Effect of Fish Oil on Ventricular Tachyarrhythmia and Death in Patients With Implantable Cardioverter Defibrillators

The Study on Omega-3 Fatty Acids and Ventricular Arrhythmia (SOFA) Randomized Trial

Ingeborg A. Brouwer, PhD
Peter L. Zock, PhD
A. John Camm, MD, PhD
Dirk Böcker, MD, PhD
Richard N. W. Hauer, MD, PhD
Eric F. D. Wever, MD, PhD
Carla Dullemeijer, MSc
Jacintha E. Ronden, PhD
Martijn B. Katan, PhD
Andrzej Lubinski, MD
Helga Buschler, MD
Evert G. Schouten, MD, PhD
for the SOFA Study Group

Context Very-long-chain n-3 polyunsaturated fatty acids (omega-3 PUFAs) from fish are thought to reduce risk of sudden death, possibly by reducing susceptibility to cardiac arrhythmia.

Objective To study the effect of supplemental fish oil vs placebo on ventricular tachyarrhythmia or death.

Design, Setting, and Patients The Study on Omega-3 Fatty acids and ventricular Arrhythmia (SOFA) was a randomized, parallel, placebo-controlled, double-blind trial conducted at 26 cardiology clinics across Europe. A total of 546 patients with implantable cardioverter-defibrillators (ICDs) and prior documented malignant ventricular tachycardia (VT) or ventricular fibrillation (VF) were enrolled between October 2001 and August 2004. Patients were randomly assigned to receive 2 g/d of fish oil (n=273) or placebo (n=273) for a median period of 356 days (range, 14-379 days).

Main Outcome Measure Appropriate ICD intervention for VT or VF, or all-cause death.

Results The primary end point occurred in 81 (30%) patients taking fish oil vs 90 (33%) patients taking placebo (hazard ratio [HR], 0.86; 95% confidence interval [CI], 0.64-1.16; *P*=.33). In prespecified subgroup analyses, the HR was 0.91 (95% CI, 0.66-1.26) for fish oil vs placebo in the 411 patients who had experienced VT in the year before the study, and 0.76 (95% CI, 0.52-1.11) for 332 patients with prior myocardial infarctions.

Conclusion Our findings do not indicate evidence of a strong protective effect of intake of omega-3 PUFAs from fish oil against ventricular arrhythmia in patients with ICDs.

Trial Registration clinicaltrials.gov Identifier: NCT00110838

JAMA. 2006;295:2613-2619 www.jama.com

SUDDEN CARDIAC DEATH IS ONE of the most common and often the first manifestation of coronary heart disease. It is responsible for approximately 50% of all mortality from cardiovascular disease in the Western world.[1] The majority of sudden deaths are directly caused by acute ventricular arrhythmia.[2] Epidemiological studies indicate that intake of very-long-chain n-3 polyunsaturated fatty acids (omega-3 PUFAs) as present in fish or fish oil is associated with a reduction in cardiovascular mortality.[3-7] These observational studies showed a strong relationship between omega-3 PUFAs and sudden death, but not between omega-3 PUFAs and nonfatal heart disease.[5,8,9] This is confirmed by the outcome of some clinical trials; in the Diet and Reinfarction Trial (DART),[10] consumption of fish or fish oil reduced fatal heart disease by more than 30%, and the open-label Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI) trial[4] found a 45% reduction in sudden death in patients consuming omega-3 PUFAs.

Animal and in vitro studies also suggest an effect of omega-3 PUFAs

Author Affiliations: Wageningen Centre for Food Sciences (Drs Brouwer, Zock, Katan, and Schouten, and Ms Dullemeijer); Division of Human Nutrition, Wageningen University, Wageningen, the Netherlands (Drs Brouwer, Zock, Katan, and Schouten and Ms Dullemeijer); Department of Cardiological Sciences, St George's Hospital and Medical School, London, England (Dr Camm); Department of Cardiology, Universitätsklinikum Münster, Germany (Dr Böcker); Department of Cardiology, Heart Lung Centre Utrecht, the Netherlands (Drs Hauer and Wever); Cardialysis BV, Rotterdam, the Netherlands (Dr Ronden); Department of Cardiovascular Diseases, Medical University of Gdansk, Gdansk, Poland (Dr Lubinski); and Department of Cardiology, Herz-und Diabeteszentrum Bad Oeynhausen, Germany (Dr Buschler).
Corresponding Author: Ingeborg A. Brouwer, PhD, Wageningen Centre for Food Sciences, Human Nutrition, Bomenweg 2, 6703 HD Wageningen, the Netherlands (ingeborg.brouwer@wur.nl).

through reduced propensity for arrhythmia.[11-18] Infusion of omega-3 PUFAs also prevented inducible sustained ventricular tachycardia (VT) in some patients.[19] In contrast, Burr et al did not show a protective effect of intake of fish or fish oil on cardiac death in a trial of 3114 patients with stable angina.[20] Furthermore, 2 recent trials on fish oil and ventricular arrhythmia in patients with implantable cardioverter-defibrillators (ICDs) yielded inconclusive results.[21,22] Thus, the potential of omega-3 PUFAs for reducing risk of life-threatening arrhythmia in patients with ICDs is unclear.

We report the effect of omega-3 PUFAs from fish on the incidence of recurrent ventricular arrhythmia and all-cause mortality in a large double-blind, randomized trial of patients with ICDs.

METHODS

The Study on Omega-3 Fatty acids and ventricular Arrhythmia (SOFA) was performed according to strict guidelines (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) for good clinical practice. A detailed description of the study design and rationale and hypotheses has been published.[23] All institutional review boards approved the protocol, and all enrolled participants provided written informed consent.

Patients

Patients were recruited from 26 cardiology clinics in 8 European countries: Poland, Germany, the Netherlands, United Kingdom, Czech Republic, Belgium, Austria, and Switzerland. Consenting men and women who were at least 18 years old were eligible if they had experienced at least 1 true, confirmed, spontaneous VT or ventricular fibrillation (VF) in the preceding year, and they either had an ICD or were about to receive one. Each ICD had to be capable of recording intracardiac electrograms for at least 10 of its (attempted) therapeutic interventions.

Exclusion criteria included receipt of an ICD for prophylactic reasons (thus, for primary prevention) with no true VT or VF in the year before participation; ICD as a "bridge" to heart transplantation; refractory supraventricular arrhythmias with rapid ventricular rates despite antiarrhythmic therapy; a projected life span of less than 1 year; use of supplemental omega-3 PUFAs during the past 3 months or consumption of more than 8 g of omega-3 PUFAs from fish or seafood per month (267 mg/d) as judged by a seafood frequency questionnaire. Pregnant women, women of childbearing age who did not use adequate contraception, and patients with a known history of recent drug or alcohol abuse were also excluded.

Study Design

This study was a double-blind, placebo-controlled, parallel-group, multicenter trial. Eligible patients were assigned to receive treatment with either 2 g of purified fish oil daily or matching placebo. The daily dose of 2 g (4 capsules) of purified fish oil contained (on average) 961 mg of omega-3 PUFAs (464 mg eicosapentaenoic acid, 335 mg docosahexaenoic acid, and 162 mg other omega-3 PUFAs; mean of 12 samples taken at regular intervals during the study). Placebo treatment consisted of 2 g of high-oleic acid sunflower oil. Both fish oil and placebo oil contained 3000 ppm of tocopherol as antioxidant. (The oils were purchased from Loders Croklaan, Wormerveer, the Netherlands, and encapsulated by Banner BV, Tilburg, the Netherlands.)

A telephone allocation service assigned patients according to a random code, with blocked stratification for cardiology clinic and use of β-blockers. Fish oil or placebo was provided in addition to the usual patient care. All possible measures were taken to hide the nature of the treatments from the participants, the investigators, the laboratory, and data analysis staff throughout the study. Fish oil and placebo capsules had identical appearance, and the difference could not be tasted if swallowed with cold liquid as instructed. Two registered dietitians unconnected to the study took delivery of the capsules and labeled the bottles containing the capsules with medication numbers that were unidentifiable for patients and investigators; each patient received a unique medication number.

Treatment lasted 12 months or until the end of the trial in January 2005. Patients visited their local cardiology clinic at baseline and at scheduled visits (4, 8, and 12 months). At each visit the ICD was telemetrically interrogated and the data were stored. Data from unscheduled visits (eg, when a patient's ICD had delivered a shock) were also collected to ensure complete follow-up of ICD data. At each visit investigators or research nurses recorded clinical data, medication use, and adverse events in a customized case report form. Clinical research associates regularly visited each cardiology clinic and checked the patient files to ensure complete data collection.

At baseline and at the end of the intervention, blood samples were collected. Blood samples were obtained after an overnight fast, centrifuged, and stored at –70°C to –80°C; samples were sent on dry ice to Wageningen University and analyzed for cholesteryl ester fatty acid composition[24] to determine the proportion of omega-3 PUFAs. As an additional check of adherence, we assessed the number of returned capsules. Fish consumption during the intervention period was monitored every 4 months with a dietary recall questionnaire.

Investigators were advised to program all ICDs by predefined criteria, eg, the tachycardia detection cycle length was the slowest spontaneous VT with a safety margin of 50 ms. However, for ethical reasons, treating physicians were allowed to program the ICD differently if they thought this was more appropriate for the patient.

End Points

The primary end point was defined as an appropriate ICD intervention, ie, shock or antitachycardia pacing, for spontaneous ventricular tachyarrhythmias (true VT, or VF), or death from any cause. All retrieved ICD data were sent to a central blinded ICD Core Labora-

tory, where all ICD electrograms were assessed for arrhythmic events according to a fixed algorithm (D. A. M. J. Theuns, copy available from authors on request). The ICD Core Laboratory presented data sets of arrhythmic events—if detected—of each patient for evaluation to a blinded endpoint adjudication committee (EAC), which consisted of 7 expert cardiologists. The ICD Core Laboratory sent suspected events to the EAC in groups of 10. If the EAC declared any of these 10 to be a true VT or VF, the patient had reached his/her end point and no more data needed to be analyzed, although intervention and follow-up continued normally.

In addition, the EAC evaluated a random 10% of all ICD records in which no event had been detected by the ICD Core Laboratory. Two members of the EAC independently judged each set of data. They decided on the appropriateness of the ICD intervention and the classification of possible arrhythmic events as VT or VF. When they disagreed, a third member of the EAC gave final judgment. They also reviewed myocardial infarctions (MIs), deaths, and causes of death.

Power Calculation

We expected that 35% of patients in the placebo group would experience at least 1 life-threatening arrhythmia (true VT and/or VF) or death during the year of follow-up,[25] and that this number would decrease to 22% in patients receiving fish oil.[23] Thus, event-free survival would increase from 65% in the placebo group to 78% in the fish oil group and the hazard would decrease by 35%. To show this effect with 80% power would require 104 first events in the combined treatment groups; 352 patients would need to be treated for 1 year.[23] We recruited 546 patients as a safeguard against dropout and data loss. A post-hoc power analysis revealed that the final number of participants and events was sufficient to detect a 33% reduction in events.

Statistical Analysis

The primary intention-to-treat analysis was done on time to first event for all randomized patients.[23] We dealt with missing data for the primary end point variable by using the last available ICD reading. Participants without any ICD data or information on survival did not contribute to the total person-time. We used time-to-event Kaplan-Meier curves to describe the proportion of patients per treatment group who remained event-free during the intervention period. Differences in time-to-event between treatment groups were compared using log-rank tests. Effect of treatment was also tested using Cox proportional hazards models with backward selection, with and without adjustment for covariables. In secondary analyses we examined the effects of omega-3 PUFAs in predefined subgroups, namely patients with a prior MI, patients with VT in the year before participation in the study, patients with VF in the year before participation in the study, and patients with an ejection fraction lower than 30%. Post hoc we added a subgroup analysis for patients who were not using antiarrhythmic medication.

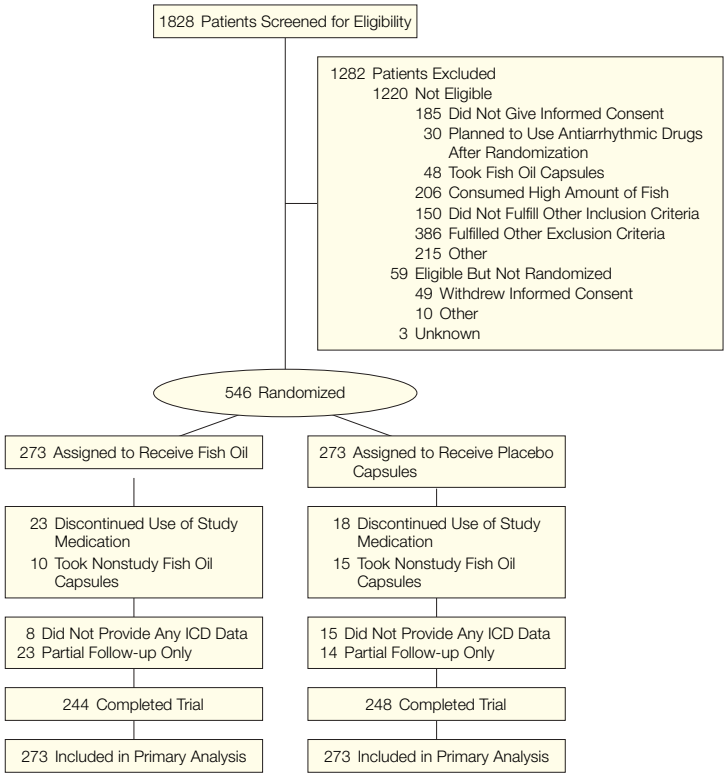
All statistical analyses were performed using SAS software (version 9.1, SAS Institute Inc, Cary, NC). A P value of $<.05$ was considered significant, and all comparisons were 2-sided.

RESULTS

Adherence, Dropouts, and Adverse Effects

We enrolled 546 patients between October 2001 and August 2004 (FIGURE 1). They randomly received either 2 g/d of fish oil (n=273) or placebo (n=273) for a median period of 356 days (range, 14-379 days). There were 23 (4%) patients who did not provide any ICD data. In addition, 23 patients (8%) in the fish oil group discontinued the use of capsules, and 10 patients (3%) took nonstudy fish oil; in the placebo group, 18 patients (6%) discontinued the use of capsules, and 15 (5%) took nonstudy fish oil capsules.

Figure 1. Flow of Participants Through the Trial



ICD indicates implantable cardioverter-defibrillator.

Table 1. Baseline Characteristics of Patients Included in the SOFA Trial*

Characteristics	No. (%)	
	Fish Oil Group (n = 273)	Placebo Group (n = 273)
Age, mean (SD), y	60.5 (12.8)	62.4 (11.4)
Sex		
Male	231 (85)	228 (84)
Female	41 (15)	44 (16)
BMI, mean (SD)	26.98 (4.40)	26.86 (4.01)
Ischemic heart disease	187 (73)	197 (79)
Previous myocardial infarction	167 (61)	175 (64)
Cardiomyopathy	59 (22)	44 (16)
Obstructive hypertropic cardiomyopathy	1 (0.4)	4 (1)
Nonobstructive hypertropic cardiomyopathy	4 (1)	1 (0.4)
Dilated cardiomyopathy	43 (16)	35 (13)
Arrhythmogenic right ventricular dysplasia	10 (4)	5 (2)
Valvular heart disease	44 (17)	52 (21)
Along with ischemic heart disease	27 (10)	30 (11)
Other congenital heart disease	3 (1)	1 (0.4)
Ventricular fibrillation	106 (39)	103 (38)
Ventricular flutter	16 (6)	9 (3)
Ventricular tachycardia	205 (75)	206 (76)
Atrial fibrillation	72 (26)	67 (25)
Atrial flutter	9 (3)	12 (4)
Previous cardiac surgery	83 (31)	83 (31)
Hypertension†	143 (53)	134 (49)
Cerebrovascular event	21 (8)	22 (8)
Obstructive coronary artery disease	159 (59)	161 (59)
Diabetes mellitus	45 (17)	42 (15)
Smoking status		
Never smoked	78 (29)	86 (32)
Previous smoker	145 (53)	154 (56)
Current smoker	44 (16)	23 (8)
Antiarrhythmic medication	80 (29)	68 (25)
Amiodarone	59 (22)	50 (18)
Sotalol	21 (8)	15 (5)
Other cardiac drugs	196 (72)	194 (71)
β-Blocker	145 (53)	155 (57)
Lipid-lowering agents	117 (43)	130 (48)
Supine blood pressure, mean (SD), mm Hg		
Systolic	122.2 (18.8)	121.2 (18.5)
Diastolic	73.4 (10.8)	74.2 (9.1)
Supine heart rate, mean (SD), beats per min	66.8 (10.8)	67.0 (12.3)
NYHA functional class		
Angina pectoris		
I	141 (52)	148 (54)
II	65 (24)	47 (17)
III	4 (1)	5 (2)
IV	0	2 (1)
Dyspnea		
I	85 (31)	102 (37)
II	100 (37)	93 (34)
III	27 (10)	25 (9)
IV	2 (1)	0 (0)
Electrophysiological study performed	151 (55)	151 (55)
VT/VF inducible	116 (42)	124 (45)
Ejection fraction, mean (SD), %	36.9 (15.0)	37.0 (15.0)
≤30%	87 (32)	95 (35)
>30%	122 (45)	132 (48)
Not assessed	64 (23)	46 (17)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); NYHA, New York Heart Association; SOFA, Study on Omega-3 Fatty acids and ventricular Arrhythmia; VF, ventricular fibrillation; VT, ventricular tachycardia.
*Values are numbers of patients (% of treatment group), except when indicated otherwise.
†Hypertension is defined as blood pressure ≥160/95 mm Hg in repeated measurements, or patients taking antihypertensive medication.

Adherence was generally good, as judged by capsule count; 207 patients (76%) in the fish oil group and 218 patients (80%) in the placebo group took more than 80% of their capsules. In the fish oil group, eicosapentaenoic acid concentrations in serum cholesteryl esters (g/100 g fatty acids) increased from a mean (SD) of 1.10 (0.60) at baseline to 2.30 (1.01) at the end of the study, which is in the expected range.[26] For the placebo group, these figures were 1.09 (0.64) and 1.23 (0.83), respectively.

The treatment groups were well matched at baseline (TABLE 1). Estimated intake of omega-3 PUFAs from fish in the background diet was 132 (79) mg of omega-3 PUFAs per day for the fish oil group and 121 (75) mg/d for the placebo group at baseline, and 123 (96) mg/d and 121 (101) mg/d, respectively, at the end of the trial. The number of patients experiencing serious noncardiac adverse events was similar in both the fish oil group and the placebo group (TABLE 2).

Primary Outcome

Event-free survival did not substantially improve in the fish oil group (FIGURE 2 and FIGURE 3). Eight patients (3%) in the fish oil group and 14 patients (5%) in the placebo group died during the intervention period; 6 (2%) of the deaths in the fish oil group and 13 (5%) of the deaths in the placebo group were cardiac deaths. In total, 75 patients (27%) in the fish oil group and 81 patients (30%) in the placebo group received appropriate ICD intervention for VT or VF (TABLE 3).

There was also no major difference in event-free survival between the treatments in a subgroup of patients who had experienced VT in the 12 months prior to the study (log-rank $P=.58$). In prespecified subgroup analyses, the hazard ratio (HR) was 0.91 (95% confidence interval [CI], 0.66-1.26) for fish oil vs placebo in the 411 patients who had experienced VT in the year before the study, and 0.76 (95% CI, 0.52-1.11) for 332 patients with prior MI. In 302 patients with solely VT in the 12 months prior to the study but no VF or flutter, 47 (32%) of

the patients who received fish oil reached the primary end point vs 58 patients (38%) in the placebo group (log-rank $P=.17$; Figure 3). There was thus no indication that patients with previous VT fared worse when taking fish oil. In patients with prior MI (n=342; Figure 2), there was a tendency toward a longer event-free survival in the fish oil group compared with the placebo group, but the difference was not significant ($P=.13$). Forty-seven MI patients (28%) in the fish oil group reached the primary end point vs 61 patients (35%) in the placebo group.

Unadjusted crude Cox proportional hazards models showed no strong protective effect of fish oil in all patients combined (Figure 3). When we added the baseline characteristics of sex, ejection fraction, current smoking, New York Heart Association (NYHA) class for angina pectoris, NYHA class for dyspnea, valvular heart disease, prior MI, cardiomyopathy, VT as index arrhythmia, VF as index arrhythmia, and use of antiarrhythmic medication at baseline as covariables to the model, only VT as index arrhythmia contributed significantly. Adjustment for VT as index arrhythmia resulted in an HR of 0.87 (95% CI, 0.65-1.18). Analyses in the predefined subgroups, adjusted for baseline characteristics if appropriate, again suggested trends toward beneficial effects of fish oil (Figure 3), but again these effects were not statistically significant.

COMMENT

To the best of our knowledge, SOFA is the largest completed and reported double-blind trial of fish oil and cardiac events. SOFA was powered to detect a 33% reduction in events, but such a large reduction was not seen. Epidemiological studies and clinical trials suggested a strong protective effect of omega-3 PUFAs on cardiac death and, more specifically, on sudden cardiac death.[4-6,8,10,27] As sudden cardiac death is in the majority of cases preceded by ventricular arrhythmia,[2] the hypothesis that omega-3 PUFAs would have strong antiarrhythmic effects was appealing. This hypothesis was also supported by evidence from human experimental studies, animal studies, and in vitro studies.[19,28,29]

In SOFA, we observed, in agreement with our power calculation prediction, 67% survival free of appropriate ICD events in the placebo group. However, event-free survival was no more than 70% in the fish oil group. Differences in baseline characteristics between the 2 treatment groups cannot explain this outcome because adjustment for these did not materially affect the effect size (adjusted HR, 0.87; 95% CI, 0.65-1.18). The total number of 171 patients with at least 1 event (including death) in SOFA would have been sufficient to detect an increase in event-free survival from 67% in the placebo group to 77% in the fish oil group. Thus, we had sufficient power to detect effects in the expected range.

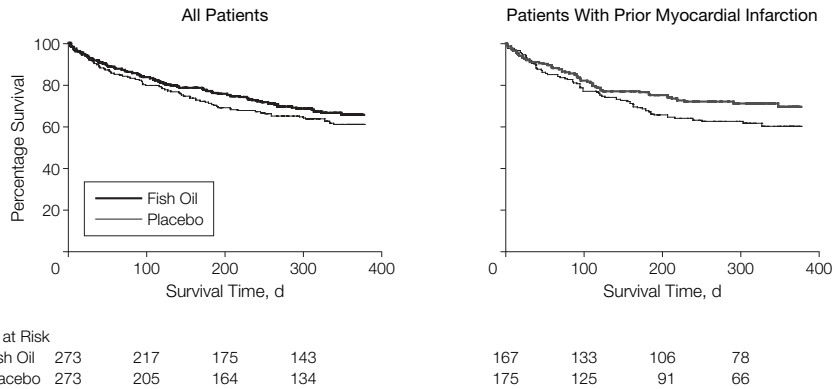
Our results suggest that the effect of fish oil on life-threatening arrhythmias or death in patients with ICDs is less than the 44% reduction in sudden death seen in the GISSI Prevenzione trial.[4] We cannot exclude the possibility of a protective effect of fish oil of up to 36%, as this figure is the upper limit of our CI, but we think that such a large effect is unlikely. Not only were differences in outcome between the intervention groups in our study small, but also the results of 2 similar studies were inconsistent and do not support such a large effect.[21,22] Thus, the overall effect of

Table 2. Adverse Events*

Adverse Events	No. (%) Fish Oil Group (n = 273)	No. (%) Placebo Group (n = 273)
Cardiac cause	65 (24)	62 (23)
Angina	10 (4)	12 (4)
Heart failure	22 (8)	19 (7)
Arrhythmia	36 (13)	34 (12)
Other cardiac cause	20 (7)	19 (7)
Cancer/malignancies	4 (1)	4 (1)
Gastrointestinal	17 (6)	12 (4)
Liver problems	3 (1)	1 (0.4)

*Values are numbers of patients (% of treatment group); patients can be in more than 1 category.

Figure 2. Kaplan-Meier Estimates of Survival



There were 546 patients (n=273 in fish oil group, n=273 in placebo group) in the trial. The curves represent survival free of appropriate implantable cardioverter-defibrillators (ICDs) intervention and death from any cause, according to intention-to-treat analysis ($P=.33$, log-rank test for equality of survival functions). Patients were at risk for a median period of 265 days (25th-75th percentile, 124-365). There were 342 patients (n=167 in fish oil group, n=175 in placebo group) with prior myocardial infarction (at any time before inclusion in the trial). The curves represent survival free of appropriate ICD intervention and death from any cause, according to intention-to-treat analysis ($P=.13$, log-rank test for equality of survival functions).

supplementation with omega-3 PUFAs on the incidence of recurrent ventricular arrhythmia or death in this population of patients with ICDs seems more modest than that observed for sudden death in earlier observational studies of apparently healthy participants and in a trial with post-MI patients.[4,6,8]

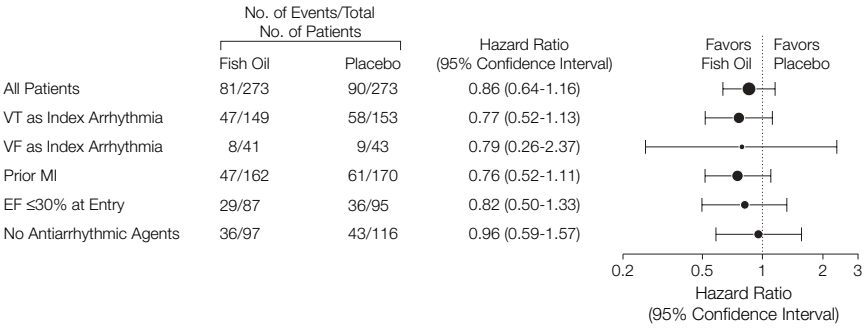
Two previous trials[21,22] also showed no significant reduction in the primary outcome of ICD therapy for VT/VF or death in a population of patients with ICDs. However, subanalyses by Leaf et al[22] point in the direction of a protective effect. Unlike Raitt et al,[21] we found no indication that patients with VT at entry into the study were at increased risk of ventricular arrhythmia. On the contrary, we found a nonsignificant reduction of hazard for patients taking fish oil who had experienced solely VT, not VF or flutter, in the 12 months prior to the study. Our data also do not suggest any harm of fish oil treatment on arrhythmia outcome in other subgroups of patients with ICDs (Figure 3).

Although our trial and the trial by Raitt et al[21] differed with respect to treatment time and dosage of omega-3 PUFAs, we do not think that this explains the apparent divergence of results. We chose a dose that was similar to the dose in the GISSI trial, which showed dramatic effects on sudden death. Our dose was on the high side of intakes in epidemiological studies that observed an association between fish and heart disease and corresponded to 2 to 3 portions of salmon or mackerel per week. Furthermore, the length of our treatment was such that we observed sufficient arrhythmias to judge the effect of treatment.

Differences between the patient populations also do not offer a ready explanation. Raitt et al[21] included only patients using no antiarrhythmic medication, whereas we included patients using and not using antiarrhythmic medication.[21] However, we did not see an adverse effect in 213 patients not using antiarrhythmic medication (HR adjusted for ejection fraction, 0.96; 95% CI, 0.59-1.57). Thus, we have no clear explanation for the differences in outcome between the studies.

In the 342 patients with prior MI, there was a nonsignificant tendency for a beneficial effect of fish oil on event-free survival (Figure 2; $P=.13$). There are other indications that the protective effect of fish oil against life-threatening arrhythmias might be confined to patients with prior MI. Two previous trials in which omega-3 PUFAs prevented cardiac death investigated post-MI patients.[4,10] Thus, the GISSI-Prevenzione trial[4] showed a marked reduction in sudden cardiac death, and the DART trial also showed fewer cardiac deaths in patients with prior MI consuming omega-3 PUFAs. In contrast, in a second trial by Burr et al,[10] patients with stable angina without MI experienced no benefit from fish oil. On the contrary, those angina patients who received fish oil capsules showed an excess risk of cardiac death.[20] However, there are some methodological concerns about this study in angina patients. Our results combined with the results of these trials suggest that the benefit of fish oil might be confined to patients with prior MI. In our study, patients had experienced MI between 2 weeks and 25 years before entry into the study. This wide range may have obscured a possible effect of a prior MI. It is conceivable that fish oil would be most effective in preventing ventricular arrhythmia in patients with a recent MI, as the amount of scar tissue is still limited in those patients; this would be a group of patients comparable to the patients in the GISSI-Prevenzione trial.[4]

Figure 3. Forest Plot of Hazard Ratios of Fish Oil Treatment for Time to First Event in Subgroups and for the Entire Study Population (Intention-to-Treat Analysis)



The subgroup analyses for ventricular fibrillation (VF) as index arrhythmia and for no antiarrhythmic medication were adjusted for ejection fraction (EF); that for prior myocardial infarction (MI) was adjusted for ventricular tachycardia (VT) as index arrhythmia. Size of data marker indicates number of patients.

Table 3. Primary and Secondary End Points*

	No. (%)			
	Fish Oil Group (n = 273)	Placebo Group (n = 273)	Hazard Ratio (95% CI)	*P* Value
Primary end point				
Sustained ICD intervention or death from any cause	81 (30)	90 (33)	0.86 (0.64-1.16)	.33
Secondary end points				
Death from any cause	8 (3)	14 (5)		
Cardiac cause	6 (2)	13 (5)		
ICD intervention for first event	75 (27)	81 (30)	0.89 (0.65-1.22)	.46
True ventricular tachycardia	72 (26)	78 (29)	0.89 (0.64-1.22)	.46
Ventricular fibrillation	3 (1)	3 (1)		
Myocardial infarction	1 (0.4)	3 (1)		

Abbreviations: CI, confidence interval; ICD, implantable cardioverter-defibrillator.
*Values are numbers of patients (% of treatment group); patients can be in more than 1 category. Two patients in the fish oil group and 5 patients in the placebo group reached the first event, namely sustained ICD intervention before dying. Analyses on secondary end points were only performed in groups with sufficient events.

CONCLUSION

In this large randomized trial we did not find evidence of strong protective effect of intake of omega-3 PUFAs from fish oil against ventricular arrhythmia in patients with ICDs. In contrast to others,[21] we did not find that fish oil may have proarrhythmic properties.

Author Contributions: Dr Brouwer had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Brouwer, Zock, Camm, Böcker, Hauer, Wever, Ronden, Katan, Schouten.
Acquisition of data: Brouwer, Zock, Böcker, Hauer, Wever, Dullemeijer, Ronden, Lubinski, Buschler, Schouten.
Analysis and interpretation of data: Brouwer, Zock, Camm, Dullemeijer, Katan, Lubinski, Schouten.
Drafting of the manuscript: Brouwer, Zock, Camm, Hauer, Schouten.
Critical revision of the manuscript for important intellectual content: Brouwer, Zock, Camm, Böcker, Hauer, Wever, Dullemeijer, Ronden, Katan, Lubinski, Buschler.
Statistical analysis: Brouwer, Zock, Dullemeijer, Schouten.
Obtained funding: Brouwer, Zock, Katan, Schouten.
Administrative, technical, or material support: Brouwer, Böcker, Hauer, Dullemeijer, Ronden, Buschler.
Study supervision: Brouwer, Zock, Camm, Böcker, Hauer, Katan, Schouten.
Financial Disclosures: None reported.
Funding/Support: Funding for this study was provided by Wageningen Centre for Food Sciences, a nonprofit alliance of major Dutch food industries, TNO Nutrition and Food Research, Maastricht University and Wageningen University and Research Centre, the Netherlands, with financial support by the Dutch government. An additional grant was received from the European Union (SEAFOODplus integrated project: No. 506359).
Role of the Sponsor: The SOFA trial was designed by the members of the executive and steering committees and then approved by the member organizations of the funder, Wageningen Centre for Food Sciences (WCFS). No industry members of WCFS were involved in the conduct of the study; in the collection, management, analysis, and intrepretation of the data; or in the preparation, review, and approval of the manuscript. Dr Peter Zock left Wageningen University on February 1, 2005, to join Unilever, which is a member organization of the trial's funder WCFS. Since February 2005 he has contributed to writing the manuscript. However, this was not in his capacity as a Unilever employee, and Dr Zock's contributions to the manuscript since February 2005 were neither submitted to, nor seen, revised, or approved by his employer, Unilever.
The SOFA Study Group: *Executive Committee/Data analyses:* I. A. Brouwer, C. Dullemeijer; *Steering Committee:* E. G. Schouten (chair), A.J. Camm (co-chair), P. L. Zock, D. Böcker, R. N. W. Hauer, E. F. D. Wever, J. E. Ronden; *Investigators:* A. Zienciuk, A. Lubinski (Medical University of Gdansk, Gdansk, Poland), J. Vogt, H. Buschler (Herz-und Diabeteszentrum Bad Oeynhausen, Bad Oeynhausen, Germany), J. Köbe, D. Böcker (Universitätsklinikum Münster, Münster, Germany), Z. Kornacewicz-Jach, R. Rzeuski (Pomeranian Academy of Medicine, Szczecin, Poland), A.R. Ramdat Misier (Isala Clinics, Zwolle, the Netherlands), E. F. D. Wever (St. Antonius Hospital, Nieuwegein, the Netherlands), H. Szwed, A. Przybylski (Instytut Kardiologii, Warzawa, Poland), R. N. W. Hauer (UMC Utrecht, Utrecht, the Netherlands), M. Sepsi, B. Semrad (FN Brno Interni Kardiologicka Klinika, Brno, the Czech Republic), A. Meijer (Catharina Hospital, Eindhoven, the Netherlands), L. J. Jordaens (Erasmus Medical Centre Rotterdam, Rotterdam, the Netherlands), A. J. Camm, I. Savelieva (St George's Hospital, London, England), R. Tavernier (University Hospital Gent, Gent, Belgium), H. R. Figulla, C. Kalmbach (Klinikum der Friedrich-Schiller-Universität, Jena, Germany), A. A. M. Wilde (Academic Medical Centre, Amsterdam, the Netherlands), M. Trusz-Gluza, A. Filipecki (I Klinika Kardiologii, Katowice, Poland), W. Haverkamp (Medizinische Klinik m. S. Kardiologie, Berlin, Germany), M. Zabel (Klinikum Benjamin Franklin Berlin, Berlin, Germany), J. M. Morgan (Southampton General Hospital, Southampton, England), H. Pitschner (Kerckhoff-Klinik GmbH, Bad Nauheim, Germany), M. J. Griffith (Queen Elizabeth Hospital, Birmingham, England), A. Podczeck, K. Steinbach (Wilhelminenspital Wien, Vienna, Austria), M. Block (Stiftsklinik Augustinum, Munchen, Germany), P. Kulakowski (Grochowski Hospital, Warszawa, Poland), J. Kautzner (Institute of Clinical and Experimental Medicine, Prague, the Czech Republic), M. Fromer (CHUV, University Hospital Lausanne, Lausanne, Switzerland).
Core Laboratory: D. A. M. J. Theuns (Cardialysis, Rotterdam, the Netherlands).
Endpoint Adjudication Committee Members: I. Savelieva, C. Wolpert (University Hospital Mannheim, Mannheim, Germany), A. A. M. Wilde, J. O. Schwab (Universitätsklinikum Bonn, Bonn, Germany), M. Fromer, M. J. Griffith, L. J. Jordaens (Erasmus University Rotterdam, Rotterdam, the Netherlands).
Data and Safety Monitoring Board Members: E. Boersma (Erasmus Medical Centre Rotterdam, Rotterdam, the Netherlands), P. J. Schwartz (University of Pavia, Pavia, Italy), K. Swedberg (Göteborg University, Göteberg, Sweden).
Acknowledgment: The data analyses were checked by E. Boersma, MSc, PhD, statistician at the Erasmus Medical Centre Rotterdam, Department of Cardiology, the Netherlands. Dr Boersma received compensation for his work as the chair of the data and safety monitoring board, but did not receive any compensation for checking the data analyses. We thank all the research nurses, co-investigators, research assistants at Wageningen University, the personnel of the Core Laboratory in Rotterdam and the Laboratory of the Division of Human Nutrition in Wageningen for their valuable contributions to the study.

REFERENCES

1. Zipes DP, Wellens HJ. Sudden cardiac death. *Circulation*. 1998;98:2334-2351.
2. Huikuri HV, Castellanos A, Myerburg RJ. Sudden death due to cardiac arrhythmias. *N Engl J Med*. 2001; 345:1473-1482.
3. Hu FB, Willett WC. Optimal diets for prevention of coronary heart disease. *JAMA*. 2002;288:2569-2578.
4. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. *Lancet*. 1999;354:447-455.
5. Albert CM, Hennekens CH, O'Donnell CJ, et al. Fish consumption and risk of sudden cardiac death. *JAMA*. 1998;279:23-28.
6. Siscovick DS, Raghunathan TE, King I, 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;274:1363-1367.
7. Kromhout D, Bosschieter EB, de-Lezenne-Coulander C. The inverse relation between fish consumption and 20-year mortality from coronary heart disease. *N Engl J Med*. 1985;312:1205-1209.
8. Albert CM, Campos H, Stampfer MJ, et al. Blood levels of long-chain n-3 fatty acids and the risk of sudden death. *N Engl J Med*. 2002;346:1113-1118.
9. Ascherio A, Rimm EB, Stampfer MJ, Giovannucci EL, Willett WC. Dietary intake of marine n-3 fatty acids, fish intake, and the risk of coronary disease among men. *N Engl J Med*. 1995;332:977-982.
10. Burr ML, Fehily AM, Gilbert JF, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: Diet and Reinfarction Trial (DART). *Lancet*. 1989;2:757-761.
11. Billman GE, Hallaq H, Leaf A. Prevention of ischemia-induced ventricular fibrillation by omega 3 fatty acids. *Proc Natl Acad Sci U S A*. 1994;91:4427-4430.
12. Billman GE, Kang JX, Leaf A. Prevention of sudden cardiac death by dietary pure omega-3 polyunsaturated fatty acids in dogs. *Circulation*. 1999;99:2452-2457.
13. Leaf A, Kang JX. Prevention of cardiac sudden death by N-3 fatty acids: a review of the evidence. *J Intern Med*. 1996;240:5-12.
14. McLennan PL, Abeywardena MY, Charnock JS. Dietary fish oil prevents ventricular fibrillation following coronary artery occlusion and reperfusion. *Am Heart J*. 1988;116:709-717.
15. Billman GE, Kang JX, Leaf A. Prevention of ischemia-induced cardiac sudden death by n-3 polyunsaturated fatty acids in dogs. *Lipids*. 1997;32:1161-1168.
16. McLennan PL. Relative effects of dietary saturated, monounsaturated, and polyunsaturated fatty acids on cardiac arrhythmias in rats. *Am J Clin Nutr*. 1993; 57:207-212.
17. McLennan PL, Bridle TM, Abeywardena MY, Charnock JS. Comparative efficacy of n-3 and n-6 polyunsaturated fatty acids in modulating ventricular fibrillation threshold in marmoset monkeys. *Am J Clin Nutr*. 1993;58:666-669.
18. Leaf A, Kang JX, Xiao YF, Billman GE. n-3 fatty acids in the prevention of cardiac arrhythmias. *Lipids*. 1999; 34(suppl):S187-S189.
19. Schrepf R, Limmert T, Claus WP, Theisen K, Sellmayer A. Immediate effects of n-3 fatty acid infusion on the induction of sustained ventricular tachycardia. *Lancet*. 2004;363:1441-1442.
20. Burr ML, Ashfield WP, Dunstan FDJ, et al. Lack of benefit of dietary advice to men with angina: results of a controlled trial. *Eur J Clin Nutr*. 2003;57:193-200.
21. Raitt MH, Connor WE, Morris C, et al. Fish oil supplementation and risk of ventricular tachycardia and ventricular fibrillation in patients with implantable defibrillators: a randomized controlled trial. *JAMA*. 2005; 293:2884-2891.
22. Leaf A, Albert CM, Josephson M, et al. Prevention of fatal arrhythmias in high-risk subjects by fish oil n-3 fatty acid intake. *Circulation*. 2005;112:2762-2768.
23. Brouwer IA, Zock PL, Wever EF, et al. Rationale and design of a randomised controlled clinical trial on supplemental intake of n-3 fatty acids and incidence of cardiac arrhythmia: SOFA. *Eur J Clin Nutr*. 2003;57: 1323-1330.
24. Zock PL, Mensink RP, Harryvan J, de-Vries JH, Katan MB. Fatty acids in serum cholesteryl esters as quantitative biomarkers of dietary intake in humans. *Am J Epidemiol*. 1997;145:1114-1122.
25. Pacifico A, Hohnloser SH, Williams JH, et al. Prevention of implantable-defibrillator shocks by treatment with sotalol. *N Engl J Med*. 1999;340:1855-1862.
26. Katan MB, Deslypere JP, van-Birgelen AP, Penders M, Zegwaard M. Kinetics of the incorporation of dietary fatty acids into serum cholesteryl esters, erythrocyte membranes, and adipose tissue: an 18-month controlled study. *J Lipid Res*. 1997;38:2012-2022.
27. Siscovick DS, Raghunathan T, King I, et al. Dietary intake of long-chain n-3 polyunsaturated fatty acids and the risk of primary cardiac arrest. *Am J Clin Nutr*. 2000;71:208S-212S.
28. Leaf A, Kang JX, Xiao YF, Billman GE. Clinical prevention of sudden cardiac death by n-3 polyunsaturated fatty acids and mechanism of prevention of arrhythmias by n-3 fish oils. *Circulation*. 2003;107:2646-2652.
29. McLennan PL. Myocardial membrane fatty acids and the antiarrhythmic actions of dietary fish oil in animal models. *Lipids*. 2001;36(suppl):S111-S114.