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Background—The long-chain n-3 fatty acids in fish have been demonstrated to have antiarrhythmic properties in experimental models and to prevent sudden cardiac death in a randomized trial of post–myocardial infarction patients. Therefore, we hypothesized that these n-3 fatty acids might prevent potentially fatal ventricular arrhythmias in high-risk patients.

Methods and Results—Four hundred two patients with implanted cardioverter/defibrillators (ICDs) were randomly assigned to double-blind treatment with either a fish oil or an olive oil daily supplement for 12 months. The primary end point, time to first ICD event for ventricular tachycardia or fibrillation (VT or VF) confirmed by stored electrograms or death from any cause, was analyzed by intention to treat. Secondary analyses were performed for "probable" ventricular arrhythmias, "on-treatment" analyses for all subjects who had taken any of their oil supplements, and "on-treatment" analyses only of those subjects who were on treatment for at least 11 months. Compliance with double-blind treatment was similar in the 2 groups; however, the noncompliance rate was high (35% of all enrollees). In the primary analysis, assignment to treatment with the fish oil supplement showed a trend toward a prolonged time to the first ICD event (VT or VF) or of death from any cause (risk reduction of 28%; $P=0.057$). When therapies for probable episodes of VT or VF were included, the risk reduction became significant at 31%; $P=0.033$. For those who stayed on protocol for at least 11 months, the antiarrhythmic benefit of fish oil was improved for those with confirmed events (risk reduction of 38%; $P=0.034$).

Conclusions—Although significance was not achieved for the primary end point, this study provides evidence that for individuals at high risk of fatal ventricular arrhythmias, regular daily ingestion of fish oil fatty acids may significantly reduce potentially fatal ventricular arrhythmias. (***Circulation*. 2005;112:2762-2768.**)

Key Words: fatty acids ■ cardioversion ■ arrhythmia ■ death, sudden ■ heart arrest

The studies of McLennan and colleagues in the late 1980s[1–3] established the antiarrhythmic effect of the n-3 fatty acids in rats and marmosets. To see whether those findings could be confirmed, a reliable dog model of sudden cardiac death (SCD) was tested. The results in the dogs were confirmatory ($P<0.005$), and the n-3 fatty acids eicosapentaenoic acid (EPA, C20;5n-3) and docosahexaenoic acid (DHA, C22;6n-3), the active ingredients in fish oil, were each found to be protective.[4–6] This finding led to a series of reports on the functional and antiarrhythmic actions of fatty acids on in vitro cultured, neonatal rat heart cells,[7–9] which were extended to electrophysiologic studies.[10–12] The latter demonstrated the ability of the fish oil fatty acids to modulate the conductance currents, especially of the fast voltage-dependent sodium and the L-type calcium channel, in the membranes of heart cells. These effects may underlie the basis of the antiarrhythmic action of the fatty acids (reviewed in Leaf et al[13,14]).

Although those studies were in progress, clinical studies by other groups were performed to learn whether the long-chain n-3 fatty acids might also be antiarrhythmic in humans. Consuming fish 1 to 2 times per week was reported to be associated with 42% to 50% reductions in the risk of SCD,[15–17] and in studies in which the n-3 fatty acids were directly measured in blood, the reported benefits on the risk of SCD were even more striking, ≈81% to 90%.[16–18]

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In addition to these observational studies, 2 large, randomized trials in post–myocardial infarction (MI) populations have demonstrated benefits on coronary heart disease mortality without a reduction in nonfatal MI. The first, published in 1989 by Burr et al,[19] found a 29% reduction in mortality among 1015 men randomly assigned to advice to eat at least 2 portions weekly of oily fish. More recently, the GISSI-Prevenzione trial tested a combination of 850 mg EPA and DHA daily among 11 324 patients with a recent MI.[20] The primary end point was a combination of death, nonfatal MI, and stroke. At 3.5 years, the n-3 fatty acid supplement significantly reduced the primary end point compared with the control group. This benefit resulted largely from a 45% reduction in SCD.

These encouraging reports led us to hypothesize that these long-chain n-3 fatty acids might prevent ventricular arrhythmias in high-risk patients. The present randomized trial was designed to test this hypothesis.

Methods

Four hundred two patients with implantable cardioverter/defibrillators (ICDs) who were at high risk for fatal ventricular arrhythmias were enrolled at 18 collaborating medical centers from April 1999 until September 2001. Power calculations assumed that 35% of patients with ICDs would experience 1 or more appropriate arrhythmic events during 12 months of follow-up. With 200 patients in each treatment arm, the trial would have 91% power (α level=0.05) to detect a 15% absolute reduction in appropriate ICD events (35% to 20%).

Subjects were included who had an ICD implanted because of a history of cardiac arrest, sustained ventricular tachycardia (VT), or syncope with inducible, sustained VT or ventricular fibrillation (VF) during electrophysiologic studies. The qualifying ICD implantation was required to have occurred within 12 months before entry into the study or if the patient had experienced at least 1 spontaneous ICD event for VT/VF in the preceding 12 months. Enrollees were randomized in a double-blinded, controlled fashion to either 4 1.0-g gelatin capsules of an ethyl ester concentrate of n-3 fatty acids (total dose of EPA plus DHA of 2.6 g) or 4 1.0-g capsules of olive oil of identical appearance daily for 12 months. Randomization was made from computer-generated randomization tables for each collaborating site and stratified by site. The fish oil preparation was provided and its composition certified by the National Institutes of Health Fish Oil Program with material from Pronova Biocare A/S of Oslo, Norway. The content of the capsules was analyzed when produced in March 1993, when sent to us in February 1998, and at the end of the trial in September 2001. The total sum of EPA and DHA per capsule by each of these 3 analyses was 65%, 65%, and 67%, respectively. Therefore, no loss or deterioration of EPA and DHA had occurred. The fish oil capsules contained the antioxidants tocopherol (2.5 mg/g) and butylated hydroxytoluene (0.02%); the placebo contained none. The study was performed with an investigational new drug (No. 32,953) granted to the principal investigator.

At baseline, clinical data and blood samples were collected. All subjects were advised to use olive oil rather than the common plant seed oils for cooking, dressings, and sauces. Subjects were asked to consume no more than 2 fish meals per month. Grains, fruits, vegetables, and legumes composed the other constituents of the prescribed diet. Eighty-seven percent of participants reported complying with these dietary recommendations for the duration of the trial. Subjects were asked to report at 3-month intervals to their respective medical centers to have their ICD reports collected and blood samples drawn. The ICD reports were then submitted to a Core Electrophysiology Laboratory, where they were interpreted. The blood samples were separated into plasma and packed cells, kept frozen at −70°C to −80°C, and mailed to the Massachusetts General Hospital, where the packed red blood cells were analyzed for their phospholipid content of fatty acids by standard gas-liquid chromatography techniques. Compliance was ascertained by pill count and by analysis of the phospholipids of red blood cells for their content of EPA and DHA. All procedures at each medical center were reviewed and approved by their respective Human Studies Committee, and all subjects gave informed consent.

End-Point Confirmation

The Core Electrophysiology Laboratory was responsible for end-point confirmation. All ICD reports showing arrhythmias and a random selection of negative reports were then reviewed by at least 2 electrophysiologists. Whenever disagreement occurred between the initial 2 interpretations, the findings were reinterpreted by a third electrophysiologist. Each made his/her interpretation blinded to supplement allocation and the interpretation of the other electrophysiologists. Agreement between 2 of the interpretations was used as the accepted interpretation. “Confirmed” events were defined as spontaneous episodes of VT and/or VF causing ICD discharges for which intracardiac electrograms were available. “Probable” events included ICD events for which no electrograms were available but for which other data recorded by the ICD supported the diagnosis of VT/VF. Such data included successful termination by antitachycardia pacing, a ventricular rate exceeding the atrial rate in dual-chamber defibrillators, and/or other episodes of VT/VF with similar cycle lengths for which electrograms were available. Most of these events occurred in patients with multiple events between follow-up visits for which the electrogram storage capacity of the ICD had been exceeded, and thus, the earliest electrograms might not have been stored. There were only 6 subjects with such probable events who did not also have a confirmed event in the course of the study. Episodes of supraventricular tachycardia and induced ventricular arrhythmias were not included in either end point.

The study was monitored every 6 months for quality and progress by an independent Data and Safety Monitoring Committee appointed by the National Institutes of Health in February 2001. Two major changes were made in the study. The first was to follow up all patients enrolled in the study, including those no longer on therapy, for a full 12 months according to the intent-to-treat principle. Records of patients who were noncompliers before the change were requested from each of the study sites. The second was to change the primary end point from the number of ICD events to the time to the first event, because this could be more reliably ascertained than the number of events from the ICD reports. These decisions were made in the course of the study, without knowledge of the results of treatment.

Statistical Analysis

Analyses were performed according to both intention to treat and actual treatment. All randomized subjects in this study were included in the intention-to-treat analysis. The primary analysis, based on confirmed events, was an intention-to-treat analysis of survival free of appropriate ICD events for VT/VF and/or death from any cause. Secondary analyses were performed that included probable events as defined. The intention-to-treat analysis included all ICD events that occurred during the 12-month period after the first dose of the study drug, irrespective of the duration of treatment. Two on-treatment analyses were conducted. The first included all ICD events that occurred no later than 2 months after treatment was stopped, because this was when the plasma membrane would have been affected.[21] In this analysis, the stop-treatment date plus 2 months was used as the censoring variable. To ensure that the time to event was independent of the time to noncompliance, conditional on covariates in the model, we also tested for associations between baseline variables and time to noncompliance and used any that were significant as covariates in this analysis.[22]

The second on-treatment analysis was limited only to those who were compliant for at least 11 months. Means or proportions for baseline clinical characteristics were compared by the χ^2 statistic for categorical variables and with the Student t test for continuous variables. Time-to-first-event analysis was calculated by the Kaplan-Meier method and compared by log-rank tests. Cox proportional-

TABLE 1. Baseline Characteristics of the Patients

	Fish Oil (n=200)	Placebo (n=202)	P
Age, y, mean±SEM	65.7±0.82	65.3±0.82	0.7283
Male sex, n (%)	169 (84.5)	165 (81.7)	0.5066
White, n (%)	191 (95.5)	195 (96.5)	0.6211
Time from ICD implant, y, mean±SEM	1.45±0.13	1.77±0.16	0.1169
ICD implanted within 1 y, n (%)	120 (60)	112 (55.4)	0.4189
Current smoker, n (%)	30 (15)	23 (11.4)	0.3760
LVEF, n (%)			0.2730
Mean±SEM %	32.9±1.00	34.2±1.05	0.3420
≤30%	102 (51)	99 (49)	
30%–40%	40 (20)	39 (19.3)	
>40%	45 (22.5)	58 (28.7)	
NYHA functional class, n (%)			0.9002
I	47 (23.5)	54 (26.7)	
II	66 (33)	75 (37.1)	
III	20 (10)	10 (5)	
IV	0 (0)	1 (0.5)	
Not applicable	51 (25.5)	45 (22.3)	
Coronary artery disease, n (%)	151 (76)	163 (81)	0.2203
History of atrial fibrillation, n (%)	36 (18)	38 (18.8)	0.8966
Medications			
β-Blockers, n (%)	132 (66)	118 (58.4)	0.1492
ACE inhibitors, n (%)	121 (60.5)	114 (56.4)	0.4783
Calcium channel blockers, n (%)	16 (8)	15 (7.4)	0.8541
Diuretics, n (%)	104 (52)	99 (49)	0.6180
Amiodarone, n (%)	31 (15.5)	31 (15.3)	1.0000
Sotalol, n (%)	23 (11.5)	33 (16.3)	0.1945
Type I antiarrhythmic agent, n (%)	12 (6)	14 (6.9)	0.8398
Indication for ICD, n (%)			0.6674
Cardiac arrest	69 (34.5)	76 (37.6)	
Spontaneous sustained ventricular tachycardia	93 (46.5)	82 (40.6)	
Syncope and inducible sustained VT/VF	35 (17.5)	41 (20.3)	
Other	3(1.5)	3 (1.5)	
Prior defibrillator therapies in past y, n (%)	118 (59)	126 (62.4)	0.4659

LVEF indicates left ventricular ejection fraction; NYHA, New York Heart Association; and ACE, angiotensin-converting enzyme.

hazards models were also used to calculate relative risks and to adjust for clinical covariates that were associated with noncompliance in the on-treatment analysis and with the primary end point in the multivariate analysis. Multivariate analyses were performed to control for subtle imbalances in baseline characteristics and to address variations due to patient heterogeneity. Cross-product terms were added to Cox proportional-hazards models to test for treatment interactions with clinical characteristics and baseline n-3 fatty acid levels. The Wilcoxon rank-sum test was used to compare the number of events between treatment arms. All significance tests were 2 sided.

Results

Randomization

A total of 402 patients were enrolled from 18 US centers. The 2 treatment groups were well matched for important clinical characteristics and use of various cardiac medications, including antiarrhythmic drugs, as indicated by the probability values in Table 1.

Compliance

One hundred forty-two subjects (35%) discontinued their prescribed supplements before completing their year in the trial (Figure 1). Time to discontinuation did not differ significantly between the 2 treatment arms (Table 2). In our intent-to-treat analysis, all individuals who discontinued their supplements were included. Patients for whom 12-month interrogation records were incomplete were censored in the analysis at the time of their last interrogation. There were 78 such patients who were censored during the first 3 months, including 8 with no follow-up interrogation, 33 censored from 3 to 6 months, and 13 censored from 6 to 9 months. In addition, 8 of the patients who died were missing a scheduled

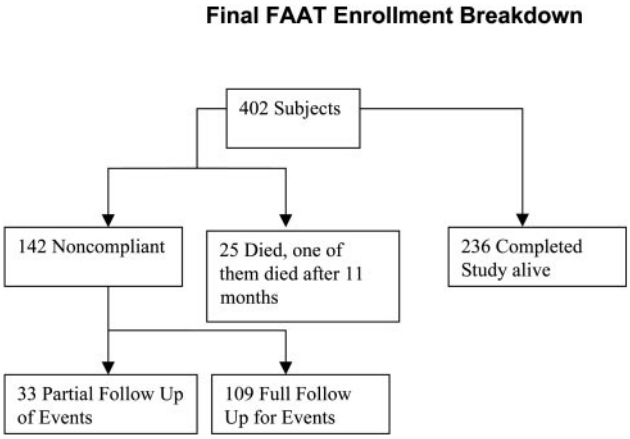


Figure 1. Final subject enrollment breakdown for the Fatty Acid Antiarrhythmia Trial (FAAT).

interrogation before death, leaving a possibility that they might have had an earlier event.

n-3 Fatty Acid Levels

Among patients who had blood samples analyzed at their last visit, the 110 subjects randomized to fish oil had a significantly higher content of EPA plus DHA as a percentage of the total fatty acids in the phospholipids of red blood cells compared with the 119 who received olive oil (mean±SEM, 7.6±0.3 versus 3.5±0.1, $P<0.0001$), whereas at baseline, there were no differences in the means, 3.4±1.2 and 3.5±1.2, respectively.

Deaths/Adverse Events

There were 25 deaths during the study, with 13 in the group assigned to fish oil and 12 in those assigned to olive oil. Eighteen of the 25 deaths were classified as due to cardiac causes. These were divided equally between the fish oil and olive oil treatment arms. The cardiac deaths were largely due to progressive congestive heart failure but also included 4 attributed to arrhythmias (3 fish oil and 1 olive oil). For 10 of these patients, death was the only event. There were no serious events in either cohort attributable to the prescribed oil supplements.

Time-to-First-Event Analyses

In the primary analysis, according to the intent-to-treat principle, there was a trend toward a longer time to first ICD event for VT/VF confirmed by electrograms or death from any cause among patients randomized to fish oil compared with those randomized to the olive oil placebo ($P=0.057$). According to Kaplan-Meier estimates (Figure 2), 28% of patients in the fish oil arm (n=57) and 39% of patients in the olive oil arm (n=78) had reached the primary end point at 12 months. This difference corresponds to a relative risk of 0.72 (see Table 3). When probable events were added to the end point, the reduction in risk became significant, with a relative risk equal to 0.69 (95% confidence limits [CLs], 0.49 to 0.97; $P=0.033$). The multivariate analysis that controlled for baseline clinical characteristics resulted in a relative risk of 0.67 (95% CLs, 0.49 to 0.97; $P=0.024$; Table 3).

TABLE 2. Noncompliers

	Fish Oil	Placebo
Noncompliers, n (%)	73 (36.5)	69 (34.2)
0–3 mo, n (%)	43 (21.5)	35 (17.3)
3–6 mo, n (%)	12 (6.0)	21 (10.4)
6–9 mo, n (%)	9 (4.5)	4 (2.0)
9 mo and after, n (%)	9 (4.5)	9 (4.5)

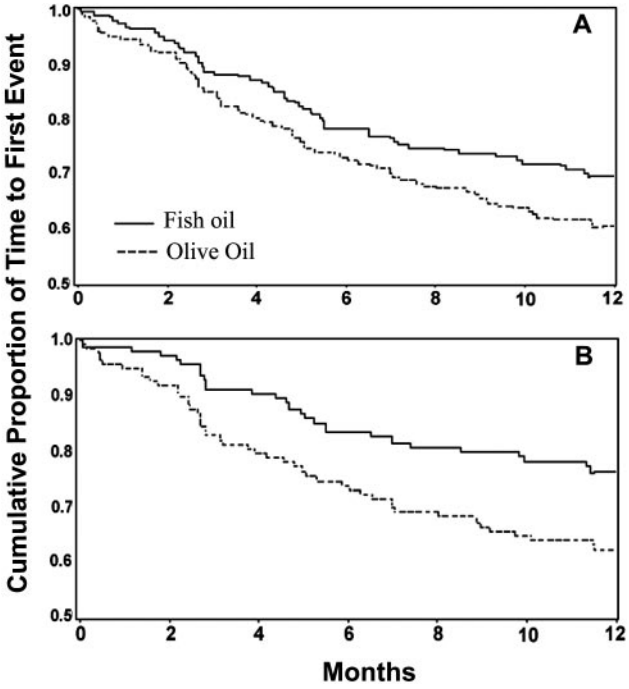


Figure 2. Kaplan-Meyer analyses of the time to ICD shock for VT/VF or death from any cause. Curves in A are based on intent to treat. Curves in B are limited to only those compliant for at least 11 months.

In the on-treatment analysis of confirmed events, which included all who had taken any prescribed oil supplements during the 12-month period, the relative risk was 0.73, which was not significant ($P=0.11$). This analysis controlled for baseline left ventricular ejection fraction, which was the only variable affecting time to noncompliance. After controlling for more baseline variables, the reduction in risk associated with the use of fish oil became significant (relative risk, 0.67; $P=0.037$; by multivariate analysis; Table 3).

In the second on-treatment analysis limited only to subjects who were compliant for at least 11 months, the relative risk was 0.62 (95% CLs, 0.39 to 0.97; $P=0.034$). Finally, when the results of these analyses were adjusted by multivariate analysis, the relative risk became 0.52 ($P=0.0060$).

Number of Events

In another secondary analysis, we compared the total number of events from enrollment to the last ICD report received in both treatment arms. The distribution of events in each treatment arm is shown in Figure 3. There was a nonsignificant trend toward a reduction in the total number of confirmed events in the fish oil group ($P=0.059$). When probable

TABLE 3. Analysis of Time to First Event

	Relative Risk	95% CL	P
Intention-to-treat analysis (N=402)			
Unadjusted			
Confirmed events	0.72	0.51–1.01	0.057
Including probable events	0.69	0.49–0.97	0.033
Multivariate analysis*			
Confirmed events	0.67	0.47–0.95	0.024
Including probable events	0.66	0.46–0.92	0.016
On-treatment analysis for all on treatment† (N=402)			
Controlling for baseline left ventricular ejection fraction			
Confirmed events:	0.73	0.50–1.07	0.11
Including probable events	0.62	0.48–1.02	0.062
Multivariate analysis*			
Confirmed events	0.67	0.46–0.98	0.037
Including probable events	0.65	0.45–0.95	0.026
On-treatment analysis for at least 11 mo‡ (n=236)			
Confirmed events	0.62	0.39–0.97	0.034
Including probable events	0.62	0.40–0.96	0.029
Multivariate analysis*			
Confirmed events	0.52	0.32–0.83	0.0060
Including probable events	0.53	0.34–0.84	0.0070

*Multivariate model controlled for sex, left ventricular ejection fraction (continuous), New York Heart Association class III congestive heart failure, history of myocardial infarction, history of prior defibrillator therapies for VT/VF, time from ICD implant (continuous), and sustained ventricular tachycardia as the indication for the ICD (all measured at baseline).

†On-treatment analysis for all subjects who had taken any of their prescribed oil supplements; the follow-up was censored at 2 months after stopping medication.

‡On-treatment only of those subjects who were on treatment for at least 11 months.

events were added, the probability value reached significance ($P=0.021$).

Hazard Ratios for Several Subgroups

Figure 4 shows hazard ratios for several subgroups of patients enrolled in the Fatty Acid Antiarrhythmia Trial. There were no differences in the effect of fish oil on the primary end point in subgroup analyses stratified according to sex, congestive heart failure New York Heart Association class, baseline blood levels of n-3 fatty acid, or indication for the ICD. With respect to left ventricular ejection fraction and coronary artery disease, the benefit appeared to be primarily observed among those with left ventricular ejection fractions ≤30% or those with a history of coronary artery disease. Although these data suggest that there was no benefit for those with ejection fractions >30%, the number of events might have been too low in this subgroup to detect a difference. Overall, our power to detect such interactions was limited. The CLs between all subgroups overlapped, and the tests for interactions were not significant.

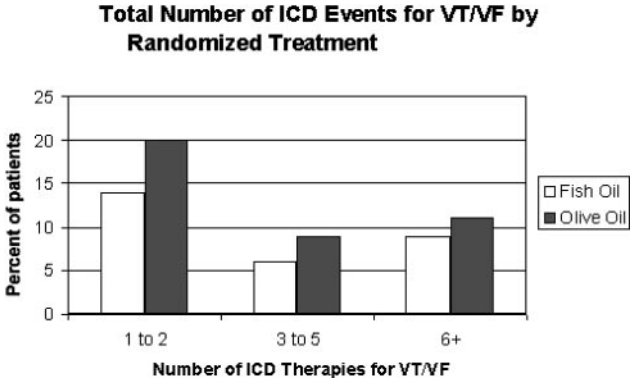
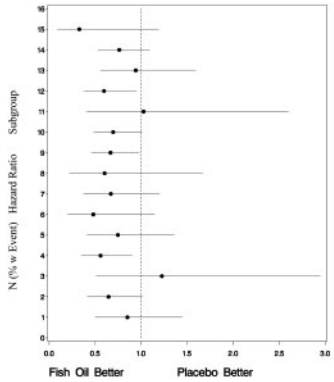


Figure 3. Proportion of patients receiving multiple ICD therapies for VT/VF (both probable and confirmed) in the randomized fish oil and placebo arms of the study.

Discussion

This prospective, randomized, placebo-controlled trial tested whether 2.5 g of EPA plus DHA daily would prolong the time to first ICD event for VT/VF or death during a 12-month period compared with an olive oil control. Difficulties were encountered during the study, mainly from poor adherence to the prescribed oil supplements and difficulties in obtaining the electrograms of all arrhythmic events. This resulted in a 35% noncompliance rate before 11 months of follow-up, which would tend to bias our results toward the null. Despite these shortcomings, analysis of the results in accord with the intent-to-treat principle for the primary end point (time to first appropriate ICD discharge for VT or VF confirmed by electrograms or death from any cause) revealed a trend toward longer time to first event in those randomized to the



68 (3)	0.328 (0.090-1.191)	Female sex
334 (28)	0.762 (0.533-1.090)	Male sex
182 (13)	0.942 (0.557-1.593)	LVEF> 30
201 (17)	0.597 (0.375-0.950)	LVEF= 30
84 (5)	1.026 (0.405-2.600)	Coronary Artery Disease - no
314 (26)	0.696 (0.481-1.007)	Coronary Artery Disease - yes
338 (24)	0.667 (0.455-0.977)	Congestive heart failure – i & ii
31 (4)	0.603 (0.218-1.666)	Congestive heart failure – iii & iv
140 (11)	0.670 (0.375-1.198)	Baseline EPA+DHA%= 3%
88 (6)	0.480 (0.201-1.145)	Baseline EPA+DHA%< 3%
145 (9)	0.748 (0.412-1.358)	Cardiac Arrest
175 (17)	0.559 (0.348-0.900)	Spontaneous Ventricular Tachycardia
76 (4)	1.225 (0.510-2.945)	Syncope and inducible sustained VT/VF
169 (18)	0.646 (0.412-1.014)	ICD implanted over 1 year
232 (12)	0.851 (0.501-1.445)	ICD implanted within 1 year

Figure 4. Hazard ratios for various subgroups of subjects enrolled in the Fatty Acid Antiarrhythmia Trial. LVEF indicates left ventricular ejection fraction.

fish oil supplement. (relative risk, 0.72; 95% CLs, 0.51 to 1.01; $P=0.057$). When probable events were added to the analysis, the risk reduction became significant (relative risk, 0.69; 95% CLs, 0.49 to 0.97; $P=0.033$).

Our results are consistent with the beneficial antiarrhythmic effects of n-3 fatty acids reported in animal and laboratory studies[1–12,14] and humans.[19,20] Therefore, these data suggest that these n-3 fatty acids may present an alternative to antiarrhythmic drugs for reducing VT/VF in ICD patients. The 38% reduction in the combined end point that included probable VT/VF events is smaller than but comparable to the 44% reduction observed with sotalol, a type III antiarrhythmic drug. However, unlike pharmaceutical antiarrhythmic drugs, the n-3 fatty acids have not been demonstrated to have proarrhythmic properties and are not toxic.

A similar antiarrhythmic mechanism of action may be responsible, at least in part, for the beneficial action of these fatty acids on total and sudden coronary heart disease mortality in epidemiologic studies (recently reviewed in Singh et al[24]) and controlled human studies.[15–20,23,24] The 28% reduction in the primary end point of our study is similar to the reduction of 29% in total mortality observed in the Diet and Reinfarction Trial[19] although lower than the 45% reduction in SCD in the GISSI-Prevenzione trial.[20] If we consider the subset of 236 patients who completed 11 months on treatment, we see a similar 48% reduction in SCD ($P=0.0060$).

Although almost all studies have reported protective associations as described earlier, there has been 1 recent adverse-event report[25]; higher mortality was reported in those advised to eat fish than in those not so advised in patients with chronic angina. However, without published autopsy findings for those who died, speculation on the increased mortality is unwarranted.

There were a number of problems with this clinical trial. First, we encountered a high noncompliance rate, 35% of enrollees. This resulted from a variety of circumstances. With many other drugs prescribed for their condition, some rebelled at having to take 4 large, 1.0-g capsules daily. The size of the capsules is intimidating to anyone who has an aversion to swallowing large capsules. Another problem was related to retrieval of data from the collaborating sites after patients stopped treatment. In some instances, this was caused by enrollees' moving from the collaborating site to some other medical center for care and becoming lost to follow-up (Figure 1). In other instances, we were simply unable to obtain ICD reports, blood samples, or clinical data from the noncompliers, even though they continued to return for their clinical follow-up to the collaborating medical center (in 23%, we failed to obtain the follow-up). Regardless, the number lost to follow up did not significantly differ between the treatment arms and therefore, is unlikely to have accounted for the results observed. The missing follow-up data would only have biased the analysis if patients who had ICD shocks and were assigned to fish oil were more likely to be missing follow-up data than patients with ICD shocks assigned to olive oil. Because this was a double-blinded, randomized trial, we consider this possibility unlikely.

As with any ICD trial of this type, reliable documentation of VT/VF events can be challenging and is subject to several limitations. Although we required that ICDs record and store each event, patients occasionally presented to another medical center during an acute event, where their electrogram tracings were inadvertently cleared and left our electrophysiologists unable to confirm the type of events or time to first event. Also, ICDs have limited electrogram storage capacity, so at times not all arrhythmias were stored. When the number of events occurring during the 3-month interval between visits exceeded the storage capacity of the ICD, only the most recent events had accompanying electrograms, and therefore, the first event might not have been stored. We attempted to address these limitations by performing secondary analyses by including probable events without electrograms, when other data supporting the diagnosis of VT/VF were available.

Whether these results in patients who have already experienced a VT or VF event will be generalizable to fatal arrhythmias that occur after MI or in the general population is unclear and can only be adequately tested in randomized trials performed in those populations. However, because most fatal arrhythmias and SCD in the general population occur in the setting of underlying coronary heart disease, and on the basis of our understanding of the mechanism of action of fish oil in the pathogenesis of arrhythmias in this setting,[13,14] we suggest that these results may be generalizable. Fish oil fatty acids functionally eliminate partially depolarized cells in the periphery of the ischemic myocardium and also prevent arrhythmias caused by large and rapid fluctuations in the cytosolic concentration of free calcium.[13,14]

Very recently, 1 published article[26] reported adverse effects of fish oil fatty acids in patients with implanted ICDs. It

seems that the baseline red blood cell levels of n-3 fish oil fatty acids were at levels that have been already reported to protect against fatal arrhythmias.[16,18] Also, those participants were allowed to eat 1 meal of fatty fish per week. Therefore, this population may have been less likely to derive a benefit than ours. Also, chance could account for the disparate findings in this small subgroup, constituting only 33% of enrollees.

In summary, this randomized, double-blinded, controlled, clinical trial provides evidence that a supplement containing long-chain n-3 fatty acids has antiarrhythmic actions in humans and may reduce the risk of potentially life-threatening arrhythmias in those at risk. These data together with the experimental data may explain, at least in part, the benefit of these fatty acids on SCD observed in randomized trials and observational studies. If the present data are confirmed, these fatty acids may also be recommended as a less toxic alternative to usual antiarrhythmic drugs to prevent recurrent episodes of VT/VF.

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