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Original Articles

Use of supplemental long-chain omega-3 fatty acids and risk for cardiac death: An updated meta-analysis and review of research gaps

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BACKGROUND: Randomized controlled trials (RCTs) assessing use of long-chain omega-3 polyunsaturated fatty acids (LC-OM3), primarily eicosapentaenoic acid, and/or docosahexaenoic acid have shown mixed results.

OBJECTIVE: The objectives of the study were to update and further explore the available RCT data regarding LC-OM3 supplementation and risk for cardiac death and to propose testable hypotheses for the mixed results obtained in RCTs regarding supplemental LC-OM3 use and cardiac risk.

METHODS: A literature search was conducted using PubMed and Ovid/MEDLINE for RCTs assessing LC-OM3 supplements or pharmaceuticals with intervention periods of at least 6 months and reporting on the outcome of cardiac death. Meta-analysis was used to compare cumulative frequencies of cardiac death events between the LC-OM3 and control groups, including sensitivity and subset analyses.

RESULTS: Fourteen RCTs were identified for the primary analysis (71,899 subjects). In the LC-OM3 arms, 1613 cardiac deaths were recorded (4.48% of subjects), compared with 1746 cardiac deaths in the control groups (4.87% of subjects). The pooled relative risk estimate showed an 8.0% (95% confidence interval 1.6%, 13.9%, $P = .015$) lower risk in the LC-OM3 arms vs controls. Subset analyses showed numerically larger effects (12.9%–29.1% lower risks, all $P < .05$) in subsets of RCTs with eicosapentaenoic acid + docosahexaenoic acid dosages >1 g/d and higher risk samples (secondary prevention, baseline mean or median triglycerides ≥150 mg/dL, low-density lipoprotein cholesterol ≥130 mg/dL, statin use <40% of subjects). Heterogeneity was low ($I^2 \leq 15.5\%$, $P > .05$) for the primary and subset analyses.

CONCLUSION: LC-OM3 supplementation is associated with a modest reduction in cardiac death.

Introduction

In recent years, several randomized controlled trials (RCTs) have assessed the effects of supplemental long-chain omega-3 polyunsaturated fatty acids (LC-OM3), primarily eicosapentaenoic acid (EPA) and docosahexaenoic

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acid (DHA), on risk for various types of cardiovascular disease (CVD) events. Results from these studies have been mixed, with some suggesting benefits and others showing neutral effects.

The outcome for which both the observational evidence on LC-OM3 intake or status and RCTs of supplementation appears to show the most consistent association is cardiac death.[1–3] For example, Rizos et al.[2] conducted a meta-analysis of the effects of supplemental LC-OM3 on the outcomes of all-cause mortality, cardiac death, sudden death, myocardial infarction (MI), and stroke. The only outcome for which the 95% confidence interval (CI) did not cross the null value was cardiac death, with a pooled relative risk (RR) estimate from 13 RCTs of 0.91 (95% CI 0.85, 0.98). This finding is in agreement with that from a pooled analysis of data from 19 observational cohort studies that evaluated LC-OM3 status based on various biomarkers, including omega-3 fatty acids in total plasma, phospholipids, cholesterol esters and adipose tissue, and coronary heart disease (CHD) risk.[4] Assessment of LC-OM3 status using these biomarkers avoids many of the issues associated with estimation of dietary intake. The overall pooled RR estimates for fatal CHD per 1 standard deviation increase in EPA and DHA biomarker level were 0.91 (95% CI 0.82, 1.00) and 0.90 (95% CI 0.84, 0.96), respectively. Results were more consistent for fatal CHD (cardiac death) than for total CHD or non-fatal MI.

The purpose of this meta-analysis and review of research gaps is 2-fold. The first aim is to update and further explore the available RCT data regarding LC-OM3 supplementation and risk for cardiac death. Secondary aims are to briefly review the evidence regarding the effects of LC-OM3 intake on cardiac event risk and propose testable hypotheses for the mixed results obtained in RCTs regarding supplemental LC-OM3 use and cardiac event risk.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed for performing this meta-analysis.[5] A comprehensive literature search was conducted using the PubMed and Ovid/MEDLINE databases, which covered studies published from January 1947 through December 2016. The search was designed to identify publications from RCTs that examined supplemental LC-OM3 use (as dietary supplements or pharmaceutical LC-OM3 concentrates) and the outcome of cardiac death. The full search strategy is included as supplemental material.

Level I screening included review of all titles and/or abstracts. Supplementary literature searches included review of the reference lists of relevant articles, including meta-analyses and the report published by the Agency for Healthcare Research and Quality (AHRQ) Technical Review in 2016. Published reviews were also assessed to identify studies that may not have been otherwise captured. Full-text publications were obtained for level II review. All search results were screened by 2 individuals (O.M.P. and K.C.M.) minor disagreements resolved through critical evaluation of study design.

To be included, publications were required to report at least 1 of the following outcomes: MI (fatal), sudden cardiac death, coronary death, cardiac death, ischemic heart disease death, sudden cardiac mortality, coronary mortality, cardiac mortality, or ischemic heart disease mortality. To be included in the primary analysis, the publication had to be an RCT with an intervention period of at least 6-month duration and provided in the form of an LC-OM3 (mainly EPA and/or DHA) dietary supplement or pharmaceutical concentrate.

An *a priori* decision was made to exclude studies from the primary analysis that provided LC-OM3 in a food vehicle and studies in which the subjects had implanted cardiac defibrillators. For the former, the reason was that the investigators had concerns about the level of LC-OM3 actually consumed in food vehicle trials. For the latter, the concern was for generalizability because a very small fraction of the population has implanted cardiac defibrillator devices. Sensitivity analyses were completed in which both categories were included, and results are reported for both the primary and sensitivity analyses. In addition, subset analyses of the primary analysis group of RCTs were completed to investigate possible influences of clinical features such as dosage (>1 g/d EPA + DHA), mean or median baseline triglycerides (TG) $\geq$150 mg/dL, and mean or median low-density lipoprotein cholesterol (LDL-C) concentration $\geq$130 mg/dL, secondary prevention, and baseline statin use $<$40%. Subset analyses thresholds for LDL-C and TG were based on levels classified as borderline high or above by the National Lipid Association.[6] Subset analyses values for EPA + DHA dosage and statin usage were both based on approximate median values for the studies included in the primary analysis.

Statistical analyses

Meta-analysis was used to compare cumulative frequencies of cardiac death events between the LC-OM3 and control groups using MIX Pro, version 2.0 for the personal computer (BiostatXL, Utrecht, The Netherlands). The primary analysis used a random-effects model to generate pooled RR estimates and 95% CIs as prespecified in a statistical analysis plan. Statistical significance for individual study and pooled RRs was declared when the 95% CI did not include the null value of 1.0 (ie, P value $\leq$.05). Weighting was based on the inverse of the variance of each study's effect as described by DerSimonian and Laird.[7] RR and 95% CIs were converted to RR reduction values using the formula $(1 - \text{RR}) \times 100$.

Statistical heterogeneity was assessed using Cochran's Q and the I^2 statistic.[8] The Cochrane Handbook defines an I^2 value of 0% to 40% as low heterogeneity, which "might not be important".[8] An I^2 value of $\geq$40% was used to designate

moderate or higher heterogeneity. For secondary, sensitivity and subgroup analyses, fixed effects models were used if the I^2 value was <40% to maximize statistical power. Sensitivity analyses were completed that included a larger number of studies than the primary analysis and that included trials that either used a food vehicle or enrolled subjects with implanted cardiac defibrillator devices. Individual exclusion of trials one at a time was used as an additional sensitivity analysis to assess the degree to which the findings from the primary analysis dataset were influenced by individual trials. The presence of publication bias was assessed visually by examining funnel plots measuring the standard error as a function of effect size, as well as statistically by using Egger's regression method.

Results

A flow diagram summarizing the results of the literature search is shown in Figure 1. A set of 14 RCTs was identified for the primary analysis.[9–22] For the 14 RCTs included in the primary analysis, we used the analyzable data reported for 71,899 total study participants, an approach similar to that used by the 2012 Rizos et al.[2] meta-analysis. For 2 studies,[21,22] the total number of cardiac deaths could not be ascertained because it was not reported in the original published article and attempts to obtain the information from the authors went unanswered.

The 2012 meta-analysis by Rizos et al.[2] included both of these studies in their analysis of cardiac death using event values for total cardiovascular deaths (as shown in their Supplemental Material) and the same approach was used for these 2 studies for the analyses reported here. As shown in Table 1 and Figure 2, the weighted, pooled RR estimate showed a modest, but statistically significant 8.0% (P = .015) lower risk in the LC-OM3 arms compared with the control arms. Heterogeneity was low (I^2 = 1.8%) and the P value for the Q-statistic was non-significant (P = .430).

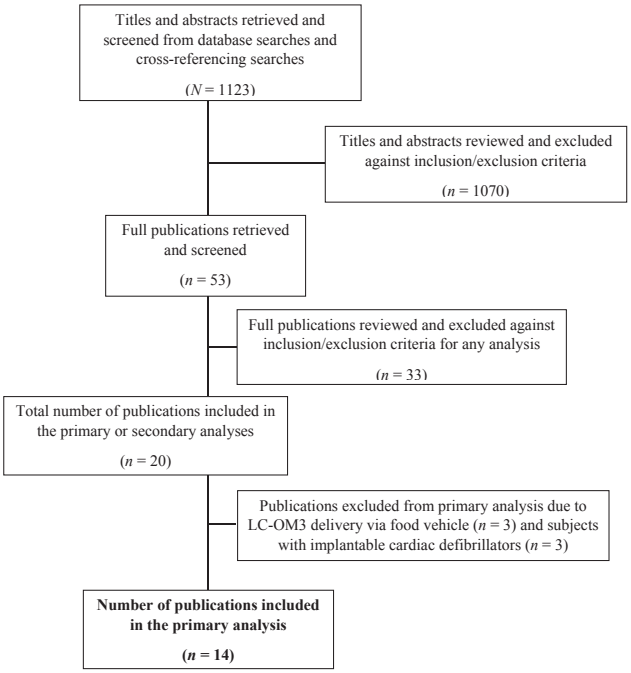

Figure 1 Flow diagram of literature search for study analyses inclusion. LC-OM3, long-chain omega-3 polyunsaturated fatty acids.

A sensitivity analysis in which 1 study was excluded at a time showed that the results were rendered non-significant by exclusion of 2 of the 3 most heavily weighted trials, the GISSI-Heart Failure study (weight 39.8%)[17] and GISSI-Prevenzione (weight 14.9%).[21] Pooled RR estimates ranged from 0.892 to 0.948 with exclusion of single RCT results. A funnel plot (data not shown) for publication bias showed no indication of substantial bias and Egger's test for zero intercept showed a non-significant P value of .197.

A secondary analysis was completed that included results from 6 RCTs excluded from the primary analysis[23–28]; 3 because food vehicles were used for LC-OM3 delivery[23–25] and 3 conducted in subjects with implantable cardiac defibrillator devices.[26–28] The fixed effects meta-analysis model for all 20 trials with 83,031 subjects showed a pooled RR of 0.929, 95% CI 0.876, 0.984; P = .013 (Table 2). The I^2 value was 35.3% with Q = 29.3, P = .061.

Table 2 also shows results for secondary and subset analyses of the primary dataset of 14 RCTs. As expected because of low heterogeneity, a fixed-effects model for the full set of 14 trials produced similar results to that of the random-effects model, showing an 8.0% lower incidence of cardiac death (P = .011). Subset analyses of trials that provided >1 g/d of EPA + DHA,[10–12,15,16,18,20] had higher mean or median levels of TG (≥150 mg/dL)[10,11,14,16,18,20–22] or LDL-C (≥130 mg/dL),[10–12,14,16,18,20,21] used LC-OM3 for secondary prevention,[11–13,15–18,20–22] and for which <40% of the study sample used statin therapy at baseline[10–12,15–18,21,22] showed numerically larger effects associated with LC-OM3 use compared with the full analysis set. Effects ranged from 12.9% to 29.1% lower incidence in the LC-OM3 arms vs control, and P values ranged from .043 to <.001. Heterogeneity was low (≤15.5%) for all these models, and all the Q-statistics were associated with P values >.31.

Discussion

The results from this meta-analysis are supportive of the recent Science Advisory from the American Heart Association that concluded LC-OM3 "treatment is reasonable" for (1) secondary prevention of CHD and sudden cardiac death among patients with prevalent CHD; and (2) secondary prevention of adverse outcomes in patients with heart failure.[29] In the present analysis, the pooled RR from 14 RCTs was 0.920 (95% CI 0.861, 0.984; P = .015) with low heterogeneity (I^2 = 1.8%) in the primary random effects model. A secondary analysis that included an additional 6 RCTs showed results that were not materially

Table 1 Random effects meta-analysis model of 14 trials assessing the outcome of cardiac death for LC-OM3 interventions

	LC-OM3		Control						
Study*	Events	Total	Events	Total	Total subjects	Relative risk	95% CI	*P* value	Weight, %
Sacks, 1995	0	31	1	28	59	0.302	0.013–7.127	.458	0.04
Singh, 1997	14	122	26	118	240	0.521	0.286–0.947	.033	1.24
Leng, 1998	2	60	2	60	120	1.000	0.146–6.869	1.000	0.12
GISSI, 1999	228	5666	292	5658	11,324	0.780	0.658–0.924	.004	14.91
CART, 1999	1	196	3	192	388	0.327	0.034–3.112	.331	0.09
Von Schacky, 1999	0	112	1	111	223	0.330	0.014–8.024	.496	0.04
Nilsen, 2001	8	150	8	150	300	1.000	0.385–2.595	1.000	0.49
JELIS, 2007	29	9326	31	9319	18,645	0.935	0.564–1.550	.794	1.74
GISSI-HF, 2008	613	3494	661	3481	6975	0.924	0.837–1.020	.119	39.81
OMEGA, 2010	28	1925	29	1893	3818	0.949	0.567–1.590	.844	1.68
DOIT, 2010	3	282	7	281	563	0.427	0.112–1.635	.214	0.25
ORIGIN, 2012	574	6281	581	6255	12,536	0.984	0.881–1.098	.772	33.29
Risk & Prev, 2013	101	6239	95	6266	12,505	1.068	0.809–1.410	.644	5.69
AREDS2, 2014	12	2147	9	2056	4203	1.392	0.539–3.024	.579	0.60
Pooled	1613	36,031	1746	35,868	71,899	0.920	0.861–0.984	.015	100.0

AREDS2, Age-Related Eye Disease Study 2; CART, Coronary Angioplasty Restenosis Trial; DOIT, Diet and Omega-3 Intervention Trial; GISSI, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico; GISSI-HF, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Heart Failure; JELIS, Japan EPA Lipid Intervention Study; ORIGIN, Outcome Reduction with an Initial Glargine Intervention; Risk & Prev., Risk and Prevention Trial.

Heterogeneity: Q = 13.2, P = .430, I^2 = 1.8%.

*Study references are as follows: Sacks, 1995[15]; Singh, 1997[16]; Leng, 1998[22]; GISSI, 1999[21]; CART, 1999[11]; Von Schacky, 1999[18]; Nilsen, 2001[12]; JELIS, 2007[20]; GISSI-HF, 2008[17]; OMEGA, 2010[13]; DOIT, 2010[10]; ORIGIN, 2012[9]; Risk & Prev., 2013[14]; AREDS, 2014.[19]

different: pooled RR 0.929 (95% CI 0.876, 0.984; P = .013), with somewhat greater heterogeneity (I^2 = 35.3%, P = .061). One notable feature of LC-OM3 supplementation is the low risk associated with its use.[30–32] Because of the low risk for adverse effects, even a modest benefit is clinically meaningful.

Larger effects (all $P < .05$) were observed in subsets of the primary analysis set for RCTs that used >1 g/d of EPA + DHA (RR = 0.709), had mean or median TG ≥ 150 mg/dL (RR = 0.826) or LDL-C ≥130 mg/dL (RR = 0.828), studied a secondary prevention sample (RR = 0.870), and in which baseline statin use was <40% (RR = 0.871). These results are consistent with the hypothesis that supplemental LC-OM3 may be most efficacious for reducing cardiac death in higher risk individuals.

The present findings are concordant with those of Alexander et al.,[1] who found that coronary death was significantly lower in a pooled analysis of 4 secondary prevention RCTs of LC-OM3 (RR = 0.80, 95% CI 0.64, 0.99). The present results do not agree with the conclusions from the 2016 AHRQ systematic review.[33] However, in that report, only the largest studies were evaluated, and exclusion of smaller studies may have materially affected the findings. Specifically, the AHRQ review identified an outcome of cardiac death for only 4 RCTs[26,28,34,35] and did not report a pooled estimate and stated that the RCTs of EPA + DHA showed "inconsistent effects" on cardiac death, with effect sizes ranging from 0.45 to 1.45.

Alexander et al.[1] also analyzed results from prospective cohort studies and reported significantly lower risks for coronary death (9 studies, RR = 0.82, 95% CI 0.69, 0.98) and sudden cardiac death (5 studies, RR = 0.53, 95% CI 0.41, 0.67). In general, results from observational cohort studies have suggested that higher LC-OM3 intake is associated with lower risks for fatal and non-fatal CHD events. For example, Alexander et al.[1] showed pooled RR estimates of 0.77 and 0.81 (both $P < .05$), respectively, for these outcomes. However, their meta-analysis of RCTs, as well as those completed by Rizos et al.[2] and the AHRQ[33] showed small, non-significant reductions in risk for non-fatal CHD events and/or MI.

Thus, for cardiac death, the aggregate RCT and observational evidence has been fairly consistent in showing benefits of higher LC-OM3 intake, particularly in higher risk subsets. However, the prospective cohort and RCT results have been discordant for the effects of LC-OM3 intake on non-fatal CHD events. These observations suggest several testable hypotheses that warrant exploration.

A possible explanation for the mixed results in RCTs regarding both fatal and non-fatal CHD events relates to dosage. In the present meta-analysis, the reduction in risk for cardiac death was numerically larger in studies that used an EPA + DHA dosage >1 g/d (RR = 0.709) compared with that in the overall primary study sample (RR = 0.920 for both the random and fixed effects models). One large RCT completed in Japan, the JELIS trial,[20] showed a statistically significant 19% reduction in major coronary event risk with

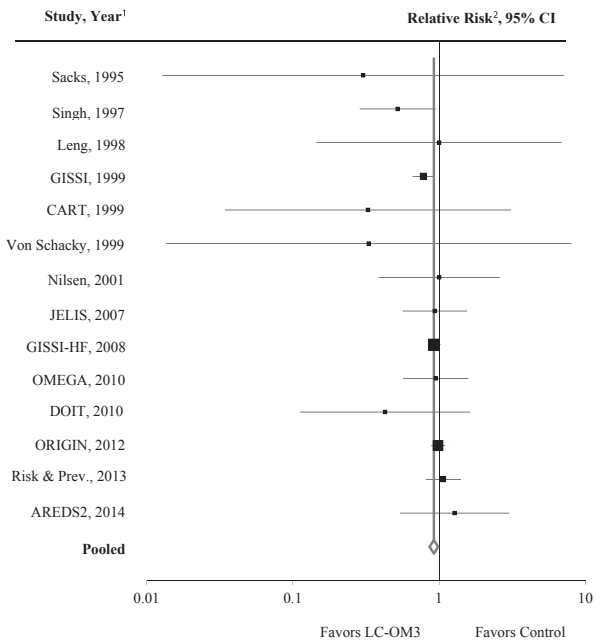

Figure 2 Forest plot of cardiac death events with LC-OM3 vs control interventions. [1]Study references are as follows: Sacks, 1995[15]; Singh, 1997[16]; Leng, 1998[22]; GISSI, 1999[21]; CART, 1999[11]; Von Schacky, 1999[18]; Nilsen, 2001[12]; JELIS, 2007[20]; GISSI-HF, 2008[17]; OMEGA, 2010[13]; DOIT, 2010[10]; ORIGIN, 2012[9]; Risk & Prev., 2013[14]; AREDS, 2014.[19] [2]Relative risks and related assessments can be found in Table 1. AREDS2, Age-Related Eye Disease Study 2; CART, Coronary Angioplasty Restenosis Trial; CI, confidence interval; DOIT, Diet and Omega-3 Intervention Trial; GISSI, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico; GISSI-HF, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Heart Failure; JELIS, Japan EPA Lipid Intervention Study; LC-OM3, long-chain omega-3 polyunsaturated fatty acids; ORIGIN, Outcome Reduction with an Initial Glargine Intervention; Risk & Prev., Risk and Prevention Trial.

an intervention of 1.8 g/d of EPA ethyl esters, but no significant reduction in cardiac death. A *post hoc* analysis of the relationship of blood EPA level with the treatment effect for the primary composite outcome showed that the benefit was mainly attributable to the subset of those in the active treatment group who had plasma EPA levels ≥150 mcg/L (approximately the top quartile).[36] Dietary intake of LC-OM3 in Japan is higher than that in the United States and most European countries[37] and the subset of JELIS participants with the highest plasma EPA levels may have been those who consumed the EPA ethyl esters and also had a high background intake of foods containing LC-OM3.

Mozaffarian et al. (2013) found a dose–response relationship between level of plasma phospholipid total LC-OM3 quintile and CHD mortality in the Cardiovascular Health Study (P for trend = .002).[38] Recently, the Omega-3 Acid Ethyl Esters on Left Ventricular Remodeling After Acute Myocardial Infarction investigators showed that 4 g/d of LC-OM3 ethyl esters, compared with a corn oil placebo, significantly improved measures of cardiac structure (fibrosis) and function (left ventricular end systolic volume index) when administered for 6 months after a MI.[35] The magnitudes of the benefit for left ventricular end systolic index rose with increasing quartiles of erythrocyte omega-3 level (P for trend < .0001). Taken together, the findings from those studies, as well as those of the current meta-analysis and that of Alexander et al. (2017),[1] are consistent with the hypothesis that higher intakes of LC-OM3 (>1 g/d of EPA + DHA) may be required to observe some of the physiological effects that could contribute to lower risks for both fatal and non-fatal CHD events.

Only 28% of the subjects included in the primary meta-analysis dataset participated in RCTs in which the dosage was >1 g/d of EPA + DHA. Furthermore, most of the RCTs assessing cardiovascular outcomes provided no data on baseline and on-treatment biomarkers of LC-OM3 status; thus, it is not possible to evaluate relationships between baseline, or on-treatment LC-OM3 status (reflecting tissue levels), and event risk. Accordingly, additional research is needed to assess larger dosages of LC-OM3 on risks for cardiac death and non-fatal cardiac events, with inclusion of biomarker analyses (eg, total plasma, erythrocyte, phospholipid, or cholesterol ester LC-OM3 levels) to define both baseline status and change in status during treatment.[39–43]

There are several pathways through which higher LC-OM3 intake could potentially alter risk for fatal and non-fatal cardiac events, including anti-arrhythmic effects (particularly arrhythmias triggered by myocardial ischemia), effects related to cardiac structure and function (eg, fibrosis, myocardial oxygen demand), endothelial and autonomic function (eg, vascular resistance and heart rate), thrombosis, blood pressure, inflammation/resolution, and lipoprotein metabolism.[44] The mechanisms through which LC-OM3 intake might alter CVD risk have been reviewed elsewhere in detail.[44] The dose–response characteristics for most of these effects have not been fully described. Also, the RCTs completed to date have generally not been designed to test specific mechanistic hypotheses. It is possible that dosages >1 g/d of EPA + DHA are required to produce clinically relevant changes in some of the pathways, such as effects on inflammation and thrombosis.[45–47] Conversely, some of the benefits associated with higher LC-OM3 intake may be produced mainly in those with low LC-OM3 intake or status, with little or no benefit observed in those with higher baseline intake or status. Such a ceiling effect has been proposed by Mozaffarian et al.[44,48] regarding effects of LC-OM3 intake on heart rate and susceptibility to ventricular arrhythmia.

One well-documented effect of LC-OM3 is to lower the circulating TG concentration, although dosages >1.5 g/d of EPA + DHA are generally required to produce a clinically meaningful change.[49] A recently published meta-analysis of the effects of TG-lowering drug therapies (fibrates, niacin, EPA ethyl esters) on cardiac or CVD event risk showed that the overall benefit in 10 studies was relatively small (12% reduction), but was larger (18% reduction) in

Table 2 Secondary and subset fixed effects meta-analysis models of trials assessing the outcome of cardiac death for long-chain omega-3 fatty acid interventions

Studies*,†,‡,§,¶,‖,#	RCTs	N	RR	95% CI	*P* Value	I^2, %
Primary analysis RCTs	14	71,899	0.920	0.863–0.981	.011	1.8
Secondary analysis RCTs	20	83,031	0.929	0.876–0.984	.013	35.3
Primary analysis subsets						
>1 g/d EPA + DHA	7	20,418	0.709	0.508–0.990	.043	0.0
TG ≥ 150 mg/dL	8	44,008	0.826	0.723–0.944	.005	14.3
LDL-C ≥130 mg/dL	8	44,188	0.828	0.725–0.946	.005	15.5
Secondary prevention	10	27,111	0.870	0.801–0.945	<.001	0.0
Statin use <40%	9	20,192	0.871	0.801–0.948	.001	6.2

CI, confidence interval; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; LDL-C, low-density lipoprotein cholesterol; RCTs, randomized, controlled trials; RR, relative risk (pooled).

*For TG and LDL-C, studies with mean or median values above the identified threshold were included in this subset.

†Secondary prevention studies are those in which the subjects had clinical evidence of atherosclerotic cardiovascular disease.

‡It should be noted that statin use increased with time, so the study samples with statin use <40% were older trials, and trials in which use of other cardioprotective agents (particularly renin-angiotensin-aldosterone system antagonists) was also less prevalent in the study samples.

§The *P* value for heterogeneity based on the Q-statistic was >.05 for each model.

¶Subset analyses were conducted among the 14 trials included in the primary analysis for the following criteria: >1 g/d of EPA + DHA, TG ≥ 150 mg/dL, LDL-C ≥130 mg/dL, trials where LC-OM3 was used for secondary prevention and baseline statin use <40% of the study sample.

‖Varying doses were provided in the Von Schackey et al. (1999) study,[18] so the weighted average was used in these analyses, which resulted in the study's inclusion in the >1 g/d of EPA + DHA subset analysis.

#Study references are as follows: DART, 1989[23]; Sacks, 1995[15]; Singh, 1997[16]; Leng, 1998[22]; GISSI, 1999[21]; CART, 1999[11]; Von Schacky, 1999[18]; Nilsen, 2001[12]; DART2, 2003[24]; Leaf, 2005[26]; Raitt, 2005[27]; SOFA, 2006[28]; JELIS, 2007[20]; GISSI-HF, 2008[17]; OMEGA, 2010[13]; DOIT, 2010[10]; Alpha Omega, 2010[25]; ORIGIN, 2012[9]; Risk & Prev., 2013[14]; AREDS, 2014.[19]

subsets with elevated TGs (≥150 mg/dL), especially if accompanied by low high-density lipoprotein cholesterol (HDL-C; 29% reduction).[50] Two ongoing RCTs are investigating the effects of higher dosage LC-OM3 pharmaceutical products (4 g/d LC-OM3, primarily EPA + DHA ethyl esters or carboxylic acids) on major adverse cardiovascular event rates in high-risk subjects with elevated TGs.[51,52]

The results of the present meta-analysis provide some reason for optimism because the studies in which subjects had higher baseline TG or LDL-C concentrations showed numerically larger benefits on the incidence of cardiac death than those of the overall primary analysis. In addition to lowering TGs, higher dosages of LC-OM3 have been shown to increase HDL and LDL particle sizes[53] although EPA and DHA show some differences regarding their effects on lipoprotein lipid levels.[54] EPA and DHA each lower TGs.[54,55] DHA tends to raise both LDL-C and HDL-C, whereas EPA does neither.[54,55] The clinical relevance of these differences in effects on lipoprotein lipids is uncertain at present.

In the current meta-analysis, the studies in which statin use was low (<40% of participants at baseline) showed a numerically larger benefit than that in the primary analysis. More recently conducted RCTs have had higher prevalence values for use of statins, as well as other cardioprotective agents such as aspirin and other anti-platelet drugs, beta-adrenergic antagonists, and renin-angiotensin-aldosterone system antagonists, reflecting changes in standards of care. Because of overlap in the mechanisms of action of some of these agents and pathways affected by LC-OM3,[56,57] it may be difficult to demonstrate a benefit of LC-OM3 supplementation, especially at a low dosage, when it is added to other therapies with established cardioprotective properties.

The results from both the present meta-analysis, and that of Alexander et al.,[1] suggest that higher risk groups may be more likely to experience reductions in risk for cardiac death with LC-OM3 supplementation, particularly when provided at a higher dosage. VITAL, the Vitamin D and Omega-3 Trial, has 25,874 men and women enrolled and is assessing the effects of 1 g/d LC-OM3 ethyl esters, as well as supplemental vitamin D (2000 IU/d), compared with placebo, using a 2 × 2 factorial design.[58] ASCEND, A Study of Cardiovascular Events iN Diabetes, is another trial assessing the effects of 1 g/d LC-OM3 ethyl esters, with or without aspirin, compared with placebo, using a 2 × 2 factorial design; the trial has randomized 15,480 men and women with diabetes.[59] Based on the current evidence base, there is reason for concern that VITAL and ASCEND may not show benefits because the LC-OM3 dosage is relatively low[53] and subjects in VITAL are at low average risk.

A limitation of the results from the present meta-analysis is that several of the studies included were small or had suboptimal trial designs. For example, 2 of the largest trials, GISSI-Prevenzione and JELIS, were not placebo controlled. Although this does raise the possibility of bias in ascertainment of event status, this is likely to be less of a concern with the outcome of cardiac death than with non-fatal events. Also, sensitivity analyses and results

from observational studies are generally aligned for cardiac death and suggest lower risk associated with higher LC-OM3 intake.

Summary and conclusions

The present meta-analysis of RCTs showed a modest, but statistically significant, benefit of LC-OM3 supplementation on risk for cardiac death (8.0% in the primary analysis). This finding supports the recent Science Advisory from the American Heart Association that concluded LC-OM3 "treatment is reasonable" for (1) secondary prevention of CHD and sudden cardiac death among patients with prevalent CHD; and (2) secondary prevention of adverse outcomes in patients with heart failure.[29] Because of the low risk for adverse effects with LC-OM3 supplementation, even a modest benefit is clinically meaningful.[33]

Subgroup analyses show numerically larger benefits (12.9%–29.1%, all $P < .05$) in studies that used >1 g/d of EPA + DHA, and in higher risk groups, including those with greater mean or median levels of TGs (≥150 mg/dL) or LDL-C (≥130 mg/dL), secondary prevention study samples, and studies with lower baseline use of statins (which is also a proxy for use of other cardioprotective agents). These results suggest that additional research is warranted to further evaluate the potential risk reduction with LC-OM3 supplementation at higher dosages and in higher risk samples. Future RCTs should include evaluation of biomarkers of omega-3 status at baseline and during treatment and should be designed to test specific hypotheses about the mechanisms through which benefits might be produced. Four RCTs evaluating CVD event risk with LC-OM3 interventions are ongoing and should provide helpful additional information to guide clinical use of LC-OM3 supplementation or drug therapy.

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Appendix

Supplementary Table 1 Summary of the 14 trials included in the primary meta-analysis for assessing the effect LC-OM3 supplementary intake on cardiac death

Author, y*	Country	Study Name	Duration (y)	Total Subjects	Agent	Dosage (g/d)	EPA + DHA (g/d)†	Control
Sacks et al., 1995	USA	–	2.3	59	Fish oil	6	4.80	Olive oil
Singh et al., 1997	India	IEIS-4	1.0	240	Fish oil	6	1.80	Aluminum hydroxide
Leng et al., 1998	UK	–	2.0	120	Ethyl esters	6	0.27	Sunflower oil
Marchioli et al., 1999	Italy	GISSI	3.5	11,324	Ethyl esters	1	0.85	No supplement
Johansen et al., 1999	Norway	CART	0.5	388	Ethyl esters	6	5.04	Corn oil
Von Schacky et al., 1999	Germany	SICMO	2.0	223	Fish oil	6, 3	1.06	Fatty acid mixture
Nilsen et al., 2001	Norway	–	1.5	300	Ethyl ester	4	3.46	Corn oil
Yokoyama et al., 2007	Japan	JELIS	4.6	18,645	Ethyl esters	1.84	1.80	No supplement
Tavazzi et al., 2008	Italy	GISSI-HF	3.9	6975	Ethyl esters	1	0.85	Placebo capsule
Rauch et al., 2010	Germany	OMEGA	1.0	3818	Ethyl esters	1	0.84	Olive oil
Einvik et al., 2010	Norway	DOIT	3.0	563	Fish oil	4	2.02	Corn oil
Bosch et al., 2012	Multi-country	ORIGIN	6.2	12,536	Ethyl esters	1	0.84	Olive oil
Roncaglioni et al., 2013	Italy	Risk & Prev.	5.0	12,505	Ethyl esters	1	0.85	Olive oil
Bonds et al., 2014	USA	AREDS2	4.8	4203	Ethyl esters	1	1.00	Unspecified placebo ± lutein, zeaxanthin

AREDS2, Age-Related Eye Disease Study 2; CART, Coronary Angioplasty Restenosis Trial; DOIT, Diet and Omega-3 Intervention Trial; GISSI, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico; GISSI-HF, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Heart Failure; IEIS-4, Indian Experiment of Infarct Survival; JELIS, Japan EPA Lipid Intervention Study; ORIGIN, Outcome Reduction with an Initial Glargine Intervention; Risk & Prev., Risk and Prevention Trial; SICMO, Study on Prevention of Coronary Atherosclerosis by Intervention with Marine Omega-3 fatty acids.

*Study references are as follows: Sacks, 1995[15]; Singh, 1997[16] Leng, 1998[22]; GISSI, 1999[21]; CART, 1999[11]; Von Schacky, 1999[18]; Nilsen, 2001[12]; JELIS, 2007[20]; GISSI-HF, 2008[17]; OMEGA, 2010[13]; DOIT, 2010[10]; ORIGIN, 2012[9]; Risk & Prev., 2013[14]; AREDS, 2014.[19]

†Varying doses were provided in the Von Schackey et al. (1999) study,[18] so the weighted average was used in these analyses.

Supplementary Table 2 Summary of the population groups used in the 14 trials included in the primary meta-analysis for assessing the effect LC-OM3 supplementary intake on cardiac death

Author, y*,†	Study name	Population group risk criteria	Prevention
Sacks et al., 1995	–	CHD	Secondary
Singh et al., 1997	IEIS-4	Recent acute (≤18 h) MI	Secondary
Leng et al., 1998	–	Intermittent claudication	Secondary
Marchioli et al., 1999	GISSI	Recent (≤3 mo) MI	Secondary
Johansen et al., 1999	CART	Coronary angioplasty	Secondary
Von Schacky et al., 1999	SICMO	Angiographically proven CAD	Secondary
Nilsen et al., 2001	–	Recent (≤3 mo) MI	Secondary
Yokoyama et al., 2007	JELIS	Hypercholesterolemia	Mixed/secondary
Tavazzi et al., 2008	GISSI-HF	Recent (≤3 mo) HF	Secondary
Rauch et al., 2010	OMEGA	Recent (3–14 d prior) MI	Secondary
Einvik et al., 2010	DOIT	Hypercholesterolemia	Mixed
Bosch et al., 2012	ORIGIN	Impaired glucose or T2DM	Mixed
Roncaglioni et al., 2013	Risk & Prev.	CV risk factors or ASCVD	Mixed
Bonds et al., 2014	AREDS2	Age-related macular degeneration	Mixed

AREDS2, Age-Related Eye Disease Study 2; ASCVD, atherosclerotic vascular disease; CAD, coronary artery disease; CART, Coronary Angioplasty Restenosis Trial; CHD, coronary heart disease; CV, cardiovascular; DOIT, Diet and Omega-3 Intervention Trial; GISSI, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico; GISSI-HF, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Heart Failure; HF, heart failure; IEIS-4, Indian Experiment of Infarct Survival; JELIS, Japan EPA Lipid Intervention Study; ORIGIN, Outcome Reduction with an Initial Glargine Intervention; MI, myocardial infarction; Risk & Prev., Risk and Prevention Trial; SICMO, Study on Prevention of Coronary Atherosclerosis by Intervention with Marine Omega-3 fatty acids; T2DM, type II diabetes mellitus.

†Varying doses were provided in the Von Schackey et al. (1999) study,[18] so the weighted average was used in these analyses.

*Study references are as follows: Sacks, 1995[15]; Singh, 1997[16] Leng, 1998[22]; GISSI, 1999[21]; CART, 1999[11]; Von Schacky, 1999[18]; Nilsen, 2001[12]; JELIS, 2007[20]; GISSI-HF, 2008[17]; OMEGA, 2010[13]; DOIT, 2010[10]; ORIGIN, 2012[9]; Risk & Prev., 2013[14]; AREDS, 2014.[19]