racial or ethnic group, diabetes status, number of traditional cardiovascular risk factors, dietary fish intake, and other

variables for the primary end point of major cardiovascular events and the secondary end point of total myocardial infarction. For myocardial infarction, these analyses are presented as explanatory analyses to assess whether the effect of the intervention was similar across subgroups. The suggestion of greater differences in the risk of myocardial infarction among blacks and among those with low fish intake, comparing the n–3 group with the placebo group, is discussed in the Supplementary Appendix. For the other secondary cardiovascular end points of stroke, death from cardiovascular causes, and the expanded composite of major cardiovascular events plus coronary revascularization, no appreciable effect modification was found (data not shown).

CANCER AND ALL-CAUSE MORTALITY

During follow-up, invasive cancer developed in 1617 participants (820 in the n–3 group vs. 797 in the placebo group), with similar risks in the two groups (hazard ratio, 1.03; 95% CI, 0.93 to 1.13; P=0.56) (Table 2). No significant differences between the randomized groups were observed with regard to the incidence of breast, prostate, or

Table 2. Hazard Ratios and 95% Confidence Intervals for the Primary, Secondary, and Other End Points, According to Randomized Assignment to n−3 Fatty Acids or Placebo, in Intention-to-Treat Analyses.*

End Point	n−3 Group (N = 12,933)	Placebo Group (N = 12,938)	Hazard Ratio (95% CI)
	no. of participants with event		
Cardiovascular disease			
Primary end point: major cardiovascular event†	386	419	0.92 (0.80–1.06)
Cardiovascular event in expanded composite end point‡	527	567	0.93 (0.82–1.04)
Total myocardial infarction	145	200	0.72 (0.59–0.90)
Total stroke	148	142	1.04 (0.83–1.31)
Death from cardiovascular causes	142	148	0.96 (0.76–1.21)
Other cardiovascular end point§			
PCI	162	208	0.78 (0.63–0.95)
CABG	85	86	0.99 (0.73–1.33)
Total coronary heart disease¶	308	370	0.83 (0.71–0.97)
Ischemic stroke	111	116	0.96 (0.74–1.24)
Hemorrhagic stroke	25	19	1.32 (0.72–2.39)
Death from coronary heart disease	37	49	0.76 (0.49–1.16)
Death from myocardial infarction	13	26	0.50 (0.26–0.97)
Death from stroke	22	20	1.10 (0.60–2.01)
Cancer			
Primary end point: invasive cancer of any type	820	797	1.03 (0.93–1.13)
Breast cancer	117	129	0.90 (0.70–1.16)
Prostate cancer	219	192	1.15 (0.94–1.39)
Colorectal cancer	54	44	1.23 (0.83–1.83)
Death from cancer	168	173	0.97 (0.79–1.20)
Death from any cause	493	485	1.02 (0.90–1.15)
Analyses excluding the first 2 yr of follow-up			
Major cardiovascular event	269	301	0.89 (0.76–1.05)
Total myocardial infarction	94	131	0.72 (0.55–0.93)
Invasive cancer of any type	536	476	1.13 (1.00–1.28)
Death from cancer	126	135	0.93 (0.73–1.19)
Death from any cause	371	381	0.97 (0.84–1.12)

* Analyses were from Cox regression models that were controlled for age, sex, and randomization group in the vitamin D portion of the trial. The 95% confidence intervals were not adjusted for multiple comparisons.
† This end point was a composite of myocardial infarction, stroke, or death from cardiovascular causes.
‡ This end point was a composite of myocardial infarction, stroke, death from cardiovascular causes, or coronary revascularization (percutaneous coronary intervention [PCI] or coronary-artery bypass grafting [CABG]).
§ These events were not prespecified as primary or secondary end points.
¶ This end point was a composite of myocardial infarction, coronary revascularization (PCI or CABG), and death from coronary heart disease.

Figure 1. Cumulative Incidence Rates of Major Cardiovascular Events and Invasive Cancer of Any Type, According to Year of Follow-up, in the n−3 Group and the Placebo Group.
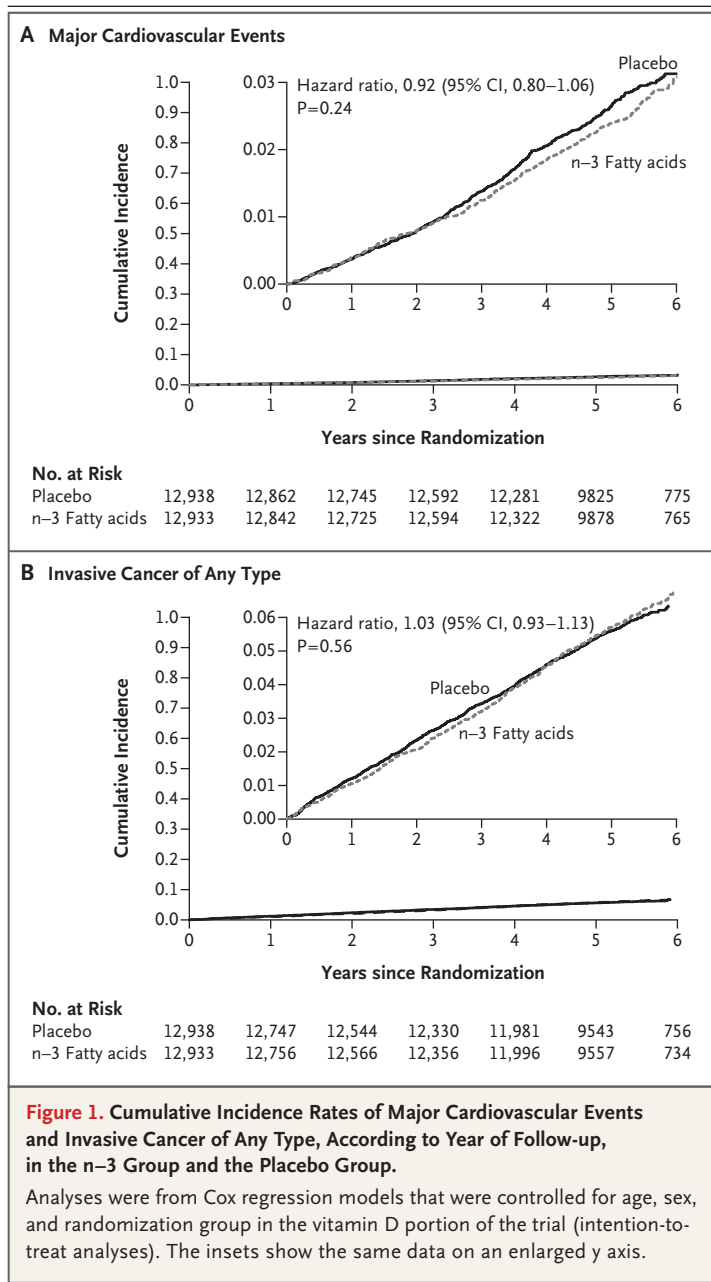
Analyses were from Cox regression models that were controlled for age, sex, and randomization group in the vitamin D portion of the trial (intention-to-treat analyses). The insets show the same data on an enlarged y axis.

hazards analysis suggested violation for cancer (P=0.08). In analyses that excluded the first 2 years of follow-up, the hazard ratio for cancer in the n−3 group, as compared with the placebo group, was 1.13 (95% CI, 1.00 to 1.28), and the hazard ratio for death from cancer was 0.93 (0.73 to 1.19) (Table 2).

In the subgroup analyses, the variable of sex may have modified the results regarding cancer incidence (P=0.02 for interaction) (Table S5 in the Supplementary Appendix). Fish intake at baseline may have modified the effects of the intervention on the incidence of death from any cause (P=0.02 for interaction) (Table S6 in the Supplementary Appendix). There were no other significant interactions regarding cancer end points or death from any cause.

ADVERSE EVENTS

The incidence of gastrointestinal symptoms, major bleeding episodes, or other serious adverse events did not differ significantly between the n−3 group and the placebo group. Details are provided in Table S7 in the Supplementary Appendix.

DISCUSSION

In this primary prevention trial with a median follow-up of 5.3 years, supplementation with n−3 fatty acids at a dose of 1 g per day did not lead to a significantly lower incidence of the primary end points of major cardiovascular events (a composite of myocardial infarction, stroke, and death from cardiovascular causes) or invasive cancer than placebo. Analyses of the components of the primary composite cardiovascular end point suggested that the risk of myocardial infarction was lower in the n−3 group than in the placebo group and that there was no significant difference in the incidence of death from cardiovascular causes or stroke. Exploratory analyses that excluded the first 2 years of follow-up suggested a nonsignificantly higher incidence of cancer in the n−3 group than in the placebo group but not a higher incidence of death from cancer.

Meta-analyses of n−3 supplementation trials involving adults who had cardiovascular disease or who were at high risk for cardiovascular disease have shown that supplementation has no, or at most a weak, preventive effect on cardiovascu-

colorectal cancer; death from cancer (341 deaths from cancer; hazard ratio, 0.97; 95% CI, 0.79 to 1.20); or death from any cause (978 deaths overall; hazard ratio, 1.02; 95% CI, 0.90 to 1.15).

The cumulative-incidence curves for cancer did not differ significantly between the trial groups at any year of follow-up (Fig. 1B). Tests for proportionality over time in the proportional-

Subgroup	No. of Participants	n–3 Fatty Acids	Placebo	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	P Value for Interaction
		no. of participants with event				
Age	25,871					0.84
<Median of 66.7 yr	12,859	129	142		0.91 (0.71–1.15)	
≥Median of 66.7 yr	13,012	257	277		0.93 (0.78–1.10)	
Sex	25,871					0.88
Male	12,786	213	233		0.91 (0.76–1.10)	
Female	13,085	173	186		0.93 (0.76–1.15)	
Race	25,304					0.26
Non-Hispanic white	18,046	292	289		1.00 (0.85–1.18)	
Black	5,106	62	83		0.74 (0.53–1.03)	
Other	2,152	26	30		0.94 (0.55–1.59)	
Current smoker	25,485					0.77
No	23,649	340	365		0.93 (0.80–1.07)	
Yes	1,836	41	44		0.94 (0.62–1.44)	
Diabetes	25,860					0.19
No	23,132	334	349		0.96 (0.82–1.11)	
Yes	2,728	52	70		0.74 (0.51–1.05)	
Hypertension	25,698					0.32
No	12,907	151	147		1.01 (0.80–1.26)	
Yes	12,791	231	270		0.87 (0.73–1.03)	
Current cholesterol medication	25,428					0.77
No	15,904	236	252		0.94 (0.79–1.13)	
Yes	9,524	140	154		0.90 (0.72–1.13)	
Parental history of myocardial infarction	22,915					0.56
No	19,262	268	288		0.93 (0.79–1.10)	
Yes	3,653	61	71		0.83 (0.59–1.17)	
Fish consumption	25,435					0.045
<Median of 1.5 servings/wk	13,514	189	232		0.81 (0.67–0.98)	
≥Median of 1.5 servings/wk	11,921	189	176		1.08 (0.88–1.32)	
Randomization in vitamin D portion of trial	25,871					0.56
Placebo group	12,944	200	209		0.96 (0.79–1.16)	
Vitamin D group	12,927	186	210		0.88 (0.72–1.08)	
No. of cardiovascular risk factors	25,871					0.19
0	7,802	92	85		1.06 (0.79–1.42)	
1	8,948	133	141		0.95 (0.75–1.20)	
≥2	9,121	161	193		0.84 (0.68–1.04)	
Baseline aspirin use	25,497					0.68
No	13,927	192	199		0.96 (0.78–1.17)	
Yes	11,570	187	209		0.90 (0.74–1.10)	
Baseline statin use	25,447					0.57
No	16,557	247	260		0.95 (0.80–1.14)	
Yes	8,890	130	147		0.88 (0.69–1.11)	

0.6 0.8 1.0 1.2 1.4 1.6

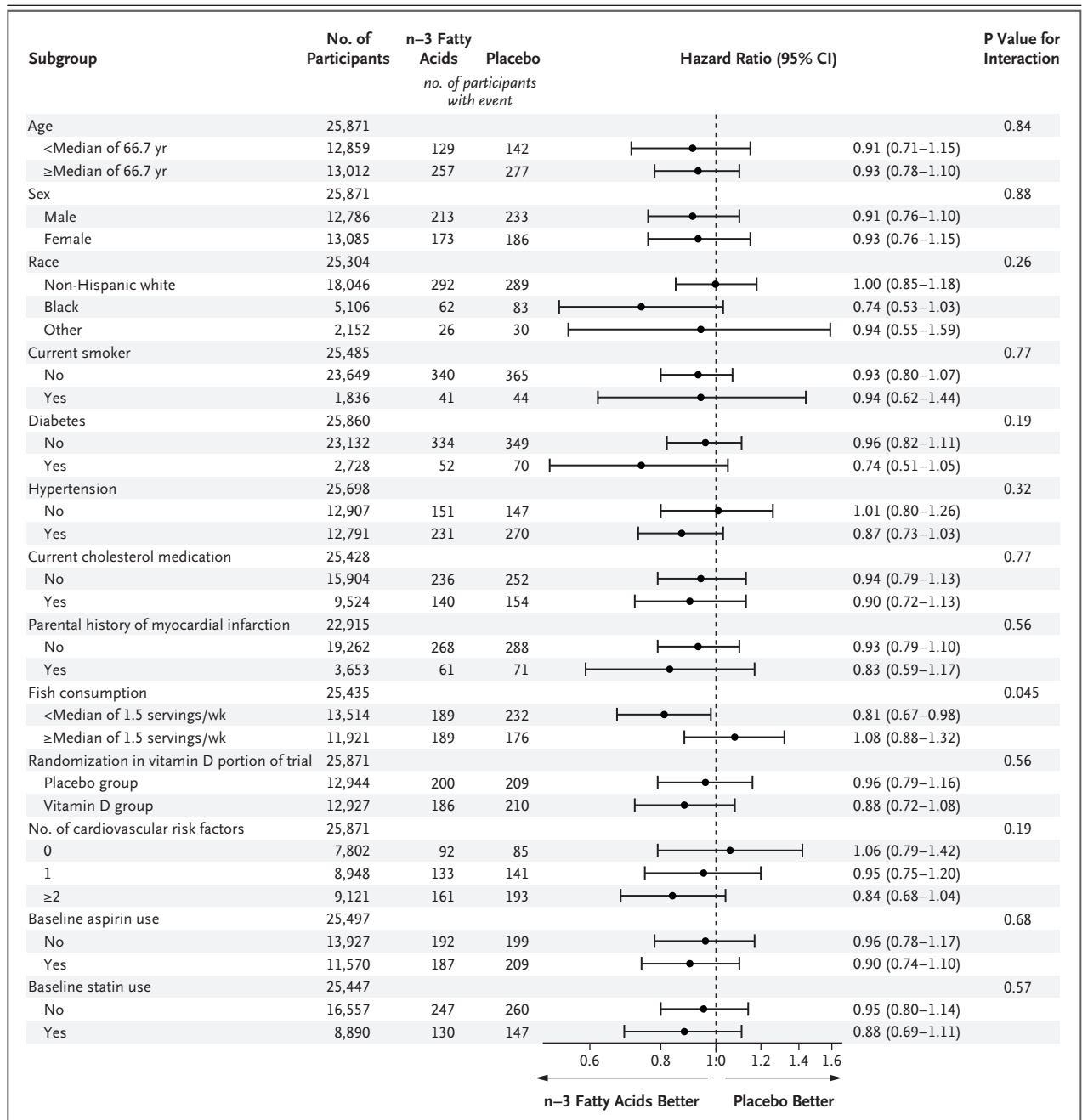n–3 Fatty Acids Better   Placebo Better

Figure 2. Hazard Ratios and 95% Confidence Intervals of Major Cardiovascular Events According to Subgroup, Comparing the n–3 Group with the Placebo Group.

Analyses were from Cox regression models that were controlled for age, sex, and randomization group in the vitamin D portion of the trial (intention-to-treat analyses). Analyses were not adjusted for multiple comparisons. Race and ethnic group were reported by the participant. Participants with diabetes and hypertension were defined as those receiving treatment for each condition. Parental history of myocardial infarction was defined as early myocardial infarction in a parent (at <60 years of age in father or <65 years of age in mother). Cardiovascular risk factors were smoking, diabetes, hypertension, a high cholesterol level, and parental history of early myocardial infarction.

lar outcomes, including major cardiovascular events, major coronary events, myocardial infarction, stroke, and revascularization.[14-16] The recent ASCEND (A Study of Cardiovascular Events in Diabetes) trial,[17] which tested n–3 supplementation (at a dose of 1 g per day) in adults with diabetes in the United Kingdom, also showed generally null results. Thus, the possible benefit of the intervention with respect to the secondary end points of myocardial infarction and PCI in our trial, which tested n–3 fatty acids for primary prevention in a usual-risk population, raises the question of potential differences between results from primary and secondary prevention trials. Neither our trial nor the secondary prevention trials indicate a benefit of n–3 supplementation with respect to stroke or composite cardiovascular end points. Our finding of a possible lower incidence of the primary cardiovascular end point with n–3 supplementation than with placebo among participants with low fish consumption — a characteristic that has rarely been examined as an effect modifier in previous trials — is hypothesis-generating.

Two early, large, open-label trials that involved more than 10,000 participants[6,18] and tested doses of 1 g or more of n–3 fatty acids per day showed significant protection against coronary events. However, all but one[19] of the subsequent placebo-controlled trials[17,19-24] (some with smaller sample sizes[19-22] and lower doses[20,22]) did not. The finding of a lower risk of coronary events with n–3 fatty acids than with placebo in our trial may be attributable in part to these design differences. Also, the prevalence of the use of medications for cardiovascular disease, including statins, beta-blockers, and anticoagulants, was higher in recent trials than in our trial, perhaps reducing the opportunity to detect incremental benefit. Although a recent meta-analysis[15] of n–3 trials showed no variation in results according to statin use, the dilution of a potential effect of n–3 supplementation by other medications cannot be ruled out. Such a dilution would probably be greater in the context of secondary prevention, in which medication use is more prevalent than in the context of primary prevention. In addition, participants in secondary prevention trials generally have more advanced atherosclerosis than those in primary prevention trials, which may necessitate the use of more powerful interventions than n–3 fatty acids (or higher doses

of n–3 fatty acids) to avert clinical events. Indeed, a greater benefit of n–3 supplementation on major cardiovascular events was observed among participants without a history of stroke in a recent meta-analysis[15] and among those without a history of cardiovascular disease in a trial involving patients with macular degeneration[25] than among those with such histories. Differences in fish consumption across study populations may have also influenced findings. Finally, there were few black participants in the secondary prevention trials, and our trial suggests that there is a greater coronary benefit of supplemental n–3 fatty acids in this racial group than in others.

The finding in subgroup analyses of the secondary end point of myocardial infarction that suggested possible greater cardiovascular benefits of n–3 supplementation in blacks than in non-Hispanic whites was unexpected, especially given that both these racial and ethnic groups had similar blood levels of EPA and DHA at baseline and similar fish intake. It may be a chance finding that would require corroboration in future trials. Recent observational studies have shown racial variation in associations of both marine and plant-derived n–3 biomarkers with the incidence of coronary disease.[26] Gene variants influence metabolism and the bioavailability of n–3 fatty acids, as has been observed in Greenland Inuits,[27] and may influence coronary risk.[28] Other racial and ethnic differences in clinical, dietary, or environmental factors may also account for this finding.[29] Finally, blacks have a higher prevalence of coexisting conditions such as diabetes and hypertension than do non-Hispanic whites. However, treatment-associated hazard ratios for myocardial infarction were lower across cardiovascular-risk strata among blacks, with lower hazard ratios than among non-Hispanic whites (Table S3 in the Supplementary Appendix).

The hypothesis that supplemental n–3 fatty acids confer coronary protection is biologically plausible. Data from laboratory studies and from studies in animals, as well as from small trials of intermediate cardiovascular end points in humans, support mechanisms including antithrombotic, hypotriglyceridemic, blood-pressure–lowering, and antiinflammatory effects; impeded growth of atherosclerotic plaques; slowing of heart rate; reduced susceptibility to cardiac arrhythmias; and the promotion of nitric oxide–induced endo-

thelial relaxation whereby n−3 fatty acids may reduce risk.[1,8] Data from experimental studies provide support for relevant molecular and gene-regulatory effects.[1] The dose–response curve for most effects plateaus at 1 g or less of n−3 fatty acids per day.[30] Observational studies suggest significant inverse associations between fish intake or n−3 fatty acid biomarkers and coronary outcomes — findings that are compatible with these mechanisms.[26,31-33]

With regard to cancer, our findings are consistent with the results of secondary prevention trials of n−3 fatty acids for cardiovascular disease, which have mostly shown neutral effects or slight (but nonsignificant) elevations in cancer incidence with n−3 fatty acids.[6,17,18,23,24,34,35] A 2014 meta-analysis of 10 trials of n−3 fatty acids showed a risk of cancer that was nonsignificantly higher, by 10%, with the n−3 fatty acids than with placebo (P=0.12).[36] A 2018 meta-analysis of n−3 trials of cardiovascular disease[15] also showed no significant association between supplementation and incidence of cancer but did not provide an effect estimate. Our finding of a more favorable effect regarding the incidence of cancer among women contrasts with the results of a European trial of n−3 fatty acids,[34] which showed a higher risk of cancer with n−3 fatty acids than with placebo among women but not among men. Among three trials investigating cancer mortality, two have shown a neutral treatment effect on the rate of death from cancer[17,19] and one has shown a possible benefit.[35] The lack of a significant treatment effect of n−3 supplementation on all-cause mortality in the present trial is consistent with the results of meta-analyses of earlier trials[14,16] and with the results of ASCEND.[17]

The strengths of our trial include a large general population sample with racial, ethnic group, and geographic diversity; high rates of follow-up and adherence to the pill regimen; high rates of obtaining blood samples; validated biomarkers of adherence to the regimen; dietary assessments; and rigorously adjudicated end points. Ancillary studies examining diabetes, atrial fibrillation, cognition, autoimmune disorders, and other outcomes in our trial are in progress and may inform the overall benefit–risk balance of n−3 supplementation.

Our trial also has certain limitations. The median duration of the trial intervention was 5.3 years. The single dose level of n−3 fatty acids that was used in this trial did not permit exploration of dose–response relationships. However, the dose that we used has been recommended by the American Heart Association for cardioprotection in persons with a history of coronary disease[5,37] and is at least twice the dose that has been recommended for cardiovascular protection in healthy populations (equivalent to 1 to 2 servings of fish per week).[31,37] The results of ongoing trials[38,39] that are testing higher doses in high-risk populations will be informative but may not apply to primary prevention. Some of our subgroup analyses are based on small numbers of events.

In conclusion, supplementation with n−3 fatty acids did not result in a lower incidence than placebo of the primary end points of major cardiovascular events (a composite of myocardial infarction, stroke, or death from cardiovascular causes) and invasive cancer of any type.

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