Care of Patients Who Have Cardiac Dysrhythmias

Do omega-3 polyunsaturated fatty acids reduce risk of sudden cardiac death and ventricular arrhythmias? A meta-analysis of randomized trials

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ABSTRACT

Introduction: Omega-3 polyunsaturated fatty acids (PUFA) have demonstrated to have antiarrhythmic properties. However, randomized studies have shown inconsistent results.
Objective: We aimed to analyze the effect of omega-3 PUFA on preventing potentially fatal ventricular arrhythmias and sudden cardiac death.
Methods: Randomized trials comparing omega-3 PUFA to placebo and reporting sudden cardiac death (SCD) or first implanted cardioverter-defibrillator (ICD) event for ventricular tachycardia or fibrillation were included in this study. A meta-analysis using a random effects model was performed and results were expressed in terms of Odds Ratio (OR) and 95% Confidence Interval (CI) after evaluating for interstudy heterogeneity using I^2. The reported data were extracted on the basis of the intention-to-treat principle.
Results: A total of 32,919 patients were included in nine trials; 16,465 patients received omega-3 PUFA and 16,454 received placebo. When comparing omega-3 PUFA to placebo, there was nonsignificant risk reduction of SCD or ventricular arrhythmias (OR = 0.82 [95% CI: 0.60–1.21], $p = 0.21$ $I^2 = 49.7\%$).
Conclusion: Dietary supplementation with omega-3 PUFA does not affect the risk of SCD or ventricular arrhythmias.

Introduction

The American Heart Association Dietary Guidelines and European Society of Cardiology recommend at least two fish servings per week. Both include fish oil or omega-3 polyunsaturated fatty acids (PUFA) dietary supplementation, the active element identified in fish, as standard therapy post infarction.[1,2] These recommendations were made on the basis of numerous epidemiologic and interventional studies that have demonstrated that the use of dietary supplementation with omega-3 PUFA leads to a marked reduction in the incidence of cardiovascular disease and mortality in diverse patient populations.[3–11] Other reports also showed that omega-3 PUFA caused a marked lowering of triglyceride levels,[12,13] altered the electrophysiology of the heart in a favorable manner, such as an improvement in heart rate variability,[14–16] lowered the risk of QT prolongation,[17] and reduced the incidence of atrial fibrillation.[18–20]

Recent animal studies and randomized clinical trials suggest that omega-3 PUFA may possess antiarrhythmic properties.[11] Consequently there has been tremendous interest in studying omega-3 PUFA as a cost effective and safe dietary supplement with a potentially large health benefit, namely preventing ventricular arrhythmias and sudden cardiac death. However, this has not been consistently supported by the literature. In fact, recent randomized controlled trials utilizing the ability of implantable cardioverter-defibrillator to record and store ventricular arrhythmias have showed unfavorable results in omega-3 PUFA's ability to reduce

sudden cardiac death (SCD).[21,22] We performed a systematic review of randomized trials to analyze the effect of omega-3 PUFA in preventing potentially fatal ventricular arrhythmias or SCD compared to placebo and to determine whether there is a difference in the antiarrhythmic effect of omega-3 PUFA in patients with and without myocardial ischemia.

Methods

Two investigators identified the published randomized trials comparing omega-3 PUFA to placebo and assessed the eligibility of each trial for inclusion. Disagreements were resolved by consensus among all authors. Patients in these trials were required to consume capsules of omega-3 PUFA or were advised to follow strict Cretan Mediterranean diet which included a high intake of alpha-linolenic acid (the precursor of omega-3 PUFA). In each study baseline and follow-up blood samples were collected and analyzed for the omega-3 PUFA content.

Trials published in English language journals were retrieved by searching Medline and the Cochrane Controlled Trials Register electronic database. Search keywords included "randomized", "trial", "fish oil", "omega-3 PUFA", "sudden cardiac death", "ventricular arrhythmias", "ICD", "cardiac arrest", "antiarrhythmic agents" and "cardiovascular disease." Abstracts from the annual meetings of the American Heart Association, American College of Cardiology, American Thoracic Society, and European Society of Cardiology were searched in the same time period. With the intention to identify additional randomized trials, the references of the relevant journals and review articles were manually reviewed and identified. Inclusion criteria for retrieved studies were a) controlled comparison between dietary or supplemental intake of omega-3 PUFA and placebo b) randomized treatment allocation, c) intention-to-treat analysis, and d) report of sudden cardiac death or ventricular arrhythmias [ventricular tachycardia (VT) or fibrillation (VF)] as primary or secondary endpoint and e) follow-up ≥6 months. Exclusion criteria included a) equivocal treatment allocation process, b) severe imbalances among baseline characteristics of study population and c) duplicate publications. Information on sample size, treatment type, medications, baseline characteristics and outcomes was extracted using a standardized protocol. An attempt was made to contact the authors of the included study to obtain missing data. The primary outcomes of interest were sudden cardiac death or confirmed ventricular arrhythmias [ventricular tachycardia (VT) or fibrillation (VF)].

Statistical analysis

The analysis in each trial was based on the intention-to-treat principle. The dichotomous endpoints from individual trials were analyzed using the odds ratio (OR) as a parameter of efficacy with its 95% Confidence Interval (CI). We assessed heterogeneity with I^2 that describes the percentage of total variation across trials due to heterogeneity rather than chance.[23,24] I^2 can be calculated as $I^2 = 100\% \times (Qv - df)/Q$, where Q is Cochran's heterogeneity statistics and df the degrees of freedom. Negative values of I^2 are put equal to 0, so I^2 lies between 0% (no heterogeneity) and 100% (maximal heterogeneity). Binary outcomes from individual studies were combined and the summary estimators of treatment effect were calculated using DerSimonian and Laird random effect method.[25,26] Weighting of trial data in the models was based on the inverse variance weight computed as the inverse of the squared standard error value of the effect size. A p value of ≤0.05 was regarded as significant. All analyses were performed using Review Manager (RevMan; Version 4.2 for Windows Oxford, England: The Cochrane Collaboration, 2003).

Results

Our literature search identified 301 citations (Fig. 1). We excluded 183 articles and 91 reviews not related to the study question and retrieved 27 articles for further review. Of these, 3 were animal studies, 2 duplicate publications, 3 were of non-experimental design. We identified 11 eligible randomized clinical trials and complete articles were retrieved and checked for compliance to the inclusion and exclusion criteria. We had to exclude one study as the end-point of "ischemic deaths" because it was too broad for the purpose of this review.[27] Furthermore, one trial contained severe imbalances among baseline characteristics of the study population due to recruitment of only non-diabetic men and therefore the trial was not included in this review.[28]

Three trials included patients with recent (≤6 months) myocardial infarction.[29–31] Two trials randomized patients who were scheduled for elective percutaneous coronary angioplasty (PTCA) and evaluated the rate of restenosis following the intervention, to omega-3 PUFA or placebo. One trial compared the reduction of major coronary events between dietary supplementation of omega-3 PUFA and placebo in hypercholesterolemic patients taking statins.[32] Three studies included patients who received an implantable cardioverter-defibrillator for an electrocardiographically documented episode of sustained ventricular tachycardia or fibrillation that was not related to ongoing myocardial ischemia or any other reversible causes.[21,22,33]

Of the nine studies included in the final analysis, one involved dietary advice[31] and eight involved supplementation with omega-3 PUFA.[21,22,29,30,33–35] Although the study with dietary advice did not supplement omega-3 PUFA they documented blood levels of major fatty acids, which were significantly different between the intervention and the control group. We felt that their intervention was equivalent to studies with dietary supplementation of omega-3 PUFA.
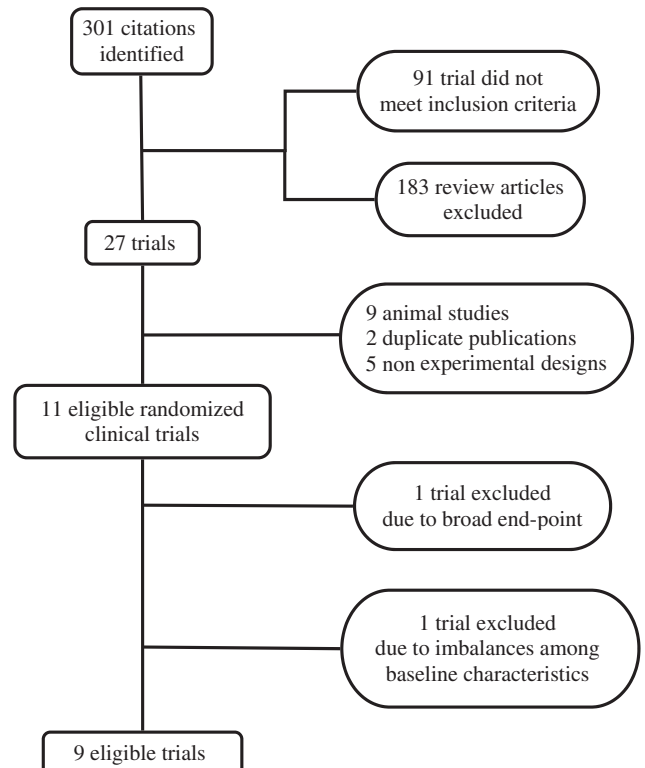

Fig. 1. Flow diagram of identification of randomized trials for inclusion.

In total 32,919 patients were randomized: 16,465 in the treatment group and 16,454 in the control group. In trials of supplementation with n-3 PUFA, the dose for eicosapentaenoic acid varied from 0.72 to 1.08 g/day, and the dose for docosahexaenoic acid ranged from 0.5 to 0.9 g/day.

The baseline characteristics included in each trial are shown in Table 1. The mean age was 58 ± 6 years and average follow-up was 1.8 years. On average, males accounted for 83% of subjects. All trials included patients with previous myocardial infarctions (32%–100%). Most of the trials did not show a significant difference in mean total cholesterol levels, mean low-density lipoprotein (LDL) cholesterol, mean high-density lipoprotein (HDL) cholesterol level and mean triglyceride levels between the intervention and control group. There was a trend toward reduction in triglycerides levels in patients on PUFA seen in 1 trial.[7] Use of other lipid lowering agents ranged from 13 to 48% (documented only in 5 trials) and use of antiarrhythmic medications (seen in 2 trials) ranged from 7 to 46%. The three trials that included patients with an implanted ICD and history of prior ventricular arrhythmias had mean left ventricular ejection fractions less then 36%. Three trials did not report ejection fraction.[7,32,35] Singh et al did not report average EF but noted "poor EF" in a significant number of patients taking placebo compared to omega-3 PUFA capsules (22.8% versus 47.4 $p < 0.01$).[30] The average left ventricular ejection fraction in the remaining 2 trials was greater than 50%.

Outcomes

We observed no significant reduction in risk of sudden death or ventricular arrhythmias in patients taking omega-3 PUFA as compared to controls but with a strong trend favoring treatment (OR = 0.82 [95% CI: 0.58–1.16, $p = 0.27$]) (Fig. 2). Six trials trended in favor of omega-3 PUFA, one trended in favor of placebo and two were equivocal. Out of the trials favoring the omega-3 PUFA, two trials were statistically significant. The trial-favoring placebo was

not statistically significant. There was moderate but significant heterogeneity ($I^2 = 55.2\%$) when all trials were combined, presumably due to the differences in the population characteristics studied in each trial.

In view of the significant heterogeneity we performed two sub-analyses combining studies that included patients with recent myocardial ischemic events[29–31,34,35] and studies that included patients with a history of ventricular arrhythmias.[21,22,33] The sub-analysis of studies that enrolled patients with recent myocardial ischemia showed a greater reduction in sudden death or ventricular arrhythmias than the main analysis. Although there was still no statistical difference between omega-3 and placebo groups (OR = 0.49 [95% CI: 0.23–1.05], $p = 0.07$) there did exist a trend in favor of omega-3 PUFA. The heterogeneity among the trial that included patients with recent myocardial ischemia was not significant ($I^2 = 23.8\%$) (Fig. 3). The JELIS Study was not included in the sub-analysis because it excluded patients with a history of myocardial infarction, angina pectoris and PTCA or coronary artery bypass grafting within the past 6 months from enrollment.[35]

The sub-analysis of the three trials that included patients with only a prior history of ventricular arrhythmias and implanted ICD showed no difference in the risk of sudden death and ventricular arrhythmias between omega-3 PUFA supplementation and placebo (OR = 1.01 [95% CI: 0.55–1.85], $p = 0.92$) (Fig. 4). This data should be interpreted with caution as the number of patients for this analysis was small and heterogeneity was significant ($I^2 = 79.0\%$).

Discussion

Our meta-analysis shows that dietary supplementation with omega-3 PUFA does not significantly reduce or increase the risk of ventricular arrhythmias and sudden cardiac death when compared to placebo in the overall population. The study found that the protective effect of omega-3 PUFA against life threatening arrhythmias might be confined to patients with recent myocardial ischemia as the pooled analysis showed a nonsignificant trend favoring treatment with omega-3 PUFA. There was no beneficial effect seen in patients with prior episodes of ventricular arrhythmia and implanted internal cardioverter-defibrillator outside the setting of myocardial ischemia.

This meta-analysis revealed a trend suggesting a 22% relative risk reduction in SCD favoring the antiarrhythmic effect of omega-3 PUFA. However, that was not statistically significant. Omega-3 PUFA supplementation did not significantly change blood lipoprotein levels in this analysis.

Our search revealed that randomized controlled trials published regarding the beneficial effects of omega-3 PUFA on SCD and ventricular arrhythmias are diverse in the population enrolled, discordant in the magnitude of risk reduction, and possess significant difference in study design quality. The variability between studies is exemplified by the significant heterogeneity quotient in the overall analysis. Other confounders contributing to heterogeneity of the studies might be differences in diagnostic criteria for patient population and endpoints, variable follow-up time, and heterogeneity of underlining pathology and mechanisms of arrhythmias (ischemia induced or due to a fixed reentrant substrate). These factors could have contributed to the wide confidence interval of the overall effect for the total and sub-group analysis.

The sub-analysis of trials that included patients with recent myocardial infarction revealed a strong trend toward a greater risk reduction of SCD than in the overall analysis (Fig. 3). The heterogeneity of the studies was significantly decreased exemplifying more uniform population groups among the included trials. Although not statistically significant the trend is not entirely

Table 1
Baseline characteristics of all the studies.

Trial	No. of Patients	Mean f/u (months)	Age	Hx of MI (%)	Male (%)	B-blockers (%)	EF (%)
Singh et al[30]							
Placebo	118	12	49.2 ± 7	100	95	29	N/A
ω-3 PUFA	122	12	48.5 ± 6.5	100	92	25	
CART study[34]							
Placebo	192	6	59 ± 9	50	80	72	68 ± 14
ω-3 PUFA	196	6	60 ± 9	51	74	77	69 ± 13
GISSI study[29]							
Placebo	5668	42	59.2 ± 11	100	85	27	52
ω-3 PUFA	5666	42	59.4 ± 10	100	73	28	52
JELIS trial[32]							
Placebo	9319	55	61 ± 9	5	31	8	N/A
ω-3 PUFA	9326	55	61 ± 8	6	32	9	
Leaf et al[33]							
Placebo	202	12	65.3 ± 0.8	N/A	82	58	34 ± 10
ω-3 PUFA	200	12	65.7 ± 0.8		85	66	33 ± 10
Leaf et al[35]							
Placebo	221	6	N/A	33	81	N/A	N/A
ω-3 PUFA	226	6		33	77		
Lyon study[31]							
Placebo	303	27	53.5 ± 10	100	92	63	N/A
ω-3 PUFA	302	27	53.5 ± 10	100	89	60	
Raitt et al[22]							
Placebo	100	24	62 ± 13	56	86	73	34
ω-3 PUFA	100	24	63 ± 13	55	86	74	36
SOFA study[21]							
Placebo	273	12	62.4 ± 11	61	84	57	37 ± 15
ω-3 PUFA	273	12	60.5 ± 12	64	85	53	37 ± 15

Hx = history; EF = left ventricular ejection fraction; N/A = not available; f/u = follow-up.
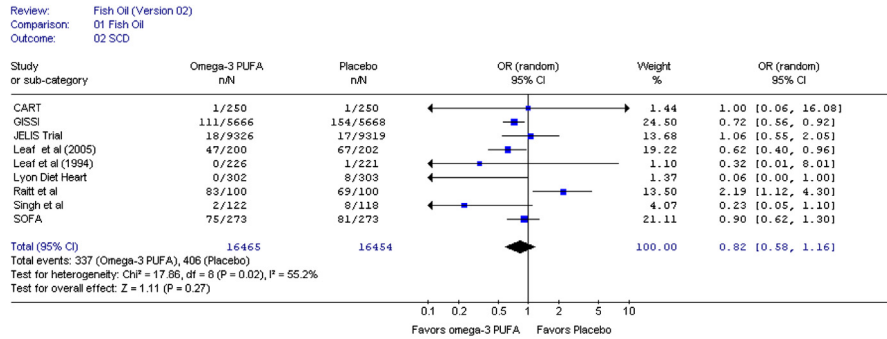
Fig. 2. Forest plot comparing supplementation with omega-3 PUFA versus control or placebo for the composite endpoint of sudden cardiac death or ventricular arrhythmias.

unexpected. Our results resemble the findings of a meta-analysis performed by Boucher et al which suggests that intake of omega-3 PUFA reduces overall mortality and SCD without reducing non-fatal MI in patients with coronary artery disease.[36] Our study extends this finding into the endpoint of SCD in a larger patient population.

Prior animal and tissue investigations studying the effect of fish oils supported the antiarrhythmic properties of omega-3 PUFA in prevention of ischemia-induced ventricular arrhythmias. The omega-3 PUFA's antiarrhythmic effect was first shown by McLennan et al who ligated the coronary artery of rats and, by administration of a diet rich in omega-3 PUFA, prevented the animals from dying from sustained ventricular arrhythmias.[37] Later these results were repeated and confirmed in dogs and monkeys.[38,39] Moreover, omega-3 PUFAs have been shown to change the spontaneous beating rate of myocardial cells and also prevent and terminate drug-induced arrhythmias in cultured myocardial cells.[40]

At the molecular level, Xiao et al has shown that the primary action of omega-3 PUFA seems to be on the phospholipid bilayer of the myocardial cells in the micro domains through which the ion channels penetrate; particularly, the fast, voltage-dependent sodium current channel.[41,42] This hypothesis supports the antiarrhythmic effect of omega-3 PUFA in the setting of acute ischemia by shifting the voltage required to change sodium channels from inactive to active. The partially depolarized cells in the periphery of the ischemic myocardium are therefore functionally eliminated.[43,44] It is also believed that the other major antiarrhythmic mechanism of omega-3 PUFA is inhibition of L-type calcium current channel and prevention of triggered arrhythmic after potential discharges caused by excessive cytosolic Ca^{2+} fluctuations.[45] These mechanisms explain the benefit of omega-3 PUFA in prevention of SCD in patients following acute myocardial ischemia.

A recently published meta-analysis examined the effect of fish oil supplementation on ventricular fibrillation and ventricular tachycardia in patients with implantable cardioverter-defibrillators.[46] At one-year follow-up there was no effect of fish oil supplementation on relative risk of implantable cardioverter-defibrillator discharge [relative risk 0.93 (0.70–1.24), $p = 0.63$, $I^2 = 67.9\%$]. Our results are consistent with the above meta-analysis (Fig. 4). Reassuringly there is no evidence of increased arrhythmic risk in this closely monitored group of high-risk patients taking omega-3 PUFA. This may relate to the fact that three trials included in this sub-analysis included patients with non-ischemic cardiomyopathy where it would not be expected to offer any benefit.[21,22,30,33] Furthermore, in ischemic cardiomyopathy patients, the mechanism of ventricular arrhythmias and SCD is likely myocardial scarring based reentry phenomena and not polymorphic ventricular tachycardia or ventricular fibrillation due to ischemia.[47] In this instance omega-3 PUFA would not be expected to confer any benefit. The lack of antiarrhythmic benefit from omega-3 PUFA might be also related to its insufficient concentration in the myocardial tissue. A study by von Schacky has shown a dose dependent reduction in blood pressure with meaningful effects achieved only at high doses of 4 g/day of omega-3 PUFA.[48] Improvement of endothelial function has been also described in patients ingesting at least 3.4–4 g/day of omega-3 PUFA.[49,50]

There was no evidence of harm seen with omega-3 PUFA in the overall population and in both sub-group analyses. The Cardiac Arrhythmia Suppression Trial (CAST) that evaluated the effect of antiarrhythmic therapy with class IC sodium channel blocking agents (encainide, flecainide, or moricizine) in patients with ventricular ectopy after myocardial infarction showed an increased risk for potential lethal proarrhythmia in patients treated with these agents.[51] The synergistic effect of myocardial ischemia and
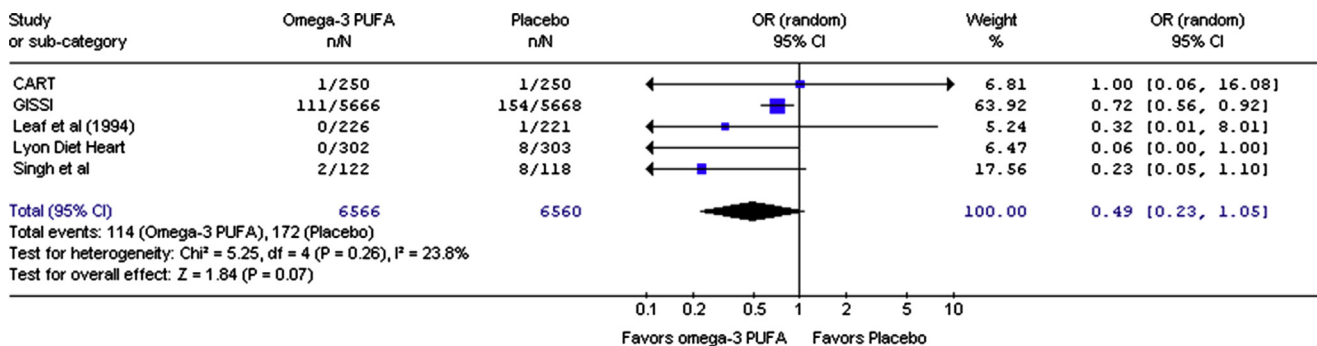

Fig. 3. Forest plot comparing supplementation with omega-3 PUFA versus control or placebo for the composite endpoint of sudden cardiac death or ventricular arrhythmias in trials which included patients with recent myocardial ischemia.
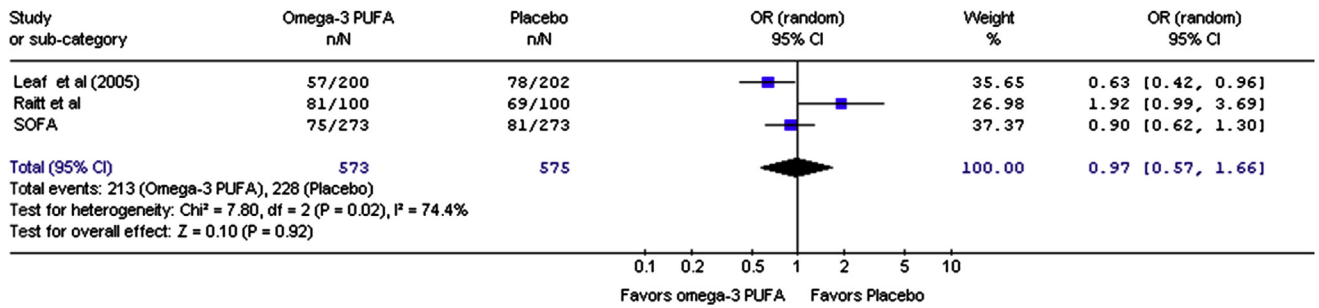
Study or sub-category	Omega-3 PUFA n/N	Placebo n/N	OR (random) 95% CI	Weight %	OR (random) 95% CI
Leaf et al (2005)	57/200	78/202		35.65	0.63 [0.42, 0.96]
Raitt et al	81/100	69/100		26.98	1.92 [0.99, 3.69]
SOFA	75/273	81/273		37.37	0.90 [0.62, 1.30]
Total (95% CI)	573	575		100.00	0.97 [0.57, 1.66]

Total events: 213 (Omega-3 PUFA), 228 (Placebo)
Test for heterogeneity: Chi² = 7.80, df = 2 (P = 0.02), I² = 74.4%
Test for overall effect: Z = 0.10 (P = 0.92)

0.1   0.2   0.5   1   2   5   10
Favors omega-3 PUFA   Favors Placebo

Fig. 4. Forest plot comparing supplementation with omega-3 PUFA versus control or placebo for the composite endpoint of sudden cardiac death or ventricular arrhythmias in trials which included patients with history of ventricular arrhythmia and implantable cardioverter-defibrillator.

class IC agents-induced dispersion of repolarization between the epicardium and endocardium played an important role behind the excess arrhythmic mortality.[52] As described above, omega-3 PUFA have sodium channel blocking effects. Conversely, our analysis shows no potential proarrhythmic effect but a possible benefit of omega-3 PUFA in a setting of myocardial ischemia.

Our meta-analysis has several limitations. Although we performed a comprehensive literature search, publication bias cannot be ruled out. The primary analysis demonstrated moderate heterogeneity between the studies (Fig. 1). There were distinct differences in the baseline characteristics especially in the ejection fraction. The majority of the patients included in the meta-analysis was comprised from two studies and had greatly contributed to the overall treatment effect that may have skewed the results. Several studies had an open intervention design and used an open clinical endpoint assessment, which lowers the trial quality as well as results in an overestimation of treatment effects. The placebo used in trials varied, ranging from olive, corn, sunflower to mustard oil. The effects of these, if any, are largely unknown, though it is doubtful that these products have any significant cardiovascular effect. There was variable use of antioxidants such as vitamin E in these trials. The cardiovascular effects of vitamins are also inconsistent. Only three of the trials included in the meta-analysis examined ventricular tachyarrhythmias as the primary endpoint. Three other trials reported SCD but not as a predetermined endpoint. Therefore, it is plausible that events of SCD or ventricular tachyarrhythmias may have been underreported in these studies. The highest risk of ventricular arrhythmias has been observed to be in the first month after MI. Therefore initiation of fish oil therapy early after myocardial infarction may have different benefits then a delayed treatment. However the data in the reported studies did not quantify the time of MI as early or late.

Many trials did not report use of other antiarrhythmic medications and in one of the trials with restenosis as the primary endpoint,[34] no information on the diagnostic criteria or blinded outcome assessment of clinical endpoints was provided and bias may have been introduced.

Our findings concur with the recent published data showing no benefit on the incidence of sudden cardiac death or ventricular arrhythmias with omega-3 PUFA.[53] One possible explanation of this divergent outcome from the older large trials is the advance in medical therapy such as statins, antiplatelets and heart failure medications. In addition in the last era there was significant advance in revascularization and implantable cardioverter-defibrillator therapy in preventing sudden cardiac death. Therefore, perhaps the slight benefits of omega-3 fatty acids that formerly improved cardiovascular outcomes have been obviated by newer more potent therapies. For this reason we think that there is no additional benefit to treat those patients with omega-3 PUFA in preventing SCD or arrhythmias as we show in our meta-analysis.

In conclusion, the present meta-analysis shows that supplementation with omega-3 PUFA had overall no effect on the incidence of sudden cardiac death or ventricular arrhythmias. There was a statistically nonsignificant trend suggesting potential benefit in patients with a recent myocardial ischemic event. This needs to be further verified in larger randomized trials. We found no additional harm in any patient population with supplementation of omega-3 PUFA in our meta-analysis. A greater utilization of omega-3 PUFA in a more tailored patient population of coronary artery disease to reduce arrhythmic events merits further investigation.

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