

Double-Blind, Randomized, Controlled Trial of Fish Oil Supplements in Prevention of Recurrence of Stenosis After Coronary Angioplasty

Isabelle Bairati, MD, PhD; Louis Roy, MD; and François Meyer, MD, DSc

Background. Previous studies suggest that recurrence of coronary stenosis after percutaneous transluminal coronary angioplasty (PTCA) might be prevented with dietary supplements rich in ω -3 fatty acids. The purpose of the present study was to evaluate this hypothesis. In addition, the relation between usual dietary consumption of ω -3 fatty acids and restenosis was assessed.

Methods and Results. A double-blind, randomized, controlled trial was conducted in which 205 patients undergoing a first PTCA received 15 capsules per day containing 1 g of either fish oil (2.7 g/day of eicosapentaenoic acid, 1.8 g/day of docosahexaenoic acid) or olive oil. The treatment was started 3 weeks before PTCA and continued for 6 months thereafter. Dietary intake was assessed by food frequency questionnaire. At 6 months after PTCA, patients underwent a control angiography. All angiographic lesions were measured by quantitative computer analysis. Four criteria were used to define restenosis. Restenosis occurred less often in the fish oil group (22.0–35.6% depending on the definition) than in the control group (40.0–53.3%). After controlling for other risk factors of restenosis, the association of fish oil supplementation with a lower frequency of restenosis was statistically significant ($p=0.03$) for three of four definitions. After adjustment, a dietary intake of ω -3 fatty acids of more than 0.15 g/day was also associated with a lower frequency of restenosis ($p\leq 0.03$).

Conclusions. This trial documented the protective effect of fish oil supplements on the recurrence of coronary stenosis 6 months after PTCA. The study results suggest that a dietary intervention could be useful in preventing restenosis. (*Circulation* 1992;85:950–956)

KEY WORDS • atherosclerosis • angiography • ω -3 fatty acids • diet • clinical trials

Since its introduction by Andreas R. Gruentzig in 1977,¹ percutaneous transluminal coronary angioplasty (PTCA) has become a standard treatment for patients with coronary artery disease. The National Heart, Lung, and Blood Institute (NHLBI) reported important changes between 1977–1981 and 1985–1986 in patient selection and strategy of PTCA and noted an improvement in angiographic success rates immediately after PTCA.² However, the recurrence of stenosis 6 months after PTCA remains frequent: about 30–45% in recent reports.^{3–6}

Studies of Inuit populations drew attention to the relation between their diet, which is rich in ω -3 fatty acids, and their low incidence of coronary artery disease.^{7,8} Numerous studies have documented the biolog-

ical effects of ω -3 fatty acids, in particular, the inhibition of platelet activity^{9–14} and the effects on smooth muscle cells,^{14–18} which might be important factors in the prevention of restenosis after PTCA. It was suggested that supplementing the diet with fish oil concentrate, rich in ω -3 fatty acids, might help prevent restenosis after PTCA. Six clinical trials,^{19–24} with different study designs, have evaluated this hypothesis but have led to divergent results. These discrepancies could be ascribed in part to differences in the assessment of angiographic lesions. Quantitative computer analysis (QCA) provides a reliable instrument with which to improve the validity of the measurements of the angiographic lesions.

A double-blind, randomized, controlled clinical trial was conducted to evaluate the effect of fish oil supplements in the prevention of restenosis as assessed by QCA. The relation of ω -3 fatty acid dietary intake and consumption of fish, mollusks, and crustaceans to the recurrence of stenosis was also documented.

Methods

Study Design

From February 1987 through December 1989, patients referred to the Quebec Heart Institute for a first angioplasty of a not completely obstructed coronary

From the Department of Social and Preventive Medicine (I.B., F.M.), Faculty of Medicine, Laval University, Quebec City, and the Quebec Heart Institute (L.R.), Ste-Foy, Quebec, Canada.

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Address for correspondence: Dr. François Meyer, Cancer Prevention Program, Fred Hutchinson Cancer Research Center, MP 702, 1124 Columbia Street, Seattle, WA 98104.

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vessel were invited to participate in a randomized trial of fish oil supplementation in the prevention of restenosis. The research protocol and the informed consent form were approved by the ethics committees of Laval University and the Quebec Heart Institute. Two hundred five eligible patients gave informed consent to the trial. Subjects were assigned to the treatment or control group by simple randomization using random-number tables. The patients, treating physicians, angiographers, and people involved in the data collection for the study were all blinded to treatment assignment. Fish oil and olive oil capsules were counted and stored in coded bottles prepared in advance in the hospital pharmacy. All subjects were requested to take five capsules three times daily for 3 weeks before PTCA and for 6 months thereafter. The treatment period before PTCA was considered necessary to ensure modifications of cell membrane phospholipids by fish oil before angioplasty.^{12,13,25} The fish oil-treated patients received 15 g/day of MaxEPA, supplying 2.7 g eicosapentaenoic acid (EPA) and 1.8 g docosahexaenoic acid (DHA) daily. The patients in the control group received 15 g of olive oil daily. Before PTCA and during the follow-up period, all patients continued their usual antianginal treatment. Pharmacological preparation for angioplasty included tranquilizers and aspirin (325 mg). During PTCA, all patients received 100 μ g/ml (5 ml/hr) nitroglycerin and 10,000 units heparin IV, repeated depending on the duration of the intervention. No nitroglycerin was given during baseline or control angiographies.

Seventeen patients were excluded because PTCA was not performed as scheduled because of complete stenosis ($n=6$), emergency PTCA ($n=5$), refusal of PTCA ($n=2$), noncompliance with treatment ($n=1$), pulmonary embolism ($n=1$), improvement of stenosis ($n=1$), and allergy ($n=1$). Twenty-five subjects were excluded because PTCA was tried unsuccessfully ($n=16$) or led to severe complications ($n=9$). These 42 patients were equally distributed in the two groups. For 21 patients in the fish oil group and 11 in the olive oil group, PTCA was considered successful by visual assessment but not by QCA. Of these 32 subjects, 14 had a reduction in the percentage of stenosis of the vessel diameter of less than 20% (mean, 12.8%) and 26 had more than 50% stenosis of the vessel diameter after PTCA (mean, 57.1%). These exclusions after randomization were inherent to the study design, which imposed both a preangioplasty supplementation period and a successful PTCA. Twelve patients, six in each group, were not evaluated angiographically after 6 months; the control angiography was not performed because of medical ($n=2$) or personal ($n=10$) reasons. Thus, the study population was restricted to the 119 subjects with one-vessel or multivessel disease who had a control angiography at 6 months.

QCA of Angiography

A single angiographer, trained in QCA (ImageComm Systems Inc., Santa Clara, Calif.), measured the lesions on the angiographies performed at enrollment, before and immediately after PTCA, and at 6 months.^{26,27} These measurements were taken blindly with no knowledge of patients' clinical data and treatment assignment. All images were selected for QCA at the end of diastole and on the view with the most severe stenosis. For

each patient, identical views were selected on all angiographies. A circular region centered on the stenosis was drawn, and edge detection was automatically performed based on the arterial center line. When the adjacent radiographic structure caused a noisy edge contour, the center line or borderline of the vessel was corrected manually. With the catheter for calibration, QCA provided absolute measurements in millimeters for minimal luminal diameter and diameter of the normal vessel and computed percentage of vessel diameter stenosis. To assess the intraobserver variability, these measurements were repeated at the end of the study on 59 randomly selected images: 19 at enrollment, 20 immediately after PTCA, and 20 at the end of the study. QCA and visual measurements in the 151 subjects were compared with successful PTCA by visual assessment. Compared with QCA measurements, visual assessment in the present study consistently overestimated the percentage of stenosis before PTCA and the percentage gained by PTCA.

Diet Assessment

At enrollment, a quantitative food frequency questionnaire with 103 food items was administered by a trained research assistant and completed by all patients. The questionnaire assessed usual food consumption during the 3 months preceding the enrollment, with special emphasis on dietary fat. Dietary intakes of nutrients (i.e., total fat, polyunsaturated fat, monounsaturated fat, saturated fat, ω -3 fatty acids, and cholesterol) were estimated using the Canadian nutrient file and data from the US Department of Agriculture for EPA and DHA; the conjunction of EPA and DHA is referred to as ω -3 fatty acids in the present study.

Clinical Follow-up

Clinical visits were scheduled at baseline and at 1, 3, and 6 months after PTCA. Medical history was updated and a physical examination was performed by the treating physician. The study nurse administered a life-style questionnaire and assessed compliance by counting the remaining capsules in the bottles. An ECG and standard laboratory examinations, including blood lipids, were performed at enrollment, 1 month after PTCA, and at the end of the study. A standard Bruce protocol exercise treadmill test and exercise ²⁰¹Tl scintigraphy²⁸ were performed 1 and 3 months, respectively, after PTCA.

Definitions

The most severe lesion on enrollment or immediately before PTCA angiography was selected as the baseline value. Success of PTCA was defined as reduction in the percentage of vessel diameter stenosis of at least 20%, a post-PTCA percentage of vessel diameter stenosis of less than 50%, and no major complication related to angioplasty.²⁰ To assess the effect of fish oil supplementation on restenosis, four definitions of restenosis were considered. First, restenosis was defined by a final percentage of vessel diameter stenosis $\geq 50\%$ (definition 1).²⁹ This commonly used definition is based on the physiological concept of coronary flow reserve and on experimental evidence in animals.²⁹ Second, restenosis was considered to have occurred when at least half of the gain in the percentage of vessel diameter stenosis achieved at PTCA was lost at the end of the follow-up

(definition 2).³⁰ This definition proposed by the NHLBI is frequently used in clinical settings. Third, restenosis was present when the final minimal luminal diameter (mm) was less than the post-PTCA minimal luminal diameter minus 2 SDs of the difference between two measurements of the minimal luminal diameter on the same image (definition 3).³¹ This new concept for defining restenosis was introduced by Serruys et al^{29,31} as a consequence of the development of QCA evaluation of angiographic lesions. The fourth definition required the presence of all of the above criteria (definition 4). Thus, with this last definition, only the most definite cases of restenosis were considered as such.

Without knowledge of the patients' clinical status and treatment group, a physician reviewed blindly all data from ²⁰¹Tl scintigraphy and classified the patients into one of four ordinal categories using a computerized linear profile program (MICRODATA, Siemens): 1) definite ischemia when the difference between stress and redistribution images was $\geq 15\%$, 2) possible ischemia when the difference between stress and redistribution images was $>7\%$ and $<15\%$, 3) probable absence of ischemia when this difference was $\leq 7\%$ or scintigraphy was negative but not realized in optimum conditions, and 4) absence of ischemia when there was no defect at a scintigraphy realized in optimum conditions. During exercise testing, ischemia was defined on ECG as the presence of ≥ 1 mm horizontal or downsloping depression of the ST segment at 80 msec after the J point.

Statistical Analysis

Baseline risk factors were compared between the two treatment groups by Student's *t* test for continuous variables and by χ^2 for categorical variables. Level of agreement between repeated measures by QCA was assessed by intraclass correlation coefficients.³² Proportions of patients with ischemia at the Bruce exercise test were compared between the two groups by χ^2 . For ²⁰¹Tl scintigraphy, ordinal polytomous logistic regression analysis was used to compare the results of patients in the two treatment groups.³³ Proportions of patients with restenosis were compared between the two groups by χ^2 . Multiple logistic regression models were used to determine the effect of fish oil concentrate on restenosis while controlling for other risk factors.³⁴ The relation between ω -3 fatty acid dietary intakes and restenosis was also assessed in these models. All dietary variables were converted from continuous variables to ordered categorical variables based on the terciles of their distribution in the entire study population. In each case, the lowest tercile was the reference category. This trial was undertaken with the a priori hypothesis that fish oil concentrate would help prevent restenosis after PTCA, but a conservative standpoint was adopted in the presentation of the study results. A difference was considered to be statistically significant when the two-sided *p* value was ≤ 0.05 under the null hypothesis.

Results

Baseline Characteristics

For the 205 patients enrolled, there was no statistically significant difference between the two groups in age, sex, medical history, class of angina,³⁵ smoking status, and measurements of stenosis. Fifty-nine pa-

TABLE 1. Percentages of Patients in Treatment and Control Groups With Known or Suspected Risk Factors for Restenosis at Time of Enrollment

	Patients (%)		<i>p</i>
	Treatment (<i>n</i> =59)	Control (<i>n</i> =60)	
Male	81	82	0.97
History of hypertension	36	35	0.95
History of myocardial infarction	29	27	0.79
History of diabetes	7	7	0.99
History of smoking	80	83	0.61
Current smoking	36	20	0.06
Body mass index $\geq 27^*$	49	48	0.93
Angina classes III and IV†	61	63	0.79
Stenosis of vessel diameter $>95\%$	15	8	0.24
Diameter of normal vessel <2.4 mm	34	18	0.05
Proximal left anterior descending coronary artery	10	20	0.14
Ejection fraction $\leq 50\%$	15	8	0.24
Multiple stenoses to be dilated	10	13	0.59

*Body mass index=wt/ht².

†Canadian Cardiovascular Society classes.

tients in the treatment group and 60 in the control group completed the study after a successful angioplasty according to QCA. Their mean ages were similar (54 ± 9 and 55 ± 8 years, respectively). The distribution of known or suspected risk factors for restenosis^{5,6,30,36-38} is presented in Table 1 for these two groups. Compared with patients in the control group, patients assigned to receive MaxEPA were more often in the high-risk category for current smoking, high-grade stenosis ($>95\%$), lesion on a small vessel (normal diameter, <2.4 mm), and poor left ventricular function. On the other hand, patients receiving olive oil more often had a stenosis on the proximal left anterior descending coronary artery.

Duration of treatment and compliance were similar in the two groups. The mean duration of treatment before PTCA was 20 ± 5 days, and the total follow-up period was 197 ± 45 days. Compliance was high in both groups, and 93% of the prescribed capsules were taken. The well-established effect of fish oil on triglyceride levels^{11,14,39,40} provides indirect evidence of compliance. Mean plasma triglycerides at 1 (1.5 mmol/l) and 6 months (1.6 mmol/l) after PTCA were significantly lower than at baseline (2.3 mmol/l) in the treatment group ($p \leq 0.0001$). In the olive oil group, these levels remained similar: 2.4, 2.5, and 2.6 mmol/l at enrollment and 1 and 6 months, respectively. In the fish oil group, 86% and 75% of the patients had a reduction in triglycerides after 1 and 6 months, respectively. In contrast, a decrease in the level of triglycerides was observed in 43% and 32% of the patients receiving olive

TABLE 2. Percentages of Patients in Treatment and Control Groups With Ischemia at Exercise Test and on Thallium Scintigraphy

	Patients (%)		<i>p</i>
	Treatment	Control	
Exercise test 1 month after PTCA	(<i>n</i> =58)	(<i>n</i> =55)	
Clinical symptoms of ischemia	12	22	0.17
Ischemic signs on ECG	38	48	0.27
Thallium scintigraphy 3 months after PTCA*	(<i>n</i> =54)	(<i>n</i> =52)	
Definite ischemia	11	23	0.02
Possible ischemia	24	31	
Probable absence of ischemia	6	10	
No ischemia	59	36	

PTCA, percutaneous transluminal coronary angioplasty.

*Statistical analysis by ordinal polytomous logistic regression.

oil after 1 and 6 months, respectively. Fifty percent of all subjects in both groups reported mild side effects, mainly gastrointestinal discomfort. None of the patients reported bleeding, infection, or any major adverse outcome attributable to fish oil supplements. There was no difference between the two groups in medication taken by the patients regularly (e.g., calcium channel blockers, β -blockers) or occasionally (e.g., aspirin).

Myocardial Ischemia

No difference (Q wave, aberrant conduction, extrasystoles) was observed between the two groups on the standard ECGs performed at 1, 3, and 6 months after PTCA. Patients in the treatment group had signs of myocardial ischemia less frequently than those in the control group (Table 2). During the exercise test conducted 1 month after PTCA, clinical symptoms of ischemia were less frequent in the treatment group than in the control group (12% versus 22%, $p=0.17$). The same tendency was found for ischemic signs on the ECG with 38% and 48% of subjects with ischemia in the treatment and control groups, respectively ($p=0.27$). With polytomous logistic regression, a statistically significant difference ($p=0.02$) was observed for ischemia on ^{201}Tl scintigraphy at 3 months. The effect of fish oil supplementation on ischemia documented by ^{201}Tl scintigraphy was present among patients later diagnosed with restenosis at 6 months and among those without.

Angiographic Results

The intraobserver variability in QCA measures is presented in Table 3. No statistical difference was observed for the 59 randomly selected angiographic images between the repeated measurements of stenosis and normal vessel. Mean values were almost identical, and intraclass correlations were high, especially for measurements of stenosis. Based on the 40 post-PTCA images, the SD of the difference between the two measurements of minimal luminal diameter of the same lesion was 0.25 mm. According to the third definition, restenosis was thus defined by a reduction of at least 0.50 mm (2 SD) in the minimal luminal diameter during the post-PTCA follow-up period.

TABLE 3. Intraobserver Variability for 59 Angiographic Images Assessed by Quantitative Computer Analysis

	Measurement 1	Measurement 2	Intraclass
			correlation
Stenosis of vessel diameter (%)	56.4 \pm 21.0	56.7 \pm 20.5	0.94
Minimal luminal diameter (mm)	1.23 \pm 0.61	1.21 \pm 0.55	0.92
Normal vessel diameter (mm)	2.84 \pm 0.50	2.86 \pm 0.40	0.65

Among the 119 patients with angiographic follow-up, 14 had two lesions dilated. The outcome of angioplasty for the second dilated lesion was not an event independent of the outcome of the first dilated lesion. The risk of restenosis for the second lesion was at least twice as high, depending on the definition of restenosis considered, when restenosis had occurred for the first lesion than when it had not. Consequently, for these 14 patients, only one lesion, the most severe,³⁸ was considered in the analyses.

At enrollment, the mean percentage of stenosis of the vessel to be dilated was 78.5 \pm 13.4% for patients in the treatment group and 77.1 \pm 10.5% for those in the control group. Immediately after PTCA, these percentages were 30.6 \pm 9.9% and 32.8 \pm 12.2%, respectively, in the two groups. The percentages of restenosis at the end of follow-up are presented in Table 4 for the two groups according to the four definitions of restenosis. Restenosis occurred less often in the MaxEPA group (22.0–35.6% depending on the definition) than in the control group (40.0–53.3%). The difference was statistically significant for definitions 1, 3, and 4. However, these crude results (both measurements of association and levels of statistical significance) might be influenced by the exclusions after randomization. Therefore, a more valid assessment could be achieved by multivariate analyses. The association between treatment and restenosis was further evaluated by multiple logistic regression to control the confounding effect of the determinants of restenosis listed in Table 1. After adjustment for these variables and for the ω -3 fatty acids dietary intake, the association between fish oil supplementation and restenosis was stronger and of higher statistical significance because the analysis took into account the higher risk profile of the patients in

TABLE 4. Percentages of Patients in Treatment and Control Groups With Restenosis 6 Months After Percutaneous Transluminal Coronary Angioplasty According to Four Definitions of Restenosis

	Patients (%)		<i>p</i>
	Treatment (<i>n</i> =59)	Control (<i>n</i> =60)	
Definition 1	30.5	48.3	0.05
Definition 2	30.5	41.7	0.20
Definition 3	35.6	53.3	0.05
Definition 4	22.0	40.0	0.03

Definitions of restenosis: 1) final percent stenosis of vessel diameter \geq 50%, 2) loss of one half or more gain in percent stenosis of vessel diameter, 3) final minimal luminal diameter (mm) less than post-percutaneous transluminal coronary angioplasty minimal luminal diameter (mm) minus 0.50 mm, and 4) all of the above criteria.

TABLE 5. Adjusted Odds Ratios of Restenosis Obtained by Multiple Logistic Regression According to Four Definitions of Restenosis

	Definition 1		Definition 2		Definition 3		Definition 4	
	OR	<i>p</i>	OR	<i>p</i>	OR	<i>p</i>	OR	<i>p</i>
Fish oil	0.35	0.03	0.61	0.26	0.38	0.03	0.36	0.03
Olive oil*	1.00		1.00		1.00		1.00	
Dietary ω -3 fatty acids								
Upper tercile (>0.15 g/day)	0.20	0.01	0.28	0.02	0.30	0.03	0.24	0.02
Middle tercile (0.033–0.15 g/day)	0.31	0.04	0.29	0.02	0.53	0.21	0.42	0.11
Lower tercile (<0.033 g/day)*	1.00		1.00		1.00		1.00	

OR, odds ratio.

Definitions of restenosis: 1) final percent stenosis of vessel diameter $\geq 50\%$, 2) loss of one half or more gain in percent stenosis of vessel diameter, 3) final minimal luminal diameter (mm) less than post-percutaneous transluminal coronary angioplasty minimal luminal diameter (mm) minus 0.50 mm, and 4) all of the above criteria.

In addition to treatment and dietary intake of ω -3 fatty acids, all models included age and all of the variables presented in Table 1.

*Reference category.

the fish oil group (Table 5). The adjusted odds ratios for restenosis according to definitions 1, 3, and 4 were very similar (about 0.36) and statistically significant ($p=0.03$), indicating a protective effect of fish oil supplementation on restenosis. With definition 2, the association was also in the same direction but somewhat weaker (odds ratio, 0.61; $p=0.26$).

Dietary Intakes and Other Risk Factors

The average dietary intake of ω -3 fatty acids was 0.17 g/day. The relations between ω -3 fatty acid intake and restenosis are presented in Table 5 for the entire study population (119 patients) after adjustment for treatment group and for potential risk factors for restenosis. Compared with the patients in the lower tercile of ω -3 fatty acid consumption, those in the middle and upper terciles had a lower risk of restenosis (Table 5). For a consumption of more than 0.15 g/day, the adjusted odds ratios ranged from 0.20 to 0.30 and reached statistical significance for all definitions of restenosis. For the middle tercile of ω -3 fatty acids consumption, the adjusted odds ratios varied from 0.29 to 0.53 and were statistically significant for definitions 1 and 2. The association of ω -3 fatty acid intake with restenosis was also considered separately in each treatment group. The association between ω -3 fatty acids intake and restenosis was observed both in patients receiving fish oil supplements and in those receiving olive oil. These associations, however, did not reach statistical significance because of small numbers in each group. No association was observed between other nutrient intakes (total fat, saturated, monounsaturated and polyunsaturated fatty acids, and cholesterol) and restenosis. Similarly, there was no relation between the ratio of polyunsaturated to saturated fats and restenosis. The average weekly consumption of seafood (fish, mollusks, and crustaceans) was 212 g. For patients with seafood intake in the upper tercile (>227 g/wk) compared with those in the lower tercile (<56 g/wk), the odds ratios adjusted for treatment varied from 0.45 to 0.63 depending on definition ($p<0.32$).

The relation between other potential risk factors for restenosis and restenosis itself was also assessed in the logistic models. For only one of them (percentage of vessel diameter stenosis >95%) was a statistically significant association observed (odds ratio, 6.89; $p=0.01$, with definition 1). Procedural characteristics of angioplasty (e.g.,

pressure, time, number of insufflations, and balloon diameter) and immediate consequences of PTCA (e.g., dissection, thrombosis, and percent reduction of the stenosis) were distributed similarly in the two groups, and none had a statistically significant effect on restenosis.

Discussion

In this double-blind, randomized, controlled trial, fish oil supplementation reduced the frequency of recurrence of coronary stenosis angiographically documented at 6 months. Furthermore, fish oil supplements reduced myocardial ischemia observed on ^{201}Tl scintigraphy. In addition, a higher usual dietary consumption of ω -3 fatty acids was associated with a lower frequency of restenosis.

Because this trial required a treatment period before PTCA and successful angioplasty, some patients had to be excluded from the study population after randomization. After this initial loss, only 9% of the patients were lost to follow-up during the 6 months after PTCA. The confounding effect resulting from the slight imbalance of restenosis risk factors in the two treatment groups compared at the end of follow-up was controlled by multiple logistic regression. Thus, a valid evaluation of the effect of fish oil on restenosis was achieved in these analyses despite the exclusions after randomization. In these models, a preventive effect of fish oil supplementation on the recurrence of stenosis at 6 months was observed.

A more valid assessment of angiograms can be achieved by QCA than by visual evaluation. Compared with QCA measures, the visual assessment in this study consistently overestimated the percentage of stenosis before PTCA and the percentage gained by angioplasty. With the visual evaluation of the angiograms, patients with unsuccessful PTCA would have remained in the study and would have later been wrongly diagnosed with recurrence of stenosis. To prevent this misclassification bias, we excluded 32 subjects who did not meet the QCA criteria for success. This problem might have prevented previous investigators from observing a preventive effect of fish oil on coronary restenosis.^{21,23} Percentages of restenosis in this study are similar to those reported in studies using QCA assessment.⁴ There was very good agreement between the first and third definitions of restenosis. With these definitions, large and significant differences in the percentage of resteno-

sis were observed between the two treatment groups. With the second definition of restenosis, the difference was only moderate. To determine restenosis by this last definition, three angiographic measures are required, whereas two are necessary for definition 3 and only one for definition 1. With definition 2, measurement errors, mostly random by QCA assessment, are cumulated and lead to nondifferential misclassification that underestimates the true difference between the two groups.⁴¹ The preventive effect of fish oil on restenosis was confirmed with the fourth definition by which only the most definite cases of restenosis are considered as such.

Clinical evaluation of restenosis by recurrence of angina¹⁹ or by exercise tests is not appropriate. Restenosis is observed angiographically in approximately 11–33% of patients without symptoms or with negative exercise test.^{21,30,42–44} For the same reason, studies using a combination of clinical or angiographic evaluation of restenosis^{22,23} are also prone to misclassification bias. Three trials^{20,21,24} have evaluated the influence of fish oil on the recurrence of stenosis defined angiographically and reported divergent results. Grigg et al²¹ reported similar percentages of restenosis using definitions identical to our definitions 1 and 2 in the patients receiving fish oil (30% and 34%, respectively, for definitions 1 and 2) and in those in the control group (32% and 33%, respectively). This negative result could be in part explained by the small dosage of ω -3 fatty acids (3 g/day), the absence of treatment before PTCA, and the short duration of follow-up (3.5 months). Nye et al²⁴ reported a protective effect of fish oil on restenosis using a definition that combined definitions 1 and 2. No information was given on the percentages of patients with restenosis among the 35 patients receiving ω -3 fatty acids supplements (3.6 g/day) and among the 34 patients in the control group. However, the authors compared the percentages of restenosed lesions in the fish oil (11%) and control (30%) groups. Because the outcomes of multiple dilated lesions in the same subject are not independent, this type of analysis is flawed and tends to increase the statistical power of the analysis. The last trial,²⁰ which was unblinded and uncontrolled, showed a protective effect of fish oil supplements. In this latter study, the treatment was started 1 week before PTCA, the dosage of ω -3 fatty acids was relatively high (5.4 g/day), and restenosis was evaluated with definition 1 by visual assessment validated with QCA. Percentage of restenosis was significantly lower in the fish oil group (19%) than in the comparison group (46%). Angiographic evaluation was performed for all subjects 3–4 months after PTCA, but this was repeated thereafter only for patients with symptoms. In the trial conducted by Dehmer et al,²⁰ all subjects received aspirin (325 mg/day) and dipyridamole (225 mg/day) throughout the study period. In the present study, the protective effect of fish oil was observed in the absence of any systematic pharmacological treatment.

In the present study, a higher usual dietary intake of ω -3 fatty acids was associated with a lower frequency of restenosis. The associations with restenosis of ω -3 fatty acids from both the diet and the supplements appear to corroborate each other, but it is difficult to explain why associations of similar magnitude with restenosis could be attributed to such different amounts of the same ω -3 fatty acids. The average contribution of diet (0.17 g/day)

to the total ω -3 fatty acids intake was 25-fold lower than that of the supplements (4.5 g/day). There still are many unresolved questions concerning the physiological mechanisms by which ω -3 fatty acids could influence coronary artery disease.^{14–16} The usual dietary intake of ω -3 fatty acids documented in the present study resulted from an average weekly consumption of about 210 g of fish, mollusks, and crustaceans. Significantly lower mortality from coronary heart disease has been reported for people consuming similar quantities of fish.^{45–47}

In conclusion, this trial documented the protective effect of fish oil supplements on the recurrence of coronary stenosis 6 months after PTCA. The results suggest that a dietary intervention could be useful in preventing restenosis.

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