Association Between Omega-3 Fatty Acid Supplementation and Risk of Major Cardiovascular Disease Events
A Systematic Review and Meta-analysis

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TREATMENT WITH MARINE-derived omega-3 polyunsaturated fatty acids (PUFAs) for the prevention of major cardiovascular adverse outcomes has been supported by a number of randomized clinical trials (RCTs) and refuted by others.1-3 Although their mechanism of action is not clear, their postulated effect on cardiovascular outcomes may be due to their ability to lower triglyceride levels, prevent serious arrhythmias, or even decrease platelet aggregation and lower blood pressure.6 Current guidelines issued by major societies recommend their use, either as supplements or through dietary counseling, for patients after myocardial infarction (MI),7,8 whereas the US Food and Drug Administration has approved their administration only as triglyceride-lowering agents in patients with overt hypertriglyceridemia,9 and some (but not all) European national regulatory agencies have approved the omega-3 administration for cardiovascular risk modification.10

The controversy stemming from the varying labeling indications causes confusion in everyday clinical practice about whether to use these agents for cardiovascular protection. The controversy stemming from the varying labeling indications causes confusion in everyday clinical practice about whether to use these agents for cardiovascular protection. The controversy stemming from the varying labeling indications causes confusion in everyday clinical practice about whether to use these agents for cardiovascular protection. The controversy stemming from the varying labeling indications causes confusion in everyday clinical practice about whether to use these agents for cardiovascular protection.
Systematic reviews and meta-analyses of RCTs published in the field add further to the existing controversy because they report conflicting findings; however, other than the emergence of new evidence, reasons include the appraisal of a single outcome, the inclusion of double-blind–only RCTs, the inclusion of supplement-only RCTs, or the exclusion of populations with specific clinical characteristics.

In the present study, we attempted a large-scale synthesis of the available randomized evidence under 1 updated systematic review and meta-analysis to determine the association between omega-3 PUFAs and major patient-important cardiovascular outcomes.

METHODS
We considered all randomized trials evaluating omega-3 PUFAs supplementation in adult participants. Eligible outcomes included all-cause mortality, cardiovascular death, sudden death, MI, and all types of stroke. Omega-3 administration could be achieved either through diet or supplements. Trials were eligible if they were randomized, controlled using another diet or placebo, and implemented in primary or secondary cardiovascular disease (CVD) prevention settings. We excluded studies with treatment duration less than 1 year, allowing for enough time for the treatment to prove efficacy on CVD prevention. Whenever reports pertained to the same patients at different follow-up periods, we retained the one with the longer follow-up to avoid data duplication.

We searched PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (up to August 2012) using a predefined algorithm (eMethods, available at http://www.jama.com). Moreover, we screened references included in pertinent systematic reviews.

Data Extraction
We recorded information on study characteristics and demographics such as authors, publication year and journal, per-group sample size, population characteristics, treatment indication, omega-3 dose and mode of administration, study duration, CVD-related outcome and definition thereof, relative risk and 95% CI, as well as information regarding randomization mode, allocation concealment, blinding, loss to follow-up, and intention-to-treat analysis. Data extraction was performed independently by 2 investigators and discrepancies were resolved by another.

Assessment of Methodological Quality
We assessed the methodological quality of the included trials and the risk of bias conferred by using elements of the Cochrane collaboration tool for assessing risk of bias. The domains used in the present systematic review pertained to randomization and allocation concealment (selection bias), blinding (performance and detection bias), and loss to follow-up and adherence to the intention-to-treat principle (attrition bias). Among the established strategies, we chose to present the meta-analysis of all studies while providing a summary of the risk of bias across studies. We then performed a sensitivity analysis excluding open-label studies.

Main and Subgroup Analyses
Given the dose standardization issues, we chose to analyze separately studies in which the omega-3 administration was achieved through dietary counseling from those in which omega-3 was administered as supplements. We also analyzed separately each major outcome.

We further assessed potential associations of the treatment effect with study-level variables in subgroup analyses and meta-regression analyses. Prespecified subgroup analyses were performed based on the patient history of CVD (primary vs secondary CVD prevention setting) and the presence of implantable cardioverter-defibrillator (ICD). Meta-regression analyses considered the administered omega-3 dose (continuous variable).

Statistical Analyses
The principal summary measures were the relative risk (RR) and the absolute risk reduction (RD). For each trial, we retrieved or calculated the crude RR and RD estimates and corresponding 95% CIs for the assessed outcomes. The presence of statistically significant heterogeneity was assessed by the Q statistic (significant at \( P < .10 \)) and the extent of the observed heterogeneity was assessed by the \( I^2 \) (ranging from 0% to 100%).

We summarized RR and RD estimates using random-effects models. Fixed-effects models assume that there is a common underlying effect and the variability observed is attributed to chance alone; random-effects models acknowledge that true between-study heterogeneity exists and take into account the presence of heterogeneity into their calculations. In the absence of heterogeneity, fixed- and random-effects models yield the same results.

We examined whether the subgroup-specific effects were significantly different beyond chance by using a z score. To detect publication bias, we visually examined funnel plots per assessed outcome and further assessed asymmetry by using the Begg-Mazumbar test. In addition, the trim-and-fill approach was used to obtain an adjusted effect size that takes into account publication bias. Finally, we performed a cumulative meta-analysis to assess the evolution of the observed effects over time.

Analyses were performed in RevMan version 5 (Cochrane Collaboration, 2010) and Stata version 10 (StataCorp). All P values are 2-tailed. Within each assessed outcome, we adopted a level of statistical significance adjusted for multiple comparisons testing by a factor of 8 equaling.
the number of overall and subgroup analyses performed using the 2 measures of effect (RR and RD); thus, statistical significance was assumed at a P value threshold of .0063. The study is reported according to the PRISMA checklist.23

RESULTS

Of the retrieved 3635 citations, 20 studies of 68 680 randomized patients were included, reporting 7044 deaths, 3993 cardiac deaths, 1150 sudden deaths, 1837 MIs, and 1490 strokes1-5,24-38 (FIGURE 1).

Summary and study-specific characteristics are shown in TABLE 1 and TABLE 2. Trials were published as early as 1989, and half of the included trials had been conducted during the period where statins were routinely recommended for cardiovascular risk modification (1998 or later). The majority of the randomized participants had European ancestral backgrounds (15 studies, 49 134 participants), and the largest trial included 18 645 Japanese participants.3 With the exception of 2 trials where omega-3 administration was based on dietary counselling,30,31 omega-3 PUFA supplements were used; the mean omega-3 dose was 1.51 g per day (0.77-g/d eicosapentaenoic acid [EPA], 0.60-g/d docosahexaenoic acid [DHA]), while 10 studies used an omega-3 dose of 1 g or greater per day. The median treatment duration was 2 years (maximum, 6.2 years), and usually omega-3 PUFA were administered for secondary CVD prevention (13 studies1,4,24-32,36,38). All-cause mortality, cardiac death, and MI were the outcomes more extensively assessed (19, 15, and 14 studies, respectively); MI refers to nonfatal MI, except for 4 studies.5,32,33,35 Most studies were of high methodological quality (eTable 1); 16 studies used an intention-to-treat analysis and 16 studies were double-blind, although methods used to ensure adequate allocation concealment were not always clearly reported.

Assessed Outcomes and Evidence Synthesis

Omega-3 PUFA Administration Through Diet. The available randomized evidence indicates a knowledge gap regarding the administration of omega-3 PUFA through dietary counseling. Omega-3–targeted dietary counseling was assessed in 2 studies on 5147 randomized patients of European ancestry reporting 749 deaths, 513 cardiac deaths, 120 sudden deaths, and 82 non-fatal MIs.30,31 For the 2 outcomes that were assessed in both studies (all-cause mortality and cardiac death), these 2 studies showed associations of opposite direction that differed beyond chance (FIGURE 2). Study-specific characteristics could not explain the observed discrepancy; both studies were open-label, conducted by the same research group in participants of European ancestry, using omega-3 PUFA doses greater than 1 g for secondary prevention. Due to the observed discrepancies, a quantitative synthesis of these trials was not deemed informative and therefore was not conducted.
Table 2. Characteristics of the Eligible Randomized Clinical Trials

<table>
<thead>
<tr>
<th>Source (Country)</th>
<th>Age, Median (Range), y</th>
<th>Omega-3 PUFA Supplements</th>
<th>Duration, y</th>
<th>Indication</th>
<th>No. of Participants, Treatment/Control</th>
<th>Outcomes Assessed</th>
<th>Funding Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burr et al (DART1), 1999 (UK)</td>
<td>57 (NR)</td>
<td>0.24 (D), 0.86 (S)</td>
<td>2</td>
<td>Secondary</td>
<td>1015/1018</td>
<td>All-cause mortality, cardiac death, MI</td>
<td>Mixed</td>
</tr>
<tr>
<td>Sacks et al, 1995 (US)</td>
<td>62 (30-75)</td>
<td>6</td>
<td>2</td>
<td>Secondary</td>
<td>31/28</td>
<td>All-cause mortality, cardiac death, MI, stroke</td>
<td>Mixed</td>
</tr>
<tr>
<td>Singh et al, 1997 (India)</td>
<td>49 (NR)</td>
<td>1.8</td>
<td>1</td>
<td>Secondary</td>
<td>122/111</td>
<td>Cardiac death, sudden death, MI</td>
<td>NR</td>
</tr>
<tr>
<td>Leng et al, 1998 (UK)</td>
<td>66 (NR)</td>
<td>0.27</td>
<td>2</td>
<td>Secondary</td>
<td>60/60</td>
<td>All-cause mortality, cardiac death, MI, stroke</td>
<td>NR</td>
</tr>
<tr>
<td>von Schacky et al, 1999 (Germany)</td>
<td>58 (18-75)</td>
<td>3.3 (3 mo), 1.7 (21 mo)</td>
<td>2</td>
<td>Secondary</td>
<td>112/111</td>
<td>All-cause mortality, cardiac death, MI, stroke</td>
<td>Mixed</td>
</tr>
<tr>
<td>Marchiol et al (GISSI), 1999 (Italy)</td>
<td>60 (NR)</td>
<td>0.85</td>
<td>3</td>
<td>Secondary</td>
<td>5666/5658</td>
<td>All-cause mortality, cardiac death, sudden death, MI, stroke</td>
<td>Industry</td>
</tr>
<tr>
<td>Nilsen et al, 2001 (Norway)</td>
<td>64 (29-88)</td>
<td>3.4</td>
<td>1.5</td>
<td>Secondary</td>
<td>150/150</td>
<td>All-cause mortality, cardiac death, MI, stroke</td>
<td>Industry</td>
</tr>
<tr>
<td>Burr et al (DART2), 2003 (UK)</td>
<td>61 (NR)</td>
<td>0.34 (D), 0.86 (S)</td>
<td>5</td>
<td>Secondary</td>
<td>1571/1543</td>
<td>All-cause mortality, cardiac death, sudden death</td>
<td>Mixed</td>
</tr>
<tr>
<td>Leaf et al, 2005 (US)</td>
<td>65 (NR)</td>
<td>2.6</td>
<td>1</td>
<td>ICD</td>
<td>200/202</td>
<td>All-cause mortality, cardiac death, sudden death</td>
<td>Non-industry</td>
</tr>
<tr>
<td>Raitt et al, 2005 (US)</td>
<td>63 (NR)</td>
<td>1.8</td>
<td>2</td>
<td>ICD</td>
<td>100/100</td>
<td>All-cause mortality, cardiac death, sudden death</td>
<td>Mixed</td>
</tr>
<tr>
<td>Brouwer et al (SCFA), 2006 (multiple)</td>
<td>61 (NR)</td>
<td>0.96</td>
<td>1</td>
<td>ICD</td>
<td>273/273</td>
<td>All-cause mortality, cardiac death, MI, stroke</td>
<td>Non-industry</td>
</tr>
<tr>
<td>Svensson et al, 2006 (Denmark)</td>
<td>67 (NR)</td>
<td>1.7</td>
<td>2</td>
<td>Secondary</td>
<td>103/103</td>
<td>All-cause mortality, cardiac death, MI, stroke</td>
<td>Mixed</td>
</tr>
<tr>
<td>Yokoyama et al (JELIS), 2007 (Japan)</td>
<td>61 (40-75)</td>
<td>1.8</td>
<td>4.6</td>
<td>Primary/secondary</td>
<td>7503/7478 (1823/1841)</td>
<td>All-cause mortality, cardiac death, sudden death, MI, stroke</td>
<td>Industry</td>
</tr>
<tr>
<td>Tavazzi et al (GISSI-HF), 2008 (Italy)</td>
<td>67 (NR)</td>
<td>1</td>
<td>3.9</td>
<td>Primary/secondary</td>
<td>3494/3481</td>
<td>All-cause mortality, cardiac death, sudden death, MI, stroke</td>
<td>Mixed</td>
</tr>
<tr>
<td>Garbagnati et al, 2009 (Italy)</td>
<td>65 (NR)</td>
<td>0.5</td>
<td>0.25</td>
<td>Placebo</td>
<td>20/18</td>
<td>All-cause mortality</td>
<td>Mixed</td>
</tr>
<tr>
<td>Gaïn et al (SU.FOL.OM3), 2010 (France)</td>
<td>61 (54-69)</td>
<td>0.6</td>
<td>4.7</td>
<td>Secondary</td>
<td>1253/1248</td>
<td>All-cause mortality, cardiac death</td>
<td>Mixed</td>
</tr>
<tr>
<td>Kromhout et al, 2010 (Netherlands)</td>
<td>69 (60-80)</td>
<td>0.4</td>
<td>3.4</td>
<td>Secondary</td>
<td>2404/2433</td>
<td>All-cause mortality, cardiac death</td>
<td>Mixed</td>
</tr>
<tr>
<td>Rauch et al, 2010 (Germany)</td>
<td>64 (NR)</td>
<td>1</td>
<td>1</td>
<td>Secondary</td>
<td>1925/1983</td>
<td>All-cause mortality, cardiac death, sudden death</td>
<td>Industry</td>
</tr>
<tr>
<td>Einik et al, 2010 (Norway)</td>
<td>70 (64-76)</td>
<td>2.4</td>
<td>3</td>
<td>Primary</td>
<td>282/281</td>
<td>All-cause mortality, cardiac death, sudden death</td>
<td>Mixed</td>
</tr>
<tr>
<td>Bosch et al (ORIGIN), 2012 (multiple)</td>
<td>64</td>
<td>0.47</td>
<td>6.2</td>
<td>Primary</td>
<td>6281/6255</td>
<td>All-cause mortality, cardiac death, MI, stroke</td>
<td>Industry</td>
</tr>
</tbody>
</table>

Abbreviations: D, diet; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; ICD, implantable cardioverter defibrillator; NR, not reported; Primary, primary prevention; S, supplement; Secondary, secondary prevention.


*Mixed refers to both industry and nonindustry.

*96% European ancestry.

*Poland, Germany, Switzerland, United Kingdom, Czech Republic, Austria, Belgium, Netherlands.

*Primary and secondary prevention populations reported separately.

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In a cumulative meta-analysis for all-cause mortality (FIGURE 5), the originally proposed significant omega-3 PUFA effect was refuted by the accumulated evidence by 2007 and remained unchanged since, lingering around a small effect and borderline statistical significance, although 49,899 more patients have been randomized. There was no evidence for an association between treatment effect and the presence of blinding, the omega-3 PUFA dose, the prevention setting, or the presence of ICD (TABLE 3). Although visual inspection of the funnel plot including all studies showed asymmetry, the Begg-Mazumbar test was not statistically significant, and the trim-and-fill approach gave an identical imputed estimate indicating a low risk of publication bias (eFigure 2A).

From 13 studies analyzed, there were 3480 cardiac deaths among 56,407 participants. Evidence synthesis for cardiac death did not show a statistically significant association for omega-3 PUFA supplements after correction for multiple comparisons (RR, 0.91; 95% CI, 0.83 to 0.98; P = .01; F = 78%) (eFigure 1A). There was no evidence for an association between the observed treatment effect and the presence of blinding, the omega-3 PUFA dose, the prevention setting, or the presence of ICD (Table 3, eFigure 1B). The Begg-Mazumbar test was not statistically significant, and visual inspection of the funnel plot including all studies showed symmetry, indicating a low risk of publication bias (eFigure 2C). With the trim-and-fill approach, the imputed estimate was identical to that in the main analysis, indicating that results are unlikely to be explained by publication bias.

Thirteen studies were included for the outcome MI, involving 53,875 participants and 1030 events. Omega-3 supplementation was not statistically significantly associated with reduced rates of sudden death (RR, 0.87; 95% CI, 0.75 to 1.01; P = .06; F = 8%; RD, −0.03; 95% CI −0.12 to 0.006; P = .49; F = 91%). There was no evidence for an association between treatment effect and the presence of blinding, the omega-3 PUFA dose, the prevention setting, or the presence of ICD (Table 3, eFigure 1B). The Begg-Mazumbar test was not statistically significant, and visual inspection of the funnel plot including all studies showed asymmetry, indicating a low risk of publication bias (eFigure 2B).
participants and 1755 events. Overall, omega-3 PUFA supplementation was not significantly associated with a reduced risk of MI (RR, 0.89; 95% CI, 0.76 to 1.04; \( P = .14; I^2 = 35\% \); RD, −0.002; 95% CI, −0.007 to 0.002; \( P = .23; I^2 = 35\% \)). There was no evidence for an association between treatment effect and the presence of blinding, the omega-3 PUFA dose, the prevention setting, or the presence of ICD (Table 3, eFigure 1C). Visual inspection of the funnel plot including all studies showed asymmetry, and the Begg-Mazumbar test for publication bias was statistically significant (\( P = .01 \)), although the trim-and-fill approach gave an identical imputed estimate (eFigure 2D).

Nine studies were included in the analysis of stroke; there were 1490 events among 52 589 participants. The available evidence for stroke points to an opposite but not statistically significant effect (RR, 1.05; 95% CI, 0.93 to 1.18; \( P = .47; I^2 = 35\% \)); RD, 0.001; 95% CI, −0.002 to 0.004; \( P = .46; I^2 = 14\% \)) (eFigure 1D). All available studies included non-ICD patients treated with omega-3 supplements. There was no evidence for an...
association between treatment effect and the presence of blinding, the omega-3 PUFA dose, or the prevention setting (Table 3), and the available data did not allow for a separate analysis for hemorrhagic and nonhemorrhagic stroke. The Begg-Mazumbar test was not statistically significant, and visual inspection of the funnel plot including all studies showed symmetry, indicating a low risk of publication bias (eFigure 2E). With the trim-and-fill approach, the imputed estimate (RR, 1.03; 95% CI, 0.93 to 1.15, P = .56) was similar to that in the main analysis, indicating that results are unlikely to be explained by publication bias.

**COMMENT**

Our study incorporating the available published randomized evidence shows that omega-3 PUFAs are not universally statistically significantly associated with major cardiovascular outcomes across patient populations at increased cardiovascular risk. Omega-3 supplementation was not significantly associated with all-cause mortality, cardiac death, sudden death, MI, or stroke. The observed effect was not associated with study-specific or population-specific characteristics, and the majority of the large studies in the field agree with the results of our work.

Systematic reviews and meta-analyses published on the same topic posed variably different key questions, thus assessing different subgroups of studies. In our study, we chose to include all the available published randomized evidence addressing the cardiovascular benefit of the omega-3 supplementation regardless of methodological study characteristics, the prevention setting, or the supplementation mode, opting for the totality of the evidence and thus a valid interpretation of the results. Despite the variation in the research questions assessed, the results of the previously published meta-analyses are in accordance with our findings regarding the evolution of the omega-3 supplementation effect over time and its replication validity. The first quantitative synthesis in the field showed a strong, significant effect across all major cardiovascular outcomes. As more randomized evidence accumulated, the effect became weaker and nonsignificant and lost its universal aspect.

### Table 3. Subgroup Analyses for the Omega-3 PUFA Supplements Effect Across the Assessed Randomized Controlled Trials

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Subgroup</th>
<th>No. of Studies</th>
<th>RR (95% CI)</th>
<th>P Value</th>
<th>I² Value, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-cause mortality</strong></td>
<td>Secondary</td>
<td>10</td>
<td>0.95 (0.86-1.04)</td>
<td>.51</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>ICD</td>
<td>3</td>
<td>0.69 (0.39-1.23)</td>
<td>.20</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mixed</td>
<td>4</td>
<td>0.97 (0.90-0.05)</td>
<td>.39</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac death</strong></td>
<td>Secondary</td>
<td>8</td>
<td>0.81 (0.70-0.93)</td>
<td>.07</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>ICD</td>
<td>3</td>
<td>0.65 (0.35-1.18)</td>
<td>.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mixed</td>
<td>3</td>
<td>0.95 (0.89-1.02)</td>
<td>.00</td>
<td></td>
</tr>
<tr>
<td><strong>Sudden death</strong></td>
<td>Secondary</td>
<td>4</td>
<td>0.78 (0.61-1.01)</td>
<td>.22</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>ICD</td>
<td>1</td>
<td>5.00 (0.2-102.9)</td>
<td>.20</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mixed</td>
<td>3</td>
<td>0.94 (0.81-1.09)</td>
<td>.00</td>
<td></td>
</tr>
<tr>
<td><strong>Myocardial infarction</strong></td>
<td>Secondary</td>
<td>9</td>
<td>0.82 (0.63-1.06)</td>
<td>.42</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>ICD</td>
<td>2</td>
<td>0.33 (0.07-1.64)</td>
<td>.40</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Mixed</td>
<td>3</td>
<td>0.96 (0.77-1.17)</td>
<td>.47</td>
<td></td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td>Secondary</td>
<td>6</td>
<td>1.17 (0.90-1.53)</td>
<td>.33</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Mixed</td>
<td>3</td>
<td>1.01 (0.89-1.14)</td>
<td>.20</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Open-label</td>
<td>2</td>
<td>1.09 (0.92-1.30)</td>
<td>.64</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Blinding</td>
<td>7</td>
<td>1.04 (0.86-1.26)</td>
<td>.23</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ICD, implantable cardioverter-defibrillator; PUFA, polyunsaturated fatty acid; RR, relative risk. 

aP value for the meta-regression. 

bPrimary and secondary prevention populations reported separately for the JELIS study.
trials, predominantly in women, failed mainly primary prevention JELIS from the DART1 trial. The Japanese, statistically significantly different mate of opposite direction that was GISSI findings and gave an effect estimate of opposite direction that was statistically significantly different from the DART1 trial. The Japanese, open-label, high-baseline-intake, mainly primary prevention JELIS trial, predominantly in women, failed to replicate the GISSI trial for the outcomes assessed (sudden and cardiac death) even in the secondary prevention subgroup analysis. The GISSI-HF, a double-blind, statin-era study performed on high-risk (heart failure) patients with a staggering control event rate of almost 30% for all-cause mortality, also failed to replicate the magnitude of the GISSI effect but yielded marginal statistical significance in adjusted analyses. Moreover, the recent double-blind Alpha-Omega Trial on secondary prevention with comparable control event rates to the GISSI trial but with patients with a longer history of clinical CVD showed that low-dose omega-3 supplementation was not significantly associated with a reduced rate of major cardiovascular events among patients who had an MI and who were receiving state-of-the-art antihypertensive, antithrombotic, and lipid-modifying therapy. Similarly, the double-blind OMEGA trial and the SU.F.O.OM3 trial concluded that omega-3 fatty acids do not seem to add to the guideline-adjusted treatment of secondary prevention CVD patients at a low rate of sudden cardiac death. Finally, the recently published ORIGIN trial performed in 12,536 patients found that omega-3 did not prevent death or any cardiovascular outcomes in high-risk patients for cardiovascular events who had (or were at high risk for) diabetes and were receiving all antihypertensive, antithrombotic, antidiabetic, and lipid-modifying medications proposed by the current guidelines.

The observed effect variation poses a challenge to the interpretation of the evidence synthesis results, and one approach toward explaining it would be through the postulated underlying pathophysiology, namely the omega-3 effect on triglycerides, arrhythmias, and hypertension. Overall, the proposed protective role of omega-3 PUFAs by lowering triglyceride levels is not supported by our study, because our findings do not support an advantage of higher (triglyceride-lowering) doses compared with lower doses of omega-3; this could be attributed to the limited strength of the primary association between triglycerides and CVD or varying baseline triglyceride levels. Life-threatening ventricular arrhythmias are the most common cause of sudden cardiac death in the early stages after MI.

Our meta-analysis did not find any significant protective association with sudden death in the various groups of patients examined, thus rejecting a distinct antiarrhythmic mediated omega-3 PUFA effect, although the accumulated evidence would still be underpowered to detect a small underlying effect. Hypertension is another important risk factor for CVD, and several studies have indicated that high doses of omega-3 PUFAs are associated with a modest reduction in systemic blood pressure (0.66 mm Hg systolic and 0.35 mm Hg diastolic blood pressure reduction per 1 g of omega-3 PUFAs). Interestingly, our meta-analysis did not show a protective effect on stroke (the CVD outcome most profoundly influenced by hypertension).

Our study has certain limitations. Our findings come from published evidence including and not limited to large RCTs. Publication and language bias is a major concern when dealing with efficacy trials, but the assessed studies were published from 1989 to 2012, pertained to a cumulative sample size of more than 68,500 randomized patients, and included several large studies; furthermore, to enhance comprehensiveness, our searches were extended to the Cochrane Controlled Trials Registry, which is built from multiple large databases. We would thus expect that the incorporation of unpublished evidence would not substantially alter the status of the evidence, a notion supported by the observed consistency of the effect when small studies (<1000 participants) were excluded from the analysis. Moreover, although randomized evidence is protected from selection bias, performance and detection bias could be operating in the field. An approach toward dealing with such a situation would be to exclude open-label studies. Unfortunately, 2 of the open-label trials are also by far the largest in the field, and should we choose to exclude them, we would be excluding almost half of the accumulated randomized evidence. The subsequent effect estimate cannot be validly attributed to the substantial reduction in sample size or the possible correction for performance bias.

Another consideration pertains to the differential influence of co-interventions (ie, background treatment strategies) that could be considerable in quantifying the underlying therapeutic effect of any given intervention. Yet omega-3 PUFAs have been tested under various baseline risk settings and background treatment strategies (including and not limited to statin therapy) without showing an association toward a differential effect based on co-interventions. Finally, although omega-3 PUFAs are usually administered as an EPA/DHA combination, a component-specific effect has been previously proposed. Among the assessed studies, only the relatively small study by Leung et al and the large, high-baseline-intake Japanese JELIS study used EPA-only interventions. Thus, a subgroup analysis investigating the role of the separate...
components in the observed study variability would be considerably underpowered and particularly vulnerable to a biased interpretation. Moreover, regarding adherence, we acknowledge that varying compliance rates could create effect variation; yet the fact that most studies were of reported high compliance (>80%) and the considerable variation in noncompliance definitions make a compliance-based subgroup analysis less informative for the available published reports.

Finally, the varying event rates and baseline risk estimates in the assessed trials could explain some of the effect variation. Even among the large studies investigating high-risk populations (GISSI, GISSI-HF, Alpha-Omega, ORIGIN), which could attain maximum precision for the therapeutic effect quantification, inconsistency prevails. If the observed summary effects were consistent in the direction of the association or the results of the large studies, we could claim that the observed heterogeneity represents an overinflation of the true underlying clinical heterogeneity. Nevertheless, we confirmed the previously extensively discussed major divergence of the observed effect in the field, even though we chose to assess only randomized, well-designed, less-bias-prone clinical trials.

In conclusion, omega-3 PUFAs are not statistically significantly associated with major cardiovascular outcomes across various patient populations. Our findings do not justify the use of omega-3 as a structured intervention in everyday clinical practice or guidelines supporting dietary omega-3 PUFA administration. Randomized evidence will continue to accumulate in the field, yet an individual patient data meta-analysis would be more appropriate to refine possible associations related to, among others, dose, adherence, baseline intake, and CVD risk group.

Author Contributions: Dr Rizos 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. Dr Rizos and Dr Ntzani contributed equally to the work.

Study concept and design: Rizos, Ntzani, Bika, Kostopanagos, Eliaf. Acquisition of data: Rizos, Bika, Kostopanagos. Analysis and interpretation of data: Rizos, Ntzani, Eliaf. Drafting of the manuscript: Rizos, Ntzani, Eliaf. Critical revision of the manuscript for important intellectual content: Rizos, Ntzani, Bika, Kostopanagos, Eliaf. Study supervision: Rizos, Ntzani, Eliaf.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Eliaf reported having given talks, attended conferences, and participated in trials sponsored by industry not associated with those that manufacture or market omega-3 supplements.


REFERENCES


