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Received 25 March 2008; revised 16 December 2008; accepted 24 December 2008; online publish-ahead-of-print 4 February 2009

Aims

To determine the effects of omega-3 polyunsaturated fatty acids (omega-3 PUFAs) from fish on the incidence of recurrent ventricular arrhythmia in implantable cardioverter defibrillator (ICD) patients by combining results from published trials.

Methods and results

We searched in the Medline, EMBASE, and Cochrane databases and performed a meta-analysis on all three available trials on fish oil and ventricular arrhythmia. Furthermore, we pooled individual data of two of these randomized, double-blind, placebo-controlled trials (Raitt *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 and Brouwer *et al.* 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. *JAMA* 2006;**295**:2613–2619). The main outcome was time to first confirmed ventricular fibrillation (VF) or ventricular tachycardia (VT) combined with death for the meta-analysis, and time to first spontaneous confirmed VF or VT for the pooled analysis. The meta-analysis ($n = 1148$) showed no convincing protective effect of fish oil (RR 0.90; 95% CI 0.67–1.22). The hazard ratio for the subgroup of patients with coronary artery disease at baseline (0.79; 0.60–1.06) tended towards a protective effect. The pooled analysis ($n = 722$) showed that time to appropriate ICD intervention was similar for fish oil and placebo treatment (log-rank $P = 0.79$).

Conclusion

These findings do not support a protective effect of omega-3 PUFAs from fish oil on cardiac arrhythmia in all patients with an ICD. Current data neither prove nor disprove a beneficial or a detrimental effect for subgroups of patients with specific underlying pathologies.

Keywords

ICD • Arrhythmia • Fish oil • Omega-3

Introduction

Observational studies strongly suggest that the intake of very long-chain omega-3 polyunsaturated fatty acids (omega-3 PUFAs) as found in algae and fish protects against fatal coronary heart disease.^{1,2} Trials in patients with myocardial infarction (MI) also

indicate that fish or omega-3 PUFA reduce the incidence of fatal coronary heart disease.^{3,4} The effect seems most pronounced for fatal heart disease and sudden death.^{3–7} Furthermore, sudden death is in many cases preceded by life-threatening cardiac arrhythmia.⁸ This supports the hypothesis that omega-3 PUFA from fish oil may prevent cardiac arrhythmia. Animal and

in vitro studies also indicate that omega-3 PUFA prevent fatal heart disease and sudden death by reducing susceptibility for ventricular arrhythmia.^{9–11} Three double-blind, randomized intervention studies in patients with implantable cardioverter defibrillators (ICDs) investigated the direct effects of fish oil on ventricular tachyarrhythmia. None of the three trials convincingly showed whether or not supplementation with omega-3 PUFA has preventive effects in ICD patients. Therefore, we combined the results of these three trials to assess the effect of fish oil on ventricular tachyarrhythmia in the total group of ICD patients and in subgroups with different disease history.

Methods

Literature search and selection

We performed a literature search in Medline, EMBASE, and the Cochrane Library. The search terms were fish oil or omega-3 AND implantable cardioverter defibrillator. We included only trials that investigated the effects of fish oil vs. placebo on spontaneous ventricular arrhythmia. This search resulted in 30 publications up until May 2008. Fourteen of these publications were reviews, 1 was a design paper, 1 was a cross-sectional analysis, 1 an uncontrolled experimental study, and 10 were opinions or letters to the editor. Only three were trials on the effects of fish oil on ventricular arrhythmia in patients with an ICD. These three were included in this analysis.

Use of data and quality

We used the data of all three trials on the effects of fish on ventricular arrhythmia that are currently available. In a meta-analysis, we combined the data of all three available studies. The studies were randomized, double-blind, placebo-controlled trials with high quality control standards. However, the non-compliance rate in the trial of Leaf *et al.*¹² was rather high (~35%). We had complete original individual data available for the Raitt *et al.*¹³ and Brouwer *et al.* studies.¹⁴ The data of Leaf *et al.* were extracted from the publication.¹² The studies did not use the same clinical endpoints for all analyses. Therefore, we defined common clinical endpoints and re-analysed the data of Raitt *et al.* and Brouwer *et al.* before combining the outcomes with those of Leaf *et al.* Because two of the three studies lasted only 1 year, we used data from each study up to 1 year of intervention to standardize the duration of treatment across studies.

The data of Raitt *et al.* and Brouwer *et al.* were also used in a pooled analysis.

Patients

Patients in all studies had an ICD and prior malignant ventricular tachycardia (VT) or ventricular fibrillation (VF). Raitt *et al.* excluded patients using class I and class III anti-arrhythmic medication; Brouwer *et al.* and Leaf *et al.* included both patients using and not using these medications. Raitt *et al.* and Brouwer *et al.* excluded patients with high fish intake at baseline; patients of Leaf *et al.* were asked not to consume more than two fish meals per month during the trial.

Intervention

Patients randomly received either placebo or fish oil capsules in all three trials; the dose of very long-chain omega-3 PUFAs (main forms were EPA+DHA) from fish oil was 1.3 g/day in the study of Raitt *et al.* ($n = 200$) in the form of ethyl esters in 2 g of oil, 0.9 g/day in the form of triglycerides in 2 g of oil in the study of Brouwer *et al.*

($n = 546$), and 2.6 g/day in the form of ethyl esters in 4 g of oil in the study of Leaf *et al.* ($n = 402$).

Main outcome measurement

The primary outcome of the meta-analysis was time to first confirmed spontaneous ventricular tachyarrhythmia (VT or VF) or death from any cause. To optimize the meta-analysis of three trials, we adjusted the definition of clinical outcomes and subgroups of patients for the studies of Raitt *et al.* and Brouwer *et al.* We analysed relevant subgroups for which there was information available for all three trials. These subgroups consisted of patients having a left ventricular ejection fraction of ≤ 30 or > 30 , patients with coronary artery disease or ischaemic heart disease, and patients entering the trial having had a spontaneous VT. We re-analysed the data of Raitt *et al.* and Brouwer *et al.* in such a way that the subgroups and outcome variables were the same as for Leaf *et al.* For Raitt *et al.*, data were used only up to 1 year of intervention. The main outcome measurement of the pooled analysis of the studies of Raitt *et al.* and Brouwer *et al.* was appropriate ICD treatment—shock or pacing—for a spontaneous VF or VT, as confirmed by judgement by cardiologists.

Statistical analysis

We performed statistical analyses on intention-to-treat data. We dealt with missing data by using the last available ICD reading. Participants without any ICD data or information on survival did not contribute to the person-time.

Meta-analyses

Meta-analyses were performed with STATA version 10. Combined estimates of treatments effects were calculated by applying a random effects model on hazard ratios (HRs) from the individual studies (Cox proportional hazards). We used the published data from Leaf *et al.*, and for the other two trials, we adjusted the analysis (as described earlier) so as to fit with the subgroups and outcome variables as reported for Leaf *et al.* The random effects analysis accounts for heterogeneity among trials in any condition that may influence the true underlying effect. From each study, we used the subgroup outcomes corrected for baseline characteristics of patients to calculate the overall outcome of the meta-analysis. Statistical significance level was defined as $\alpha < 0.05$ at two-sided tests.

Pooled analyses

Pooled analyses were performed with SAS software version 9 (SAS Institute Inc., Cary, NC, USA). Time-to-first-event graphs were generated using the Kaplan–Meier method. We created log cumulative hazard plots and used these plots to visually check the proportional hazards assumption. We checked parallelism across the two strata to be sure that the proportional hazards assumption was met. The statistical significance of observed differences between treatments was determined using log-rank tests. Cox proportional hazard models were used to assess outcomes when controlling for relevant baseline characteristics. We included a variable named ‘trial’ to take into account differences between studies/trials such as supplemented dose into account. Other variables were age, gender, ejection fraction (squared because of skewness of the distribution), current smoking, NYHA class for angina pectoris, NYHA class for dyspnoea, valvular heart disease, prior MI, cardiomyopathy, VT as index arrhythmia, VF as index arrhythmia, and use of anti-arrhythmic medication at baseline. The adjusted models were based on subjects with complete data on the characteristics included in the model.

Seventy to 80 per cent of the patients reported a history of coronary artery disease or ischaemic heart disease, and the mean ejection fraction was in the order of 35% (Table 1).

The meta-analysis of 1148 patients in the three trials showed a combined HR of fish oil vs. placebo of 0.90 [95% confidence interval (CI) 0.67–1.22] for time to first ICD intervention for a confirmed ventricular tachyarrhythmia or death (Figure 1). Meta-analyses in subgroups of patients (Figure 2) also revealed no statistically significant differences in risks of fish oil vs.

placebo. The HR of fish oil vs. placebo in patients with an ejection fraction ≤ 30 was 0.80 (95% CI 0.58–1.12), and in patients with ejection fraction > 30 , it was 1.18 (95% CI 0.64–2.18). Heterogeneity in the last group was rather high ($I^2 = 70.1\%$, $P = 0.035$). The HR was 0.79 (95% CI 0.60–1.06) in patients with coronary artery disease at baseline (Figure 2B).

The pooled analysis on 746 patients from Raitt *et al.* and Brouwer *et al.* studies showed that time to first appropriate ICD intervention was similar in the treatment and placebo groups

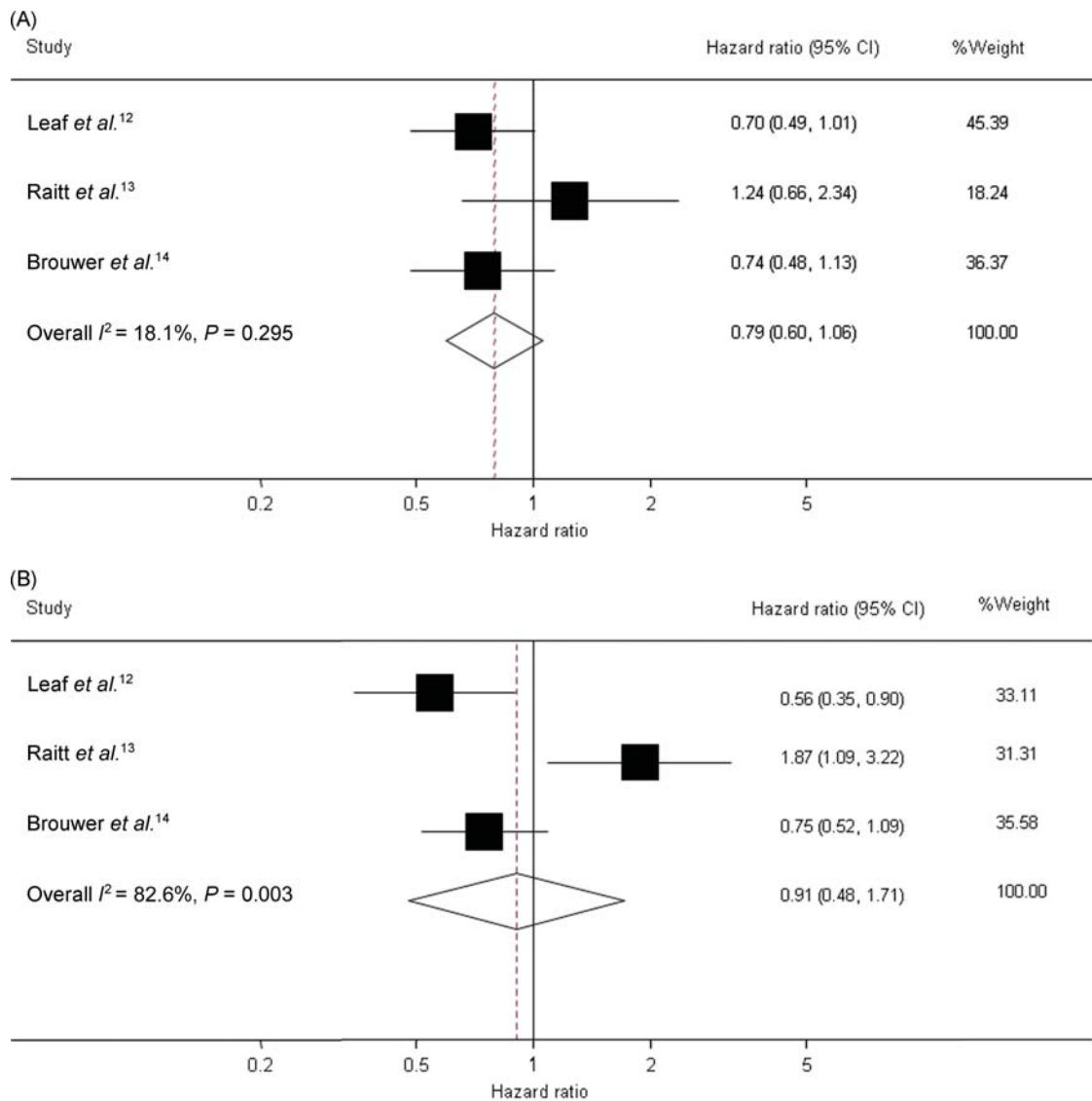


Figure 2 Forest plot of hazard ratios and overall estimate of the effect of fish oil on the first occurrence of tachyarrhythmia or death after inclusion in the studies until 1 year of intervention in the subgroups of patients with a history of coronary heart disease or ischaemic heart disease (A) and in a subgroup of patients with ventricular tachycardia at entry (B). Leaf *et al.* and Brouwer *et al.* lasted 1 year and Raitt *et al.* 2 years; data refer only to the first year of intervention. Shaded squares indicate the point estimates for each trial (hazard ratios adjusted for baseline characteristics), with the size of the square proportional to the contribution (inverse variance random effects weight) of the study to the overall estimate. The overall pooled estimate and 95% confidence interval are indicated by the dotted line and the clear diamond. (A) Subgroup of patients with coronary heart disease/ischaemic heart disease at entry. Heterogeneity $\chi^2 P = 0.295$. I^2 (variation in ES attributable to heterogeneity) = 18.1%. (B) Subgroup of patients with ventricular tachycardia at entry. Heterogeneity $\chi^2 P = 0.003$. I^2 (variation in ES attributable to heterogeneity) = 82.5%.

(Figure 3, log-rank $P = 0.79$). The primary endpoint of appropriate ICD intervention for ventricular tachyarrhythmia or death occurred in 126 (34%) patients receiving fish oil and in 121 (32%) patients taking placebo [crude HR 1.04, 95% CI 0.81–1.33; $n = 722$]. Figure 4 shows the adjusted value.

Subgroup analyses did not show profound effects for any of the subgroups of patients, but there was a suggestion that some groups of patients may respond differently towards the use of fish oil than other groups (Figure 4). In 220 patients who did not use class I or III anti-arrhythmic medication and entered the study with a VT, the adjusted HR for the use of fish oil was 1.48 (0.97–2.25). In a *post hoc* analysis in 333 patients in whom the use of lipid-lowering

medication was confirmed, the adjusted HR for the use of fish oil was 1.48 (1.01–2.18). In total, 423 patients had experienced an MI in the past. The HR for the crude effect of fish oil in these patients was 0.84 (0.61–1.17). The HR of the fully adjusted model for 344 patients with a previous MI was 0.91 (0.63–1.32).

Discussion

This combined analysis of three large randomized, controlled trials in the USA and Europe does not support a protective effect of omega-3 PUFAs from fish oil on recurrent life-threatening cardiac arrhythmia in patients with an implanted cardioverter defibrillator. This is line with the findings of an earlier published combined analysis of these studies.¹⁵ In contrast to the study of Jenkins *et al.*,¹⁵ we had access to the original data of two of the three studies which enabled us to pool the data of two studies and standardize the outcome variables across the three studies. Furthermore, we could analyse the effects in the subgroups of patients.

Although considerable heterogeneity existed between the trials, the similarity in designs and in baseline characteristics allowed a combination of the data. We used a random-effects model that took heterogeneity into account. The major difference between the studies was in the dose of fish oil: 900 mg/day fish fatty acids in Brouwer *et al.*, 1300 mg/day in Raitt *et al.*, and 2600 mg/day in Leaf *et al.* However, we think that this cannot explain the absence of a significant effect in the combined analysis. The lowest applied dose of 900 mg in Brouwer *et al.* was as high as the dose shown to have a clear protective effect on sudden death in the GISSI trial of patients with a previous MI.⁴ Furthermore, the outcomes of the individual ICD trials do not show a pattern that is consistent with a dose effect relationship in the 900–2600 mg/day range.

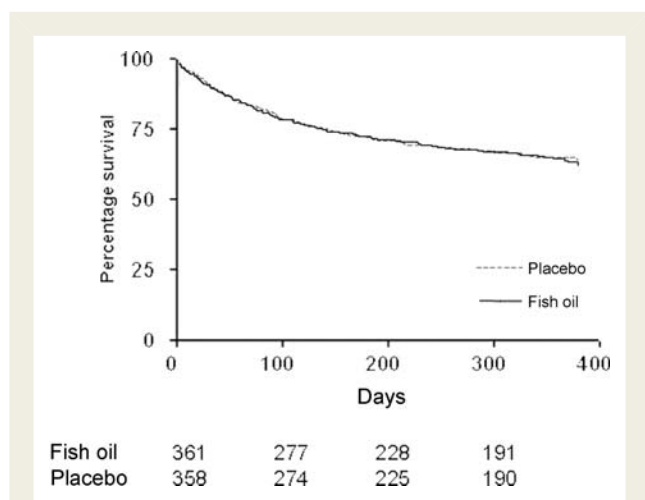


Figure 3 Time to first ventricular tachycardia (sustained ventricular tachycardia or ventricular fibrillation) for all patients in the pooled analysis (Raitt *et al.* and Brouwer *et al.*) (log-rank $P = 0.79$).

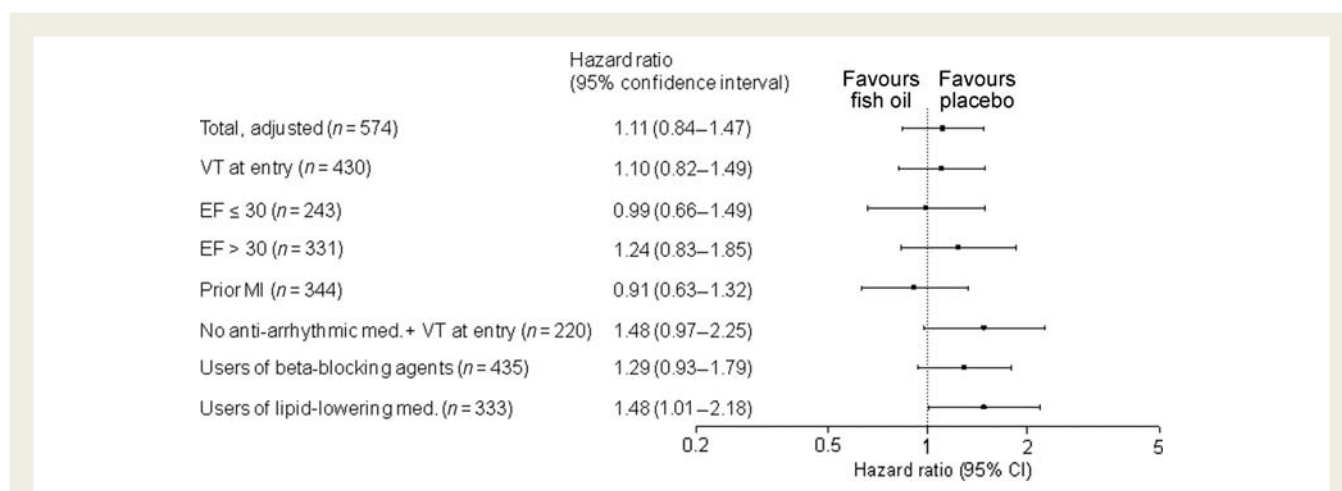


Figure 4 Hazard ratios of fish oil treatment for time to first ventricular tachyarrhythmia in the pooled analyses (Raitt *et al.* and Brouwer *et al.*) in the entire study population (primary analysis) and subgroups (subgroup analyses). Analyses are adjusted for age, gender, ejection fraction (squared because of skewness of the distribution), current smoking, New York Heart Association class for angina pectoris, New York Heart Association class for dyspnoea, valvular heart disease, prior myocardial infarction, cardiomyopathy, ventricular tachycardia as index arrhythmia, ventricular fibrillation as index arrhythmia, and use of anti-arrhythmic medication at baseline.

Both our pooled analysis and our meta-analysis showed that fish oil was not efficacious in patients who entered the studies with a VT. However, there was considerable heterogeneity between the patient populations that entered the studies with a VT. Therefore, it is difficult to interpret the results. In our pooled analysis, the risk of VT or VF in patients with a previous VT who did not use anti-arrhythmic medication tended to be increased in patients using fish oil (HR 1.48; 95% CI 0.97–2.25). This is in line with the finding in the study of Raitt *et al.*, where the effect was even statistically significant. Although the effect was not statistically significant in this pooled analysis and confined to Raitt *et al.*, fish oil supplementation might not be advisable for this group of patients.

Burr *et al.*¹⁶ suggested that interaction between fish oil and medication could play a role in determining the effect of fish oil. They showed in their population of patients with stable angina that excess mortality—both total and cardiac death—in the fish group was restricted to the men who were not taking beta-blockers.¹⁶ In contrast, in our analysis, ICD patients taking beta-blockers tended to have a higher risk on fish oil (HR 1.29; 95% CI 0.93–1.79). Although not significant, this would point in the direction of excess risk for patients using rather than not using beta-blocking agents. In any case, the available evidence shows no consistent interaction between fish oil and beta-blocking agents.

The pooled analysis also suggested a higher risk of ventricular tachyarrhythmia (adjusted HR 1.48; 95% CI 1.01–2.18) for users of fish oil on lipid-lowering medication, e.g. statins. However, separate analyses of the data of the two trials showed that this effect was only seen in patients in the Portland trial (HR 2.24; 95% CI 1.18–4.3). Risk in the same patients in the SOFA trial was essentially the same on fish oil and placebo. Therefore, this might be a chance finding. Nevertheless, it would be prudent to address this possible interaction between fish oil and statins in future studies.

Intake of fish or fish oil prevented fatal coronary heart disease in two earlier open-label trials in patients with a recent previous MI.^{4,17} In addition, the Japanese JELIS trial in hypercholesterolaemic patients showed a significant reduction of non-fatal cardiovascular events, although not of fatal events.¹⁸ In the DART 2 trial patients with stable angina, intake of fish oil did not show protective effects.¹⁹ The present pooled analysis on 423 patients with a previous MI also did not show a significant protective effect, although the observed difference and its CI cannot definitely exclude the benefit of fish oil in this patient group (HR 0.91; 95% CI 0.63–1.32). Furthermore, the meta-analysis of all three studies on outcomes in patients with previous coronary artery disease or ischaemic heart disease (Figure 2A) may also be interpreted as a trend towards a protective effect (HR 0.79; 95% CI 0.60–1.06). Animal and cell studies support the notion that the effects of fish oil on cardiac electrophysiology and arrhythmia may be dependent on the nature of the underlying disease.^{20–22} Dietary fish oil promoted arrhythmia during acute regional myocardial ischaemia in isolated pig hearts.²⁰ This study showed a moderate increase in inexcitable ventricular tissue after fish oil feeding, which favoured the onset of re-entrant arrhythmias. In other circumstances, fish oil showed anti-arrhythmic properties.^{22–24} On the basis of these experimental studies plus the findings in our combined analyses of subgroups, we speculate that fish oil could be harmful in

patients vulnerable for life-threatening arrhythmia based on re-entry, whereas it might be protective in patients with a recent prior MI or acute myocardial ischaemia. In patients with a recent prior MI, arrhythmias may have been based on triggered activity and prolonged action potentials.²¹ This is the type of arrhythmias that are probably prevented by fish oil.^{21,23,25,26} A differential effect of fish oil dependent on disease history and consequent cardiac electrophysiological condition might explain why fish oil caused a major reduction in death rates in the GISSI trial of patients with a recent MI⁴ and an increased risk in the DART 2 trial of patients with stable angina.¹⁹

In conclusion, combined data from the three available trials to date indicate that fish oil does not confer protection against recurrent life-threatening ventricular arrhythmia in patients with an ICD. However, the data suggest that underlying diseases might determine whether patients may benefit from fish oil or not. Furthermore, fish oil supplementation might not be advisable for all patients.

Author contributions

I.A.B. 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: I.A.B., M.H.R., P.L.Z., M.B.K., W.E.C., A.J.C., E.G.S., J.M.

Analysis and interpretation of the data: I.A.B., M.H.R., C.D., P.L.Z., W.E.C., J.M.

Drafting of the manuscript: I.A.B.

Critical revision of the manuscript for important intellectual content: I.A.B., M.H.R., C.D., D.F.K., P.L.Z., C.M., M.B.K., W.E.C., A.J.C., E.G.S., J.M.

Statistical analysis: I.A.B., C.D., D.F.K.

Acknowledgement

The authors would like to thank all the members of the SOFA Study Group and all the co-workers involved in the SOFA Study and the Portland Study.

Funding

The SOFA study was funded by the Wageningen Centre for Food Sciences (WCFS) with an additional grant from the European Union (SEAFOODplus integrated project No. 506359). The Portland study was funded by the National Institutes of Health (grant R01HL61682), Public Health Service (grant 5 M01 RRO0334), and Hoffman-LaRoche Inc. The meta-analysis and pooled analysis were funded by Top Institute Food and Nutrition. TI Food and Nutrition, formerly known as WCFS, is a public/private partnership. Partners are major Dutch food companies and research organizations.

Conflict of interest: P.L.Z. is employed by Unilever, a company that produces foods enriched with omega-3 fatty acids.

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