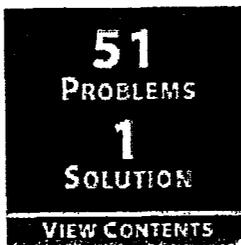


Index  
6. b.



## The Effect of Dietary Omega-3 Fatty Acids on Coronary Atherosclerosis

### A Randomized, Double-Blind, Placebo-Controlled Trial

*Annals of Internal Medicine*, 6 April 1999. 130:554-562.

Clemens von Schacky, MD; Peter Angerer, MD; Wolfgang Kothny, MD; Karl Theisen, MD; and Harald Mudra, MD

**Background:** Epidemiologic studies, studies of mechanisms of action, and many animal studies indicate that dietary intake of omega-3 fatty acids has antiatherosclerotic potential. Few trials in humans have examined this potential.

**Objective:** To determine the effect of dietary intake of omega-3 fatty acids on the course of coronary artery atherosclerosis in humans.

**Design:** Randomized, double-blind, placebo-controlled, clinically controlled trial.

**Setting:** University preventive cardiology unit.

**Patients:** 223 patients with angiographically proven coronary artery disease.

**Intervention:** Fish oil concentrate (55% eicosapentaenoic and docosahexaenoic acids) or a placebo with a fatty acid composition resembling that of the average European diet, 6 g/d for 3 months and then 3 g/d for 21 months.

**Measurements:** The results of standardized coronary angiography, done before and after 2 years of treatment, were evaluated by an expert panel (primary end point) and by quantitative coronary angiography. Patients were followed for clinical and laboratory status.

**Results:** Pairs of angiograms (one taken at baseline and one taken at 2 years) were evaluated for 80 of 112 placebo recipients and 82 of 111 fish oil recipients. At the end of treatment, 48 coronary segments in the placebo group

showed changes (36 showed mild progression, 5 showed moderate progression, and 7 showed mild regression) and 55 coronary segments in the fish oil group showed changes (35 showed mild progression, 4 showed moderate progression, 14 showed mild regression, and 2 showed moderate regression) ( $P = 0.041$ ). Loss in minimal luminal diameter, as assessed by quantitative coronary angiography, was somewhat less in the fish oil group ( $P > 0.1$ ). Fish oil recipients had fewer cardiovascular events ( $P = 0.10$ ); other clinical variables did not differ between the study groups. Low-density lipoprotein cholesterol levels tended to be greater in the fish oil group.

**Conclusion:** Dietary intake of omega-3 fatty acids modestly mitigates the course of coronary atherosclerosis in humans.

*Ann Intern Med.* 1999;130:554-562. *Annals of Internal Medicine* is published twice monthly and copyrighted © 1999 by the American College of Physicians-American Society of Internal Medicine.

From the University of Munich, Munich, Germany. For current author addresses, see end of text.

Ingestion of fish or other sources of omega-3 fatty acids has been called a comprehensive strategy toward the prevention of atherosclerosis (1). Hundreds of epidemiologic studies, studies of mechanisms of action, and studies in experimental animals have shown that dietary intake of omega-3 fatty acids has antiatherosclerotic potential (1-9).

However, few clinical trials have shown that omega-3 fatty acids have cardiovascular benefit in humans. The Diet and Reinfarction Trial (DART) (10) showed a 29% reduction in overall mortality rates in survivors of a first myocardial infarction who consumed fish rich in omega-3 fatty acids at least twice weekly for 2 years. Dietary omega-3 fatty acids do not prevent restenosis after percutaneous coronary angioplasty (11-13). One study (14) showed that fewer aortocoronary venous bypass grafts were occluded after ingestion of a fish oil concentrate, 4 g/d, for 1 year. Dietary intake of omega-3 fatty acids or olive oil, 6 g/d, did not affect the course of coronary atherosclerosis in another study totaling 59 patients (15).

To test the hypothesis that consuming omega-3 fatty acids for 2 years leads to less progression and more regression of

coronary atherosclerosis, as assessed by coronary angiography, we conducted a randomized, double-blind, placebo-controlled study in patients with coronary atherosclerosis.

## **Methods**

### **Patients**

Patients who were hospitalized for diagnostic coronary angiography at our institution between 1 September 1992 and 19 May 1994 were asked to participate in our study if they fulfilled the entry criteria: 1) stenosis greater than 20% in at least one vessel and 2) revascularization (percutaneous transluminal coronary angioplasty [PTCA] or coronary bypass surgery) planned or performed in the previous 6 months in no more than one vessel. Exclusion criteria were history of cardiac transplantation, age younger than 18 years or older than 75 years, hemodynamically relevant left main stenosis or proximal stenosis in all three main vessels, biplane left ventricular ejection fraction less than 35%, ventricular tachycardias (greater than or equal to 3 QRS complexes), hemodynamically relevant cardiac valve disease, a prognosis severely limited by noncardiac disease, bleeding tendency (for example, due to thrombocytopenia or anticoagulation), diabetes, or other evidence of increased risk. Patients were not asked to participate if they were participating in another study, had psychiatric disease, had a history of noncompliance, lived too far away, had an initial coronary angiogram of poor quality, or had a history of allergic reaction to contrast material.

Patients who agreed to participate gave written, informed consent that included consent for follow-up coronary angiography. One of the authors determined clinical status and decided whether to include patients in the study. Case report forms were filled out with data on predefined criteria relevant to history and clinical examination. A laboratory blood work-up (which included investigation of 38 routine variables plus erythrocyte phospholipid fatty acid composition), resting electrocardiography, and exercise stress test were done.

Overweight patients (body mass index  $>25 \text{ kg/m}^2$ ) were advised to restrict caloric intake, and all patients were advised to avoid eating cholesterol-rich foods; no other dietary advice was given.

Our study was approved by the Ethics Committee of the Faculty of Medicine of the Ludwig Maximilians-University of Munich and was conducted according to the Good Clinical Practice Guidelines of the European Community. These guidelines require, among an exhaustive list of prerequisites, that studies be monitored regularly by external personnel.

### **Study Design**

This Study on Prevention of Coronary Atherosclerosis by Intervention with Marine Omega-3 fatty acids (SCIMO) was a randomized, double-blind, stratified, single-center trial. It was designed to compare the effect of placebo with that of fish oil concentrate on changes on coronary angiography at 2 years, as assessed by an expert panel (the predefined primary end point) according to intention-to-treat principles. Predefined secondary end points were assessment of these changes with quantitative coronary angiography and cardiovascular events.

Before randomization, patients were stratified according to three criteria: 1) PTCA done less than 6 months before randomization, 2) current therapy with a lipid-lowering agent, and 3) the presence of more than two of four risk factors—a low-density lipoprotein (LDL) cholesterol level greater than 3.88 mmol/L (150 mg/dL), current smoking, history of myocardial infarction in a first-degree relative younger than 60 years of age, and hypertension. For the resulting nine strata, a random sequence of study group assignments was computer-generated by the trial monitor in Norway. Strata were balanced every four patients and numbered consecutively. Each patient received the next consecutive number in his or her stratum. For each number, an envelope containing the randomization result was prepared and sealed by the monitor in Norway. In Munich, these sealed envelopes (the only location of the study group assignments) were kept accessible for safety, but no seals were broken. All patients and personnel were blinded to study group assignments. To ensure blindness, patients were told that the capsules differed in composition but not in taste. At the end of the study, patients were asked what they thought the capsules contained.

### **Interventions and Measurements**

The placebo capsules and the fish oil capsules looked identical and were made of opaque soft gelatin, and each

contained 1 g of a fatty acid mixture. The fatty acid mixture in the placebo capsules was 26.0% C16:0, 4.6% C18:0, 35.8% C18:1omega-9, 16.7% C18:2omega-6, 2.1% C18:3omega-3, 0% C20:4omega-6, and 14.8% other compounds and contained no marine omega-3 fatty acids; this reflects the fatty acid composition of the average European diet (16). The fatty acid mixture in the fish oil capsules was 0.9% C16:0, 6.0% C18:0, 4.5% C18:1omega-9, 0% C18:2omega-6, 0.6% C18:3omega-3, 1.4% C20:4omega-6, 35.4% C20:5omega-3, 9.7% C22:5omega-3, 21.5% C22:6omega-3, and 20.0% other compounds. The peroxide values were 0.5 in the placebo capsules and 0.6 in the fish oil capsules. All capsules contained 4 mg of tocopherol-alpha as an antioxidant. Identical screw-top plastic containers each contained 90 capsules. The trial monitor in Norway labeled each container with identical information plus a unique randomization number. In the first 3 months of the study, six capsules per day were recommended; in the next 21 months, three capsules per day were recommended.

Patients were seen as outpatients at months 1, 6, 12, and 18. At each visit, a history was taken, clinical status was evaluated, and a laboratory work-up (including measurement of erythrocyte phospholipid fatty acid composition) was done. At month 24, all investigations were repeated, including coronary angiography (done during a 2-day hospital stay). At months 0 and 24, but not at months 1, 6, 12, and 18, blood was taken from patients after an overnight fast. Levels of LDL cholesterol were calculated according to the Friedewald formula from measurements obtained in an automated Hitachi 917 or 717 serum analyzer (Boehringer Mannheim, Germany).

Coronary angiography with highly standardized angulations was done as described elsewhere (17, 18) and included at least three biplane projections, identically repeated during follow-up angiography. Nitroglycerin, 0.8 mg, was given sublingually for maximal dilatation at the start of the procedure.

An expert panel of three experienced invasive cardiologists, who were blinded to all aspects of randomization (such as the temporal order of films) and all patient characteristics (such as name or randomization status), simultaneously assessed changes on coronary angiograms. The same three experts evaluated all pairs of films. Pairs of films (one film taken at baseline and one taken at 2 years) were randomly assigned to two 35-mm

angiographic projectors projecting in parallel. Ventriculograms were not reviewed. If PTCA had been done in one of the three coronary vessels in the 6 months before the start of the study or during the study period, the vessel—but not the patient—was excluded from primary analysis (19). Frames in identical angulations were compared in end-diastole. Lesions were identified and were then sought on the corresponding segment on the other film in the pair. With methods described elsewhere (20), angiographically detectable changes on one film were graded relative to the other film in the pair on a scale from -3 to +3. On this scale, 0 indicates no difference, 1 indicates a definitely discernible but small difference, 2 indicates an intermediate difference, and 3 indicates an extreme difference. This score was applied to global assessment of the pairs as well as to each segment of the coronary tree (primary end point). A moderator (who was blinded like the members of the expert panel) documented the results of the expert panel sessions, which were obtained after all three experts had agreed on the results. Agreement was always reached, sometimes after a short discussion. After an expert panel session, the moderator (but not the experts) was unblinded only to the sequence of films just evaluated. This was done to minimize errors. This information was added to the document generated at each session.

Quantitative coronary angiography was done with two Arripro projectors coupled with a Qansad system, version V3.2, with periodic updates (ARRI, Munich, Germany). This system is equivalent to other second-generation systems (21). Pairs of angiograms on which at least one change in a coronary segment was identified by the expert panel were analyzed according to the system manual and current algorithms (17, 18).

Cardiovascular events were predefined as sudden death, fatal or nonfatal myocardial infarction, congestive heart failure, and neurologic deficits (ischemic or hemorrhagic) according to World Health Organization definitions. Coronary bypass surgery was a predefined study end point.

Compliance was assessed by interrogation, by counting of returned capsules, and by analysis of erythrocyte phospholipid fatty acid composition. The latter reflects dietary fatty acid composition (4, 22, 23) and was analyzed as described elsewhere (7, 22). Analyses that showed arachidonic acid values less than 10% or greater than 17% were considered analytic failures and were deleted.

Study size was estimated on the basis of the study's primary end point: a change in severity of coronary artery disease, as assessed by an expert panel on a scale from -3 to +3 (24). We anticipated a difference in the change in this score of 0.5 between the two study groups. On the basis of an  $\alpha$  value of 5%, a  $\beta$  value of 10%, an anticipated dropout rate of 33%, and the Wilcoxon rank-sum test, it was deemed necessary to have 97 patients per group. In total, 223 patients were recruited to make up for an anticipated additional 10% of patients declining follow-up coronary angiography.

Data were entered into the study computers at two separate times (Data Entry, SPSS, Inc., Chicago, Illinois) and were verified. A copy of all relevant data was deposited with the trial monitor in Norway. After confirmation of receipt, the randomization code was broken and the data were processed on a Power Macintosh 7600/120 (Apple, Cupertino, California) using SPSS software, version 6.0. The paired Student *t*-test, the unpaired Student *t*-test, the chi-square test, and the Wilcoxon rank-sum test were used as predefined.

### Stratified Analysis

Because of sparse data and zero cells, we used two types of nonparametric permutation tests for stratified analyses (StatExact software, version 2.11, Cytel Corp., Boston, Massachusetts) after collapsing the two strata defined by PTCA. Thus, four strata remained. The first permutation test examines whether there is heterogeneity within strata, and it combines stratum-specific results into an overall test result. In the second permutation test, a linear trend was assumed from the original scores: -2, -1, 0, 1, 2 coded as 1, 2, 3, 4, 5 (change per patient) or -2, -1, 1, 2 coded as 1, 2, 3, 4 (change per segment).

### Role of the Funding Source

The authors collected, analyzed, and interpreted the data. No funding source had a role in these activities or in the decision to submit the study results for publication.

### Results

From 1 September 1992 to 19 May 1994, 2284 consecutive patients had diagnostic coronary angiography at our institution. Of these 2284 patients, 112 were randomly

assigned to receive fish oil and 111 were randomly assigned to receive placebo (Figure). The two study groups were similar at baseline and at month 24 in all variables assessed (Table 1).

Predefined end points were met by 8 patients in the placebo group and 4 patients in the fish oil group. In the placebo group, 1 patient died of a myocardial infarction, 1 died of other causes (a fall down a flight of stairs), 3 had coronary bypass surgery, and 3 developed another severe disease (1 had bronchial carcinoma, 1 had biliary pancreatitis, and 1 had a spinal fracture that required protracted inpatient care). In the fish oil group, 1 patient died of other causes (as a passenger in a car accident), 1 had coronary bypass surgery, and 2 developed another severe disease (1 had a gastric carcinoma, and 1 had dementia). Three patients in the placebo group and 4 in the fish oil group reported mild gastrointestinal discomfort and withdrew from the study. Fifteen patients in the placebo group and 14 in the fish oil group left the study early. Six patients in the placebo group and 7 in the fish oil group declined to undergo the second episode of coronary angiography but were available for clinical follow-up at 2 years. Thus, coronary angiography was done at month 24 in 162 patients (Figure; Table 1, Table 2, and Table 3).

#### **Primary End Point**

The expert panel evaluated 162 pairs of films. Of 80 pairs in the placebo group, 35 were considered changed in global score; of 82 pairs in the fish oil group, 35 were considered changed in global score (Table 2). One pair in each group was considered unchanged in global score because progression and regression were balanced. Coronary segments in the fish oil group showed less progression and more regression than did coronary segments in the placebo group if they were analyzed according to intention-to-treat principles ( $P = 0.041$ ) (Table 2). The  $P$  values obtained by stratified analysis were equivalent to those shown in Table 2.

#### **Other Analyses by the Expert Panel**

A similar result was obtained by limiting the analysis to angiographic changes in compliant patients ( $P = 0.039$  for clinical efficacy) (Table 2). An extended analysis by the expert panel included vessels but not segments treated with PTCA. Of 51 pairs of films with angiographic changes in the placebo group, 39 showed mild progression, 5 showed

moderate progression, and 7 showed mild regression. Of 59 pairs of films with angiographic changes in the fish oil group, 36 showed mild progression, 4 showed moderate progression, 17 showed mild regression, and 2 showed moderate regression ( $P = 0.015$ ). When this extended analysis was limited to compliant patients, of 47 pairs of films with angiographic changes in the placebo group, 35 showed mild progression, 5 showed moderate progression, and 7 showed mild regression. Of 54 pairs of films with angiographic changes in the fish oil group, 31 showed mild progression, 4 showed moderate progression, 17 showed mild regression, and 2 showed moderate regression ( $P = 0.014$ ).

### Secondary End Points

Quantitative coronary angiographic assessment of changes on coronary angiography, as defined by the expert panel, showed a mean loss ( $\pm$ SD) of minimal luminal diameter per patient of  $0.45 \pm 0.8$  mm in the 29 pairs of films in the placebo group ( $P = 0.07$ ) and of  $0.38 \pm 0.8$  mm in the 29 analyzable pairs of films in the fish oil group ( $P = 0.023$ ) (paired  $t$ -tests). Results of the unpaired  $t$ -test showed no significant differences between the groups. This form of analysis, done per changed segment (34 segments in the placebo group and 39 segments in the fish oil group), yielded similar results (data not shown).

Three patients in the placebo group and one in the fish oil group had nonfatal myocardial infarction. Three patients in the placebo group had ischemic neurologic deficits; in the fish oil group, one hemorrhagic event occurred with subsequent minimal residual neurologic disability in an inadequately treated hypertensive patient. Taken together, clinical cardiovascular events such as myocardial infarction (fatal and nonfatal) and stroke occurred in a total of seven patients in the placebo group and two in the fish oil group ( $P = 0.10$ ). One patient in the fish oil group had coronary bypass surgery but decided to remain in the study. Patients had PTCA in similar numbers in the two groups (Table 3). Of note, PTCA was usually done in the first 6 months, and the decision to perform it was based on the initial angiogram (Table 3). No significant differences were seen in Canadian Cardiovascular Society class, medication, or evidence of ischemia (on stress test or scintigraphy) between the placebo group and the fish oil group at the respective time points, except that less diuretic use was seen in the fish oil group at month 1 and more digitalis use was seen in the fish oil group at month 24

(this is probably explained by chance). Weight, blood pressure, and total cholesterol levels remained constant in both groups. Levels of LDL cholesterol were significantly greater in the fish oil group at months 6, 18, and 24; triglyceride levels were lower in the fish oil group at months 1, 6, 12, and 18 but not at month 24. At months 1, 6, 12, and 18, few patients had fasted overnight before blood was drawn.

### Compliance

Patients reported a mean intake of  $2284 \pm 313.1$  capsules during the study (2460 capsules were prescribed for each patient). Patients whose capsule count suggested ingestion of more than 1658 capsules (a deviation lesser than or equal to 2 SDs from the mean) were considered compliant. Erythrocyte phospholipid fatty acid composition was unaltered in the placebo group (data not shown). In the fish oil group, from baseline to month 1, the proportion of the erythrocyte phospholipid fatty acid composition that was eicosapentaenoic acid increased from  $0.49\% \pm 0.2\%$  to  $2.28\% \pm 0.7\%$ ; the proportion of this composition that was docosapentaenoic acid increased from  $1.25\% \pm 0.7\%$  to  $2.17\% \pm 0.8\%$ , and the proportion of this composition that was docosahexaenoic acid increased from  $2.86\% \pm 1.1\%$  to  $4.77\% \pm 1.5\%$ . At month 24, further, almost linear, increases were evident: The mean proportion of this composition that was eicosapentaenoic acid was  $2.89\% \pm 1.0\%$ , the mean proportion that was docosapentaenoic acid was  $2.91\% \pm 0.8\%$ , and the mean proportion that was docosahexaenoic acid was  $6.00\% \pm 1.2\%$  ( $P < 0.05$  for all comparisons). Of patients who were considered compliant according to capsule count, the mean percentage of erythrocyte phospholipid fatty acid composition that was eicosapentaenoic acid was calculated. Patients in whom this percentage differed by more than 2 SDs from the mean were considered noncompliant. Thus, six placebo recipients and nine fish oil recipients were considered noncompliant.

### Safety

Three placebo recipients and four fish oil recipients reported mild gastrointestinal discomfort and withdrew from the study. One patient in the fish oil group developed a mild prurigoform dermatosis (a slightly itching rash) with a possible but unlikely causal relation to his study medication. Minor hematoma, but no other complication, was associated with the second episode of coronary

angiography.

### **Blinding**

At the end of the study, 22 of the 90 patients in the fish oil group thought that they had received fish oil, 5 thought that they had received placebo, and 63 were undecided. Of the 85 patients in the placebo group, 10 thought that they had received fish oil, 9 thought that they had received placebo, and 66 were undecided (chi-square test;  $P = 0.06$ ).

### **Discussion**

In our study, patients with coronary artery disease who ingested approximately 1.5 g of omega-3 fatty acids per day for 2 years had less progression and more regression of coronary artery disease on coronary angiography than did comparable patients who ingested a placebo.

In previous studies, the angiographically assessed course of coronary atherosclerosis has been mitigated by cholesterol-lowering or LDL cholesterol-lowering therapy (24-27), lifestyle changes designed to reduce risk factors (28, 29), and vigorous exercise (30). Although the previously reported percentages for progression and regression vary, the magnitude of effect detected by our expert panel is similar (26) (Table 2). The only other study of omega-3 fatty acids with a coronary angiographic end point has thus far reported no effect (15). This difference may be explained by the fact that we had a larger, more homogeneous patient sample, used a different placebo, and used a lower dose of omega-3 fatty acids.

Although SCIMO was not designed to assess clinical outcome, its findings point to the possibility of improvement ( $P = 0.10$ ). The daily dose of omega-3 fatty acids in SCIMO approximates the calculated daily dose of omega-3 fatty acids in DART (10), which produced a 29% reduction in total mortality rates in the first 2 years after a first myocardial infarction. Because the total number of myocardial infarctions was not reduced by ingestion of fish, the results of DART were interpreted as being caused by a reduction in sudden death (10). As an alternative, we suggest that less progression and more regression of coronary artery disease, perhaps in conjunction with improvements in coronary vasomotion (31), may result in smaller, less deadly myocardial infarctions. Conversely, the reduced total mortality rates seen in DART may have been caused—at least in part—by omega-3 fatty acids.

In only one of two primary end points based on intention-to-treat principles did the effect of dietary intake of omega-3 fatty acids achieve statistical significance: in the assessment per segment of the coronary vessel but not in the global assessment of pairs of films by the expert panel (Table 2). Quantitative coronary angiography done on segments found to have changes (not a primary end point) showed no significant difference. On the other hand, our analysis of clinical efficacy (Table 2) and our extended analysis (in which we increased the number of segments analyzed by the expert panel by including vessels that contained segments treated with PTCA [but not the segments themselves]) both showed a significant effect of dietary intake of omega-3 fatty acids. Statistical corrections for multiple comparisons were not done. Our results corroborate a wealth of data supporting an antiatherosclerotic effect of omega-3 fatty acids (1-9, 22, 31). We feel justified in concluding that SCIMO showed a modest, but discernible, effect of dietary intake of omega-3 fatty acids.

In SCIMO, levels of LDL cholesterol exceeded current guidelines published in July 1995 (Table 3) (32). We conducted SCIMO from September 1992 to May 1996. Levels of LDL cholesterol were, at times, significantly greater in the fish oil group than in the placebo group (Table 3). On average, fish oil increases LDL cholesterol levels by 4% in healthy persons and 7% in hypertriglyceridemic patients (33). Unlike findings in all other similar studies (26), this finding clearly implies mechanisms of action other than LDL cholesterol lowering. We previously showed, in controlled volunteer studies, that dietary intake of omega-3 fatty acids decreases gene expression for growth factors thought to play a role in the pathogenesis of atherosclerosis: platelet-derived growth factor and monocyte chemoattractant protein-1 (7, 34). In vitro, omega-3 fatty acids decrease the production of platelet-derived growth factor by cultured endothelial cells (35). These changes in cytokine expression may be a mechanism of action. Because dietary intake of omega-3 fatty acids seems to be effective independent of LDL cholesterol levels, it might also be effective at levels conforming to current guidelines (32).

Our study was too small to detect serious side effects occurring less than once in approximately 200 patient-years. However, the omega-3 preparation that we used was safe and well tolerated. Serious side effects have not been

reported in other clinical studies of omega-3 fatty acids, most of which used other preparations (1, 9-15). We conclude that omega-3 fatty acid preparations such as that used in SCIMO carry a low probability of serious side effects.

To delineate the clinical implications of our findings, SCIMO's modest effect needs to be weighed in the context of other studies on the cardiovascular effects of fish or omega-3 fatty acids. Epidemiologic studies, studies on mechanisms of action, and many animal studies indicate that dietary intake of omega-3 fatty acids has antiatherosclerotic potential (1, 2, 5-9, 22, 31, 34, 35). In addition, several investigations (3-5) have linked dietary intake of omega-3 fatty acids with reductions in sudden death in patients with coronary artery disease. Amounts of omega-3 fatty acids calculated in DART and in epidemiologic studies were equal to those in SCIMO (10). Thus, fish eaten twice weekly, or fish oil concentrate (as used in SCIMO), can be considered a useful adjunct to the established arsenal of treatments (32) for the secondary prevention of coronary heart disease.

In conclusion, in our study, dietary intake of omega-3 fatty acids, approximately 1.5 g/d for 2 years, modestly mitigated the course of human coronary atherosclerosis, as assessed by angiography. Fewer cardiovascular events were noted. The dose and the preparation used were safe and well tolerated.

*Acknowledgments:* The authors thank Th. von Arnim, MD, for helpful discussions during study planning; J. Hasford, MD (Biometrisches Institut für Therapiestudien, Munich, Germany) for statistical and biometrical support; and S. Dacian, MD, for serving as an expert in the expert panel sessions. They also thank all of the study patients for their participation and all physicians involved in clinical care for their cooperation.

*Grant Support:* In part by the Bundesministerium für Forschung und Technologie, Germany, through Gesellschaft für Strahlenforschung (GSF, 07ERG03) and Deutsche Forschungsanstalt für Luft- und Raumfahrt (DLR, 01 EA 9501/7); Wilhelm Sander-Stiftung (93.032); Fundacion Federico; and the Deutsche Forschungsgemeinschaft (Scha 398). Pronova, A.S., Lysaker, Norway, provided the capsules and funds for monitoring.

*Requests for Reprints:* Clemens von Schacky, MD,  
Medizinische Klinik, Klinikum Innenstadt, Universität  
München, Ziemssenstrasse 1, D-80336 München,  
Germany; e-mail, vonschacky@medinn.med.uni-  
muenchen.de.

*Current Author Addresses:* Drs. von Schacky, Angerer,  
Kothny, Theisen, and Mudra: Medizinische Klinik,  
Klinikum Innenstadt, Universität München,  
Ziemssenstrasse 1, D-80336 München, Germany.

---

## References

1. von Schacky C. Prophylaxis of atherosclerosis with marine omega-3 fatty acids. A comprehensive strategy. *Ann Intern Med.* 1987;107:890-9.
2. Dolecek TA. Epidemiological evidence of relationships between dietary polyunsaturated fatty acids and mortality in the multiple risk factor intervention trial. *Proc Soc Exp Biol Med.* 1992;200:177-82.
3. Albert CM, Hennekens CH, O'Donnell CJ, Ajani UA, Carey VJ, Willett WC, et al. Fish consumption and risk of sudden cardiac death. *JAMA.* 1998;279:23-8.
4. Siscovick DS, Raghunathan TE, King I, Weinmann S, Wicklund KG, Albright J, et al. Dietary intake and cell membrane levels of long-chain n-3 polyunsaturated fatty acids and the risk of primary cardiac arrest. *JAMA.* 1995;274:1363-7.
5. Daviglus ML, Stamler J, Orenca AJ, Dyer AR, Liu K, Greenland P, et al. Fish consumption and the 30-year risk of fatal myocardial infarction. *N Engl J Med.* 1997;336:1046-53.
6. Dyerberg J, Bang HO. Haemostatic function and platelet polyunsaturated fatty acids in Eskimos. *Lancet.* 1979;324:433-5
7. Kaminski WE, Jendraschak E, Kiefl R, von Schacky C. Dietary omega-3 fatty acids lower levels of platelet-derived growth factor mRNA in human mononuclear cells. *Blood.* 1993;81:1871-9.
8. Endres S, von Schacky C. n-3 polyunsaturated fatty acids and human cytokine synthesis. *Curr Opin Lipidol.* 1996;7:48-52.
9. von Schacky C. Cardiovascular effects of n-3 fatty acids. In: Frölich JC, von Schacky C, eds. *Fish, Fish Oil, and Human Health.* Munich: Zuckschwerdt Verlag; 1992:167-78.
10. Burr ML, Fehily AM, Gilbert JF, Rogers S, Holliday RM, Sweetnam PM, et al. Effects of changes in

fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). *Lancet*. 1989;334:757-61.

11. **Gapinski JP, VanRuiswyk JV, Heudebert GR, Schectman GS.** Preventing restenosis with fish oils following coronary angioplasty. A meta-analysis. *Arch Intern Med*. 1993;153:1595-1601.

12. **Leaf A, Jorgensen MB, Jacobs AK, Cote G, Schoenfeld DA, Scheer J, et al.** Do fish oils prevent restenosis after coronary angioplasty? *Circulation*. 1994;90:2248-57.

13. **Cairns JA, Gill J, Morton B, Roberts R, Gent M, Hirsh J, et al.** Fish oils and low-molecular-weight heparin for the reduction of restenosis after percutaneous transluminal coronary angioplasty. The EMPAR Study. *Circulation*. 1996;94:1553-60.

14. **Eritsland J, Arnesen H, Gronseth K, Fjeld NB, Abdelnoor M.** Effect of dietary supplementation with n-3 fatty acids on coronary artery bypass graft patency. *Am J Cardiol*. 1996;77:31-6.

15. **Sacks FM, Stone PH, Gibson CM, Silverman DI, Rosner B, Pasternak RC.** Controlled trial of fish oil for regression of human coronary atherosclerosis. HARP Research Group. *J Am Coll Cardiol*. 1995;25:1492-8.

16. **Bull NL, Day MJ, Burt R, Buss DH.** Individual fatty acids in the British household food supply. *Hum Nutr Appl Nutr*. 1983;37:373-7.

17. **Mudra H, Klauss V, Blasini R, Kroetz M, Rieber J, Regar E, et al.** Ultrasound guidance of Palmaz-Schatz intracoronary stenting with a combined intravascular ultrasound balloon catheter. *Circulation*. 1994;90:1252-61.

18. **Reiber JH, Serruys PW.** Quantitative coronary angiography. In: Marcus ML, Schelbert HR, Skorton DJ, Wolf GL, eds. *Cardiac Imaging: A Companion to Braunwald's Heart Disease*. Philadelphia: WB Saunders; 1991:211-80.

19. **Rozenman Y, Gilon D, Welber S, Sapoznikov D, Lotan C, Mosseri M, et al.** Influence of coronary angioplasty on the progression of coronary atherosclerosis. *Am J Cardiol*. 1995;76:1126-30.

20. **Blankenhorn DH, Selzer RH, Mack WJ, Crawford DW, Pogoda J, Lee PL, et al.** Evaluation of colestipol/niacin therapy with computer-derived coronary end point measures. A comparison of different measures of treatment effect. *Circulation*. 1992;86:1701-9.

21. **Hausleiter J, Jost S, Nolte CW, Dirschinger J, Kastrati A, Stiel GM, et al.** Comparative in-vitro validation of eight first- and second-generation quantitative coronary angiography systems. *Coron Artery Dis*.

1997;8:83-90.

22. von Schacky C, Fischer S, Weber PC. Long-term effects of dietary marine omega-3 fatty acids upon plasma and cellular lipids, platelet function, and eicosanoid formation in humans. *J Clin Invest.* 1985;76:1626-31.
23. Olsen SF, Hansen HS, Sandstrom B, Jensen B. Erythrocyte levels compared with reported dietary intake of marine n-3 fatty acids in pregnant women. *Br J Nutr.* 1995;73:387-95.
24. Blankenhorn DH, Nessim SA, Johnson RL, Sanmarco ME, Azen SP, Cashin-Hemphill L. Beneficial effects of combined colestipol-niacin therapy on coronary atherosclerosis and coronary venous bypass grafts. *JAMA.* 1987;257:3233-40.
25. Waters D, Higginson L, Gladstone P, Kimball B, Le May M, Boccuzzi SJ, et al. Effects of monotherapy with an HMG-CoA reductase inhibitor on the progression of coronary atherosclerosis as assessed by serial quantitative arteriography. The Canadian Coronary Atherosclerosis Intervention Trial. *Circulation.* 1994;89:959-69.
26. Brown BG, Zhao XQ, Poulin D, Albers JJ. Regression of atherosclerosis. Does it occur and does it have clinical meaning? *Eur Heart J.* 1995;16(Suppl E):2-5.
27. Jukema JW, Bruschke AV, van Boven AJ, Reiber JH, Bal ET, Zwinderman AH, et al. Effects of lipid lowering by pravastatin on progression and regression of coronary artery disease in symptomatic men with normal to moderately elevated serum cholesterol levels. The Regression Growth Evaluation Statin Study (REGRESS). *Circulation.* 1995;91:2528-40.
28. Ornish D, Brown SE, Scherwitz LW, Billings JH, Armstrong WT, Ports TA, et al. Can lifestyle changes reverse coronary heart disease? The Lifestyle Heart Trial. *Lancet.* 1990;336:129-33.
29. Haskell WL, Alderman EL, Fair JM, Maron DJ, Mackey SF, Superko HR, et al. Effects of intensive multiple risk factor reduction on coronary atherosclerosis and clinical cardiac events in men and women with coronary artery disease. The Stanford Risk Intervention Project (SCRIP). *Circulation.* 1994;89:975-90.
30. Hambrecht R, Niebauer J, Marburger C, Grunze M, Kalberer B, Hauer K, et al. Various intensities of leisure time physical activity in patients with coronary artery disease: effects on cardiorespiratory fitness and progression of coronary atherosclerotic lesions. *J Am Coll Cardiol.* 1993;22:468-77.
31. Kothny W, Angerer P, Störk S, von Schacky C. Short term effects of omega-3 fatty acids on the radial artery of patients with coronary artery disease.

Atherosclerosis. 1998;140:181-6.

32. Smith SC Jr, Blair SN, Criqui MH, Fletcher GF, Fuster V, Gersh BJ, et al. Preventing heart attack and death in patients with coronary disease. *Circulation*. 1995;92:2-4.

33. Harris WS. n-3 fatty acids and serum lipoproteins: human studies. *Am J Clin Nutr*. 1997;65:1645S-54S.

34. Baumann KH, Hessel F, Larass I, Müller T, Angerer P, Kiefl R, et al. Dietary omega-3, omega-6, and omega-9 unsaturated fatty acids and growth factor and cytokine gene expression in unstimulated and stimulated monocytes: a randomized volunteer study. *Arterioscler Thromb Vasc Biol*. 1999;19:59-66.

35. Fox PL, DiCorleto PE. Fish oils inhibit endothelial cell production of platelet-derived growth factor-like protein. *Science*. 1988;241:453-6.

---

[ [For Internists](#) | [About ACP-ASIM](#) | [Where We Stand](#) | [News](#) | [Interact](#) | [Find It](#) ]

© 1996-2000, American College of Physicians-American Society of Internal Medicine. All rights reserved.  
[Contact us!](#)

## Medscape Medline Abstract



Include in  
selection list.

Document # 10 of 200 from MEDLINE

Relevance to Query: XXXXXXXXXX

Maximum Relevance: XXXXXXXXXX

**Omega-3 fatty acids improve blood pressure control and preserve renal function in hypertensive heart transplant recipients.**

**Eur Heart J 2001 Mar;22(5):428-36 (ISSN: 0195-668X)**

Holm T; Andreassen AK; Aukrust P; Andersen K; Geiran OR; Kjekshus J; Simonsen S; Gullestad L [[Find other articles with these Authors](#)]

Department of Cardiology, University of Oslo, Rikshospitalet, N-0027 Oslo, Norway.

**BACKGROUND:** Hypertension and cyclosporine-induced nephrotoxicity are common complications in heart transplant recipients. Omega-3 fatty acids may prevent blood pressure rise early, but have not been studied long-term after heart transplantation. **METHODS AND RESULTS:** Forty-five clinically stable hypertensive heart transplant recipients were studied 1-12 years after transplantation and randomized in a double-blind fashion to receive either 3.4 g of omega-3 fatty acids daily or placebo for 1 year. Ambulatory 24 h blood pressure monitoring and haemodynamic studies were performed before randomization and at the end of the study. Systolic blood pressure increased by 8+/-3 mmHg (P<0.01) in the placebo group, with a non-significant increase in diastolic blood pressure of 3+/-2 mmHg (P=0.10), accompanied by a 14% increase in systemic vascular resistance (P<0.05). In contrast, no change in blood pressure or systemic vascular resistance was recorded in the omega-3 group. Plasma creatinine increased (P<0.01) and glomerular filtration rate decreased (P<0.05) in the placebo group, while no changes were observed in the omega-3 group. The antihypertensive effect was related to an increase in serum eicosapentaenoic and docosahexaenoic acid. **CONCLUSION:** Treatment with omega-3 fatty acids may reduce the long-term continuous rise in blood pressure after heart transplantation and may offer a direct or indirect renoprotective effect, making these fatty acids a potentially attractive treatment for post-transplant hypertension. Copyright 2001 The European Society of Cardiology.

Major Subject Heading(s)	Minor Subject Heading(s)	CAS Registry / EC Numbers
<ul style="list-style-type: none"> <li>• Blood Pressure [drug effects]</li> <li>• Fatty Acids, Omega-3 [administration &amp; dosage]</li> <li>• Heart Transplantation</li> <li>• Hypertension [drug therapy]</li> </ul>	<ul style="list-style-type: none"> <li>• Blood Pressure [physiology]</li> <li>• Creatinine [blood]</li> <li>• Double-Blind Method</li> <li>• Kidney [blood supply] [physiology]</li> <li>• Middle Age</li> <li>• Treatment Outcome</li> </ul>	<ul style="list-style-type: none"> <li>• 0 (Fatty Acids, Omega-3)</li> <li>• 60-27-5 (Creatinine)</li> </ul>
<a href="#">Find other articles with similar Subjects.</a>		

Indexing Check Tags: Female; Human; Male; Support, Non-U.S. Gov't

Language: English  
MEDLINE Indexing Date: 200105  
Publication Type: Clinical Trial; Journal Article; Randomized Controlled Trial  
PreMedline Identifier: 0011207085  
Unique NLM Identifier: 21157345  
Journal Code: IM

[Previous Document](#)



[Next Document](#)

[Go Back To Search Results](#)

From ..

**JAMA**

January 17, 2001 (Volume 285, Number 3)

**Intake of Fish and Omega-3 Fatty Acids and Risk of Stroke in Women**

Iso H, Rexrode KM, Stampfer MJ, et al  
*JAMA*. 2001;285:304-312

The results of some prospective studies have suggested an inverse relationship between fish intake and the risk of stroke while others have demonstrated a possible link between fish consumption and the development of hemorrhagic stroke. Iso and colleagues examined the relationship between fish and omega-3 polyunsaturated fatty acid intake and the risk of stroke subtypes in women.

The study group was obtained from the Nurses' Health study, which began in 1976. The prospective cohort consisted of a total of 79,839 women who had returned the 1980 dietary questionnaire. The group aged 34 to 59 years in 1980 was followed for 14 years. The participants were free of previously diagnosed cardiovascular disease, cancer, diabetes, hypertension, and hypercholesterolemia. The relative risk of stroke in 1980-1994 compared by category of fish intake and quintile of omega-3 polyunsaturated fatty acid intake was used as the main outcome measure. The relative risk (RR) of stroke was defined as the incidence rate of stroke among women in various categories of fish intake and in quintiles of omega-3 fatty acids intake divided by the corresponding rate among women in the lowest category of intake. Strokes were included if they occurred after the return of the 1980 questionnaire and before June 1, 1994.

Of 79,839 women (followed for 14 years), 574 incident stroke cases were documented during 1,086,261 person-years of follow-up. Different stroke subtypes were recorded, including 119 subarachnoid hemorrhages, 62 intraparenchymal hemorrhages, 303 ischemic strokes (264 thrombotic and 39 embolic), and 90 undetermined strokes. Within the thrombotic stroke category, 90 were secondary to large-artery occlusive infarction and 142 were from lacunar infarcts. Compared with women who consumed fish less than once a month, women with a higher intake of fish had a lower risk of total stroke. Moreover, among stroke subtypes, there was a significant reduction in the risk of thrombotic stroke among women who consumed fish 2 or more times per week (multivariate RR, 0.49; 95% CI, 0.26-0.93). Women in the highest quintile of intake of long-chain omega-3 polyunsaturated fatty acids had a reduced risk of total stroke and thrombotic infarction. When the results were stratified by aspirin consumption, an inverse association between fish intake and the risk of thrombotic infarct was more evident among women who did not use aspirin regularly. It appeared that women who were in the highest quintile of omega-3 fatty acid intake and did not use aspirin had a significant risk reduction of thrombotic stroke. No association was found between fish or omega-3 polyunsaturated fatty acid intake and the risk of hemorrhagic stroke. The results suggest that regular fish intake may reduce the risk of thrombotic stroke in middle-aged US women.

**Abstract**

---