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Controlled Trial of Fish Oil for Regression of Human Coronary Atherosclerosis

FRANK M. SACKS, MD,*‡ PETER H. STONE, MD, FACC,*‡ C. MICHAEL GIBSON, MD, FACC,*†‡
DAVID I. SILVERMAN, MD, FACC,†‡ BERNARD ROSNER, PHD,*‡
RICHARD C. PASTERNAK, MD, FACC,†‡ FOR THE HARP RESEARCH GROUP

Boston, Massachusetts

Objectives. **This randomized clinical trial tested whether fish oil supplements can improve human coronary atherosclerosis.**

Background. **Epidemiologic studies of populations whose intake of oily fish is high, as well as laboratory studies of the effects of the polyunsaturated fatty acids in fish oil, support the hypothesis that fish oil is antiatherogenic.**

Methods. **Patients with angiographically documented coronary heart disease and normal plasma lipid levels were randomized to receive either fish oil capsules (n = 31), containing 6 g of n-3 fatty acids, or olive oil capsules (n = 28) for an average duration of 28 months. Coronary atherosclerosis on angiography was quantified by computer-assisted image analysis.**

Results. **Mean (±SD) baseline characteristics were age 62 ± 7 years, plasma total cholesterol concentration 187 ± 31 mg/dl (4.83 ± 0.80 mmol/liter) and triglyceride levels 132 ± 70 mg/dl (1.51 ± 0.80 mmol/liter). Fish oil lowered triglyceride levels by 30% (p = 0.007) but had no significant effects on other plasma lipoprotein levels. At the end of the trial, eicosapentaenoic acid in adipose tissue samples was 0.91% in the fish oil group compared with 0.20% in the control group (p < 0.0001). At baseline, the minimal lumen diameter of coronary artery lesions (n = 305) was 1.64 ± 0.76 mm, and percent narrowing was 48 ± 14%. Mean minimal diameter of atherosclerotic coronary arteries decreased by 0.104 and 0.138 mm in the fish oil and control groups, respectively (p = 0.6 between groups), and percent stenosis increased by 2.4% and 2.6%, respectively (p = 0.8). Confidence intervals exclude improvement by fish oil treatment of >0.17 mm, or >2.6%.**

Conclusions. **Fish oil treatment for 2 years does not promote major favorable changes in the diameter of atherosclerotic coronary arteries.**

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Evidence from several lines of investigation suggests that n-3 polyunsaturated fatty acids may protect against atherosclerotic vascular disease. In arctic populations, low mortality from coronary heart disease is attributed to a diet that is rich in oily fish (1). In a controlled trial in British patients with coronary heart disease, intake of fatty fish significantly reduced coronary heart disease death (2). The protective effect of fish intake could be caused by the fish oil (3,4), by other nutrients in fish or by an indirect effect of fish intake on other aspects of the diet. The n-3 polyunsaturated long-chain fatty acids unique to fish oils demonstrate several biologic effects that could be antiatherogenic, including arterial vasodilation (5,6), reduced thromboxane and enhanced prostacyclin synthesis (3,4), inhibition of platelet aggregation (3,4), decreased blood pressure (7), reduction of plasma triglyceride levels (8) and elevation of high density lipoprotein $(HDL)_2$ cholesterol (9,10). However, other effects of n-3 fatty acids may have a proatherogenic effect, including elevations of plasma low density lipoprotein (LDL) cholesterol (9,11,12) and glucose levels (13) and enhanced oxidation of LDL cholesterol (14,15). In several animal models of atherosclerosis, fish oil diminished atherogenesis (16–22), but other studies have found no effect (15,23,24) or even worsening (25–27). Studies of fish oil in human coronary atherosclerosis have been limited to attempts to prevent restenosis after coronary angioplasty, and results have been mixed (28,29). Therefore, to date, the value of n-3 fatty acids as agents for prevention or treatment of human atherosclerosis remains undetermined. In the present study, in patients with coronary artery disease, we tested the effect of a moderate dose of fish oil on atherosclerosis in native coronary arteries.

Methods

Patients. Eligible patients had narrowing of ≥30% lumen diameter of a major coronary artery, as shown by diagnostic coronary angiography at either Brigham and Women's or Beth Israel Hospitals, a total cholesterol concentraation <250 mg/dl (6.43 mmol/liter) and triglyceride level <350 mg/dl (4.0 mmol/

From the Channing Laboratory and Cardiovascular Divisons, Departments of Medicine, *Brigham and Women's Hospital, †Beth Israel Hospital and ‡Harvard Medical School, Boston, Massachusetts. This study was supported by Grants RO1 HL36392 and NCRR-GCRC-RR02635 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland; by grants from Warner Lambert-Parke Davis, East Hanover, New Jersey; and by an Established Investigator Award to Dr. Sacks from the American Heart Association, Dallas, Texas.

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Address for correspondence: Dr. Frank M. Sacks, Department of Nutrition, Harvard School of Public Health, 665 Huntington Avenue, Boston, Massachusetts 02115.

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liter) and were between the ages of 30 and 75 years. Patients were determined to be eligible by lipid criteria from measurements on two qualifying visits conducted 1 to 2 weeks apart. Qualifying visits were delayed at least 8 weeks after hospital discharge for patients who had acute myocardial infarction and at least 12 weeks for patients who underwent coronary artery bypass surgery or angioplasty. Patients with congestive heart failure; liver, renal or serious gastrointestinal disease; insulin-dependent diabetes mellitus; current cigarette smoking; or alcohol intake >14 drinks/week were excluded. Randomization of patients was stratified according to clinical management of their coronary artery disease (medical or surgical) and total/HDL cholesterol ratio (>6.0 or ≤6.0). Forty-one of 80 patients were randomized to the fish oil group and 39 to the control group. The study was approved by the Institutional Review Boards of Brigham and Women's and Beth Israel Hospitals, and written informed consent was obtained at the first qualifying visit and again before the follow-up coronary catheterization.

During the initial hospital stay for coronary catheterization, dietary instruction was provided to every patient according to the guidelines of the National Cholesterol Education Program Step I (30). The instruction was reinforced, and a 7-day diet record was collected at the randomization visit and every 3 months during the trial. The diet records were analyzed using a computerized nutrient data base (Food Processor II, ESHA Research).

Protocol. Patients in the fish oil group were given bottles containing a 3-month supply of fish oil capsules (Promega, Parke-Davis). They were instructed to take twelve 1-g capsules daily, in divided doses, preferably after meals. Each fish oil capsule contained 500 mg of n-3 polyunsaturated fatty acids composed of eicosapentaenoic acid (240 mg), docosahexaenoic acid (160 mg) and other (100 mg) (mainly docosapentaenoic acid). Therefore, the total daily dose of n-3 fatty acids was 6 g. The control group was treated similarly with capsules of olive oil that were identical in appearance to the fish oil capsules. The patients and personnel responsible for laboratory measurements, cardiac catheterization, and analysis of angiography films were blinded to treatment assignment.

Every 12 weeks, a research nurse reviewed with the patients side effects, diet, and concomitant medications and performed a pill count. Every 24 weeks, the patients received an interval medical history and physical examination by a physician. At the 12- and 24-week visits and every 24 weeks thereafter, a fasting blood sample was obtained for lipid analysis. At the end of the study, a sample of adipose tissue was aspirated from gluteal fat for fatty acid measurements.

If the total cholesterol level of any patient increased to ≥250 mg/dl (6.43 mmol/liter) on two consecutive measurements, intensified dietary instruction was given, followed by drug therapy with cholestyramine 4 to 16 g or nicotinic acid 2 g, or both, as needed to lower total cholesterol to <250 mg/dl (6.43 mmol/liter).

Lipid measurements. Plasma lipids were measured on fasting fresh plasma at the Lipid Research Laboratory, Brigham and Women's Hospital. Cholesterol and triglyceride levels were measured by enzymatic reagents (Boehringer Mannheim) in whole plasma (31). The HDL cholesterol was measured in plasma after precipitation of very low density lipoprotein (VLDL) and LDL cholesterol by dextran and magnesium chloride (32). The LDL cholesterol was calculated. The fatty acid composition of adipose tissue was determined by capillary gas chromatography (33). Apolipoprotein B was measured by immunonephelometry (Inkstar Corp.) in one batch on samples continuously stored at −80°C using calibrators provided by the Centers for Disease Control. Lipoprotein Lp(a) was measured by sandwich enzyme-linked immunosorbent assay (Terumo, Inc.).

Cardiac catheterization. At the baseline cardiac catheterization, the following conditions were recorded and reproduced at the time of the repeat procedure: cine camera angle and skew, contrast agent (ionic or nonionic), sequence of angiographic views and the dosing of vasoactive medications. To confirm reproduction of angiographic views, the initial cine film was viewed on a projector in the catheterization laboratory during the repeat procedure. On hospital admission on the day before the angiography, the patients were treated with the same cardiac medications they were taking at the time of the initial procedure unless contraindicated for medical reasons. The two catheterizations were performed at the same time of day whenever possible to eliminate any diurnal variation in vasomotor tone.

Quantitative angiography. From films unlabeled as to treatment assignment, coronary artery lumen diameter was quantitated by an operator-interactive program as previously described (34). The classification of segments was similar to that used in other trials (35). Lesions were defined as lumen obstructions >20%. New lesions were defined as vessels with an obstruction <20% at the time of initial catheterization, ≥20% at follow-up examination and a change ≥7.8% diameter stenosis, previously determined to be significant (34). For vessels without a lesion, segments >2.0 mm, were analyzed. Lesions that underwent angioplasty and adjacent vessel segments were not analyzed. Five consecutive frames from the same phase of the cardiac cycle (preferably end-diastole) were analyzed by edge detection (36,37) after threefold to fourfold optical magnification and digitization into a 512 × 512-pixel array. The minimal diameter of a stenosis was defined as the minimal diameter of a polynomial fit to the five pixels surrounding the minimal point of the diameter–length relation.

Statistics. The primary outcome variable was the change in minimal diameter of coronary artery lesions expressed as a continuous variable. The individual coronary artery lesions comprised the basic units in the analysis. Unbypassed and bypassed vessel segments were included as in a previous trial (38). The treatment effect was adjusted by multiple logistic regression for the intraclass correlation between changes in lesions in a person (39); the initial diameter of the lesions, because initial diameter has been shown to be a significant predictor of lesion change (40); and the differences between the groups in the proportion of bypassed and unbypassed

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Table 1. Baseline Characteristics of 59 Study Patients

	Fish Oil Group (n = 31)	Control Group (n = 28)
Age (yr)	62 ± 7	62 ± 7
Duration in trial (days)	829 ± 127	890 ± 123
Duration from initial to final cardiac catheterization	958 ± 136	993 ± 96
Gender (M/F)	29/2	26/2
Hypertension	15 (48%)	10 (36%)
Diabetes	5 (16%)	3 (11%)
Family history of CVD	21 (68%)	13 (46%)
CABG	16 (52%)	12 (43%)
MI	17 (55%)	16 (57%)
Medication		
Beta-blockers	17 (55%)	15 (54%)
Calcium channel blockers	16 (52%)	12 (43%)
Nitrates	13 (42%)	7 (25%)
Antiplatelet agents	30 (97%)	26 (93%)
ACE inhibitors	3 (10%)	3 (11%)
Oral hypoglycemic drugs	5 (16%)	1 (4%)

Data presented are mean value ± SD or number (%) of patients. ACE = angiotensin-converting enzyme; CABG = coronary artery bypass graft surgery; CVD = cardiovascular disease; F = female; M = male; MI = myocardial infarction.

lesions. The effects of covariates, such as age, baseline plasma lipid levels and change in lipids, were also studied. Patient-specific changes were derived using the mean of the changes in diameter of the lesions in each patient.

Results

Patients. The final study group consisted of the 59 patients who underwent follow-up cardiac catheterization (55 men, 4 women; 31 patients in the fish oil group, 28 in the control group) (Table 1). Twenty-one randomized patients did not complete the protocol (10 in the fish oil, 11 in the control group). Reasons for not completing the study were death (one in the control group); refusal to undergo the second cardiac catheterization (three in the fish oil group, nine in the control group); development of medical conditions precluding participation (three in the fish oil group, one in the control group); intolerance to the capsules (three in the fish oil group); and a missing initial angiography film (one in the fish oil group).

There were no significant differences in the baseline characteristics of the patients between the two treatment groups (Tables 1 and 2). Dietary saturated fat comprised 8 ± 2% (mean ± SD) of energy intake in both groups at baseline and during follow-up. Dietary cholesterol intake, ~200 ± 90 mg/day at baseline, decreased in the fish oil group by 28 mg compared with an increase in the control group of 22 mg ($p = 0.04$). Both groups gained a mean of 2 kg body weight during the trial ($p < 0.005$). Adherence, estimated by pill counts, averaged 80% in the fish oil group and 90% in the control group. Medication use was similar among the groups at baseline except for oral hypoglycemic drugs (Table 1), and there were no significant changes in medication use during the trial in either group.

Plasma lipoprotein changes. As a group, the patients had average levels at baseline, and there were no significant differences between the fish oil and control groups (Table 2). Plasma triglyceride levels decreased by 30% in the fish oil group compared with those in the control group ($p = 0.007$). The decrease in triglyceride levels in the fish oil group was established by 12 weeks and remained stable throughout the follow-up. There were no significant differences between the groups in changes in plasma total, LDL or HDL cholesterol or apolipoprotein B or lipoprotein Lp(a) levels. Hypocholesterolemic drug therapy for a total cholesterol level >250 mg/dl (6.43 mmol/liter) was required for four patients in the fish oil group and none in the control group. The medications used were cholestyramine (4 to 8 g/day) in three patients and cholestyramine (8 to 16 g) with nicotinic acid (2 g) in one patient.

Adipose tissue fatty acids. At the end of the trial, adipose tissue in the fish oil group was significantly enriched in the n-3 polyunsaturated fatty acids of marine origin that were contained in the fish oil ($p < 0.0001$) (Table 3). In contrast, the control group that received olive oil had a significantly higher content of oleic acid ($p = 0.0009$), the major fatty acid in olive oil, and higher levels of palmitic acid ($p = 0.05$), the major

Table 2. Body Weight and Plasma Lipid Levels at Baseline and During Fish Oil or Control Supplementation

	Fish Oil Group (n = 31)			Control Group (n = 28)		
	Baseline	Follow-Up	Difference	Baseline	Follow-Up	Difference
Body weight (kg)	80 ± 14	82 ± 14	2 ± 3*	79 ± 15	80 ± 15	2 ± 3*
Systolic BP (mm Hg)	126 ± 29	129 ± 16	3 ± 29	133 ± 19	137 ± 29	5 ± 25
Diastolic BP (mm Hg)	76 ± 16	77 ± 7	1 ± 18	77 ± 7.6	77 ± 7	0 ± 8
Cholesterol (mg/dl)	189 ± 33	194 ± 37	5 ± 17	184 ± 28	193 ± 24	9 ± 20†
HDL-C (mg/dl)	41 ± 9	42 ± 11	1 ± 6	40 ± 12	42 ± 13	3 ± 7
LDL-C (mg/dl)	122 ± 29	132 ± 30	10 ± 17*	117 ± 27	122 ± 24	6 ± 17
Triglycerides (mg/dl)	128 ± 67	101 ± 50	−28 ± 53*	137 ± 73	143 ± 67	6 ± 35‡
Apolipoprotein B (mg/dl)	80 ± 13	86 ± 15	6 ± 6*	74 ± 16	79 ± 13	5 ± 9*
Lipoprotein Lp(a) (mg/dl)	8.2 ± 4.4	9.7 ± 5.1	1.2 ± 2.8†	6.4 ± 3.6	5.7 ± 3.9	−1.1 ± 7.2

*$p < 0.01$, †$p < 0.05$ for within-group changes. ‡$p < 0.01$ for between-group changes. All differences between baseline values were not significant ($p > 0.1$). Data presented are mean value ± SD, except those for lipoprotein Lp(a), which are geometric mean values. BP = blood pressure; HDL-C (LDL-C) high (low) density lipoprotein cholesterol.

Table 3. Adipose Tissue Fatty Acid Levels (mean ± SD) After 2.4 Years of Fish Oil or Control Supplementation

Acid	Fish Oil Group (n = 29)	Control Group (n = 28)	p Value
Lauric	0.74 ± 0.57	0.86 ± 0.43	0.4
Palmitic	12.4 ± 3.7	14.1 ± 2.5	0.048
Stearic	3.37 ± 0.85	3.0 ± 0.9	0.16
Oleic	37.3 ± 6.6	42.3 ± 3.9	0.0009
Linoleic	18.2 ± 4.7	18.7 ± 3.7	0.7
Arachidonic	0.60 ± 0.28	0.89 ± 0.37	0.001
EPA (n-3)	0.91 ± 0.53	0.20 ± 0.31	< 0.0001
DPA (n-3)	0.62 ± 0.25	0.25 ± 0.15	< 0.0001
DHA (n-3)	0.84 ± 0.41	0.31 ± 0.23	< 0.0001
EPA+DPA+DHA	2.37 ± 1.14	0.76 ± 0.66	< 0.0001

Two patients refused the fat biopsy. DHA = docosahexaenoic acid; DPA = docosapentaenoic acid; EPA = eicosapentaenoic acid.

tissue saturated fatty acid. Arachidonic acid was lower in the fish oil group than in the control group (p = 0.001).

Coronary artery lesions. The principal analysis consists of 179 lesions in 31 patients in the active group (5.8 lesions/patient) and 126 lesions in 28 patients in the control group (4.5 lesions/patient) (Table 4, Fig. 1). The difference in number of lesions is mainly accounted for by a greater number of bypassed vessels in the fish oil group, by chance. The adjusted changes were −0.104 and −0.138 mm in minimal diameter (p = 0.6) and +2.4% and +2.6% in percent diameter narrowing (p = 0.8) in the fish oil and control groups, respectively, indicating slight worsening in both groups (Table 4, Fig. 1). The adjusted differences between the groups were +0.03 mm (95% confidence interval [CI] −0.10 to 0.17 mm) and −0.2% (95% CI −2.6 to 2.1%). These confidence intervals indicate that the trial excludes improvement by fish oil treatment of >0.17 mm, or >2.6% stenosis. Lesions in unbypassed vessels showed less change in minimal diameter than lesions that were in bypassed circulation (p < 0.0001), but there were no significant differences between the treatment groups. In contrast, the diameter of normal vessel segments increased in the fish oil group but not in the control group (p = 0.03 between groups for minimal diameter; p = 0.07 for average diameter).

Additional analyses of lesion change. Patient-specific analysis of the changes in coronary lesions revealed no significant differences between the groups; for all lesions, mean change was −0.12 (SD 0.29) and −0.11 (SD 0.27) in the fish oil and control groups, respectively (p = 0.9), and for unbypassed lesions the changes were −0.10 (SD 0.29) and −0.11 (SD 0.34) (p = 0.9). For a categoric analysis, lesions were classified as progressing or regressing if the changes were ≥7.8% in percent stenosis as previously determined (34). The majority of the lesions showed no change (Table 5), and there were no significant differences between the groups. Restricting the

Table 4. Effect of Fish Oil on Coronary Artery Disease: Lesion-Specific Analysis

	Fish Oil Group				Control Group				
	No. of Lesions	Pre	Post	Adjusted Change	No. of Lesions	Pre	Post	Adjusted Change	Fish Oil − Control
All abnormal segments									
Min diam (mm)	179	1.74 ± 0.82	1.62 ± 0.86	−0.104 ± 0.05	126	1.57 ± 0.71	1.46 ± 0.67	−0.138 ± 0.04*	0.03 (−0.10–0.17)
Stenosis (%)		46.5 ± 14.2	49.4 ± 12.5	2.4 ± 0.7*		48.7 ± 13.7	50.7 ± 12.2	2.6 ± 0.8*	−0.2 (−2.6–2.1)
Unbypassed abnormal segments									
Min diam (mm)	96	1.85 ± 0.85	1.82 ± 0.94	−0.06 ± 0.07	86	1.64 ± 0.71	1.55 ± 0.70	−0.10 ± 0.04	0.04 (−0.14–0.23)
Stenosis (%)		43.8 ± 13.5	46.9 ± 11.7	2.9 ± 1.3†		46.7 ± 12.8	49.2 ± 12.0	3.2 ± 1.1†	−0.3 (−3.8–3.2)
Bypassed abnormal segments									
Min diam (mm)	83	1.61 ± 0.76	1.39 ± 0.70	−0.23 ± 0.06*	40	1.43 ± 0.70	1.28 ± 0.54	−0.23 ± 0.06*	0.00 (−0.16–0.17)
Stenosis (%)		49.7 ± 14.3	52.4 ± 12.8	2.3 ± 1.1†		53.1 ± 14.5	53.8 ± 12.3	1.7 ± 1.4	0.6 (3.0–4.2)
Unbypassed normal segments									
Min diam (mm)	41	2.24 ± 0.96	2.38 ± 0.98	0.15 ± 0.07†	51	2.40 ± 0.92	2.33 ± 0.90	−0.05 ± 0.05	0.20 (0.01–0.39) (p = 0.03)
Av diam (mm)		2.73 ± 0.94	2.90 ± 0.97	0.17 ± 0.07†		2.98 ± 0.93	2.97 ± 0.98	−0.01 ± 0.07	0.19 (−0.03–0.40)

*p < 0.01, †p < 0.05 for within-group changes. Adjusted changes were computed by multiple regression analysis with adjustment for the intraclass correlation, differences in pretreatment value (Pre) and proportion of bypassed lesions. Data presented are mean values ± SD (for pretreatment and posttreatment [Post] values) or ±SE (for adjusted change). Av (Min) diam = average (minimal) diameter; Fish Oil − Control = difference between adjusted changes (95% confidence intervals).

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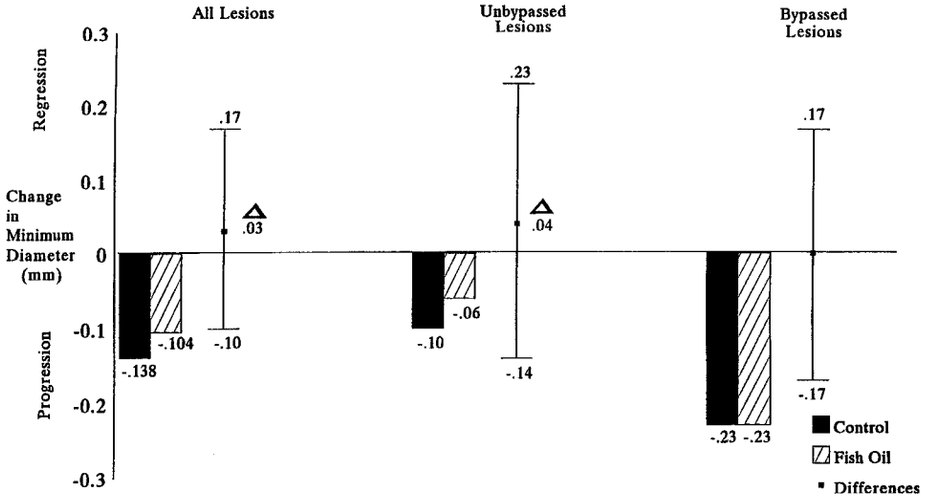

Figure 1. Changes in coronary artery lesions before and after 2.4 years of treatment with fish oil. The between-group differences are shown with 95% confidence intervals (**vertical lines**). Changes in minimal coronary artery diameter and percent stenosis in the active treatment and control groups were adjusted for the effects of differences in pretreatment values, for differences in the proportion of lesions that were in a bypassed circulation and for the intraclass correlation of the changes in lesions within a patient. Change = post-treatment minus pretreatment.

categoric analysis to unbypassed lesions produced similar results to the full group. One unbypassed vessel became occluded in the fish oil group compared with three vessels in three patients in the control group.

Subgroup analyses did not demonstrate any significant effect of fish oil in patients according to baseline lipid levels, change in lipid levels, baseline coronary lesion diameter or adipose tissue n-3 fatty acid levels.

Clinical coronary disease events are counted for all randomized patients up to the time of repeat catheterization or for 2.4 years in the dropouts. In the fish oil group, there were eight events in seven patients (one nonfatal myocardial infarction, one stroke, three coronary angioplasties, three hospital admissions for unstable angina). In the control group, there were 11 events in seven patients (1 coronary death, 2 nonfatal myocardial infarctions, 1 hospital admission for congestive heart failure, 3 coronary angioplasties, 4 hospital admissions for unstable angina). No patient had coronary bypass surgery after randomization.

Discussion

The present study found no evidence that the progression of coronary atherosclerosis over a 2.4-year period, as measured by change in lumen diameter, is affected by fish oil supplementation. The patients were proved to be compliant by the findings of a sustained decrease in plasma triglyceride levels in the fish oil group and the substantially higher n-3 fatty acid levels in adipose tissue biopsy samples. The equilibration time for dietary and adipose tissue fatty acid is ~2 years (41). We expect that the n-3 fatty acids enriched the patients' coronary lesions, as found in a previous pathologic study (42).

Limitations of the study. The confidence intervals of the differences between the groups exclude beneficial effects of >0.17 mm in minimal coronary diameter or >2.6% stenosis. This finding indicates that if fish oil were to have had a favorable effect of magnitude similar to that reported with hypocholesterolemic drug therapy or with nonpharmacologic therapy (35,43–46), then such a difference would have been detectable in the present study. This sensitivity is the result of there being 305 lesions available for analysis, the precision of the angiographic measurements and the highly powered statistical analysis technique. However, it is possible that fish oil could produce very small improvement in coronary diameter, perhaps 0.04 mm as in a recent trial of lovastatin (47), that would not have been detected in our trial. Our trial experienced a dropout rate of 26% compared with 10% to 26% in previous trials of similar duration (35,38,44,45,47). The sever-

Table 5. Effect of Fish Oil on Progression, Regression, New Lesions and Total Occlusions

	Fish Oil Group		Control Group	
	No. (%) of Patients (n = 31)	No. (%) of Lesions (n = 179)	No. (%) of Patients (n = 28)	No. (%) of Lesions (n = 126)
Progression*	11 (35%)	52 (29%)	12 (43%)	24 (19%)
Regression	4 (13%)	23 (13%)	7 (25%)	20 (16%)
Mixed	14 (45%)	—	6 (21%)	—
Total occlusions	6 (19%)	12 (7%)	6 (21%)	9 (7%)
No changes	2 (6%)	101 (51%)	3 (11%)	78 (62%)
New lesions	2 (6%)	3 (2%)	4 (14%)	4 (3%)

*Total occlusions not included.

ity of coronary disease in the present trial is similar to or worse than that of previous studies (35,38,43–47). Previous studies conflict as to whether mild or severe lesions are benefited by therapy (45,47). Finally, although the duration of the treatment, 28 months, is similar to (35,38,45,47) or longer than (43,46) previous regression trials, we cannot exclude the possibility that fish oil could produce benefit that is too gradual to be detected or that is preceded by a latent period of ≥2 years.

Potential biologic causes of lack of benefit. 1) The olive oil that the control group received for a placebo could have been beneficial, for example, by improving serum lipids (48). This seems to be unlikely, because no lipid-lowering effect was evident in our patients in the control group, and the control group showed progression of disease at a comparable extent to that in the control groups in other arteriographic trials. 2) Fish oil could have a proatherosclerotic action because the highly unsaturated fatty acids appear to increase the susceptibility of LDL for oxidation (14,15), an event that enhances the atherogenicity of LDL in cultured cells. However, the net effect of fish oil on LDL oxidation in vivo is not certain because laboratory studies found potentially beneficial counterbalancing actions of fish oil, including protection from atherogenic effects of oxidized LDL (49), diminished production of superoxide by monocytes (50), prevention of lipid peroxidation by platelets (51) and stimulation of alpha-tocopherol incorporation into cell membranes (52).

We found that the diameter of normal coronary arteries increased in the fish oil but not in the control group, a finding of borderline significance ($p = 0.07$ for average diameter; $p = 0.04$ for minimal diameter). Because the change in normal arteries was not a primary end point, this could be caused by chance in view of multiple statistical comparisons. However, it is possible that fish oil promoted vasodilation in these arteries or improved their endothelial function (3–6).

Patients with normal plasma lipid levels were studied because hypocholesterolemic drug treatment has been recommended for hyperlipidemic patients. In this normolipidemic group, the possibility that coronary atherosclerosis might be less dependent on plasma cholesterol levels made fish oil an attractive intervention because the mechanism of action could be independent of the effects on plasma lipid levels (2,3,16,21,22). In our patients, the mean plasma cholesterol level, 187 mg/dl (4.83 mmol/liter), is by far the lowest of any human atherosclerosis regression trial. Despite our patients' low cholesterol levels, the coronary lesions in the fish oil and control groups progressed at a similar rate as in hyperlipidemic patients in certain previous studies. In both groups, the progression of lesions was not correlated with plasma lipid levels, indicating that in this population, nonlipid risk factors may regulate the atherosclerotic process.

Conclusions. Epidemiologic and intervention studies do not reveal a clear picture of the effects of fish oil on coronary atherosclerosis. Arctic peoples consume marine oils in fish and sea mammals and have low rates of coronary heart disease (1). Certain observational studies in industrialized countries have found a protective association of fish intake on the development of coronary heart disease (53–55), but other studies have not (56–59). However, fish intake is much lower in these countries than in the arctic. Restenosis after coronary angioplasty is not convincingly benefited despite multiple studies (28,29,60). The most compelling evidence in favor of fish is a clinical trial of patients who had coronary heart disease (2). Patients were asked to ingest two portions per week of fatty fish, which supplied ~0.5 mg of n-3 fatty acids daily, one-twelfth of the dose in our trial. Death and recurrent nonfatal coronary heart disease were lowered early in the 5-year follow-up period in the fish group compared with that in the control group. It is possible that fish oil could prevent coronary events by retarding thrombosis or improving endothelial function that leaves coronary stenosis unchanged or by preventing fatal ventricular arrhythmias (61). Alternatively, the relatively low quantity of n-3 fatty acids consumed in the previous trial (2) raises a question about the effect of fish oil itself and supports the possibility that other constituents of the fish are cardioprotective. In view of these uncertainties, a definitive assessment of the effect of fish oil on coronary heart disease requires a sufficient number of patients to determine whether myocardial infarction and death rates are reduced.

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