REVIEW ARTICLE

Efficacy of Omega-3 Fatty Acid Supplements (Eicosapentaenoic Acid and Docosahexaenoic Acid) in the Secondary Prevention of Cardiovascular Disease

A Meta-analysis of Randomized, Double-blind, Placebo-Controlled Trials

Sang Mi Kwak, MD; Seung-Kwon Myung, MD; Young Jae Lee, MD, MS; Hong Gwan Seo, MD, PhD; for the Korean Meta-analysis Study Group

Background: Although previous randomized, double-blind, placebo-controlled trials reported the efficacy of omega-3 fatty acid supplements in the secondary prevention of cardiovascular disease (CVD), the evidence remains inconclusive. Using a meta-analysis, we investigated the efficacy of eicosapentaenoic acid and docosahexaenoic acid in the secondary prevention of CVD.

Methods: We searched PubMed, EMBASE, and the Cochrane Library in April 2011. Two of us independently reviewed and selected eligible randomized controlled trials.

Results: Of 1007 articles retrieved, 14 randomized, double-blind, placebo-controlled trials (involving 20 485 patients with a history of CVD) were included in the final analyses. Supplementation with omega-3 fatty acids did not reduce the risk of overall cardiovascular events (relative risk, 0.99; 95% CI, 0.89-1.09), all-cause mortality, sudden cardiac death, myocardial infarction, congestive heart failure, or transient ischemic attack and stroke. There was a small reduction in cardiovascular death (relative risk, 0.91; 95% CI, 0.84-0.99), which disappeared when we excluded a study with major methodological problems. Furthermore, no significant preventive effect was observed in subgroup analyses by the following: country location, inland or coastal geographic area, history of CVD, concomitant medication use, type of placebo material in the trial, methodological quality of the trial, duration of treatment, dosage of eicosapentaenoic acid or docosahexaenoic acid, or use of fish oil supplementation only as treatment.

Conclusion: Our meta-analysis showed insufficient evidence of a secondary preventive effect of omega-3 fatty acid supplements against overall cardiovascular events among patients with a history of cardiovascular disease.

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Author Affiliations: Center for Cancer Prevention and Detection (Drs Kwak, Myung, and Seo) and Cancer Epidemiology Branch, Research Institute (Dr Myung), National Cancer Center, Ilsan, Department of Family Medicine, School of Medicine, Seoul National University, Seoul (Dr Myung), and Anesthesiology and Pain Medicine, Armed Forces Capital Hospital, Seongnam (Dr Lee), Republic of Korea.
Group Information: The Korean Meta-analysis Study Group members are listed on page 693.

In the 1970s, Bang et al,[1] Bang and Dyerberg,[2] and Dyerberg et al[3] suggested that consumption of a large amount of fish or marine mammals rich in omega-3 fatty acids contributes to a low incidence of cardiovascular disease (CVD) among the Greenland Eskimos. Based on results of animal investigations, epidemiological studies, and randomized trials, numerous researchers reported cardiovascular effects of 2 major long-chain omega-3 polyunsaturated fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The evidence from those studies[4-8] indicates that omega-3 fatty acids have anti-inflammatory, antiatherogenic, and antiarrhythmic effects, which are considered plausible mechanisms for reducing the risk of CVD.

See Invited Commentary at end of article

Previous investigators reported inconsistent findings in animal studies of atherosclerosis. Some studies[9-11] found that fish oil reduced atherogenesis, while other researchers reported no effect[12,13] or negative effects.[14,15] The authors of a systematic review[16] and a meta-analysis[17] of observational investigations among case-control studies and cohort studies reported that fish or fish oil consumption has a protective effect against CVD.

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Meanwhile, the evidence from randomized, double-blind, placebo-controlled trials,[18-34] most of which involved patients with existing CVD, remains controversial. Two large randomized trials[18,19] demonstrated that supplementation with EPA plus DHA or with EPA alone significantly reduced the risk of cardiovascular events; however, these trials were of open-label design using a nonplacebo control group. Some randomized, double-blind, placebo-controlled trials[21,23,26,28-31] demonstrated a significant preventive effect of omega-3 fatty acid supplements against CVD, while other randomized, double-blind, placebo-controlled trials[20,22,24,25,27,32-34] showed no preventive effect.

Results of several systematic reviews and meta-analyses of randomized controlled trials on this issue have been reported. In 2002, a meta-analysis[35] of 11 randomized controlled trials indicated that dietary and nondietary intake of omega-3 fatty acids reduced mortality from myocardial infarction in patients with coronary heart disease. Conversely, a 2006 systematic review[36] of 48 randomized controlled trials found that long-chain and short-chain omega-3 fatty acids have no clear effect on CVDs. In 2009, the authors of a meta-analysis[37] of 11 randomized controlled trials reported that dietary supplementation with omega-3 fatty acids significantly reduced the risk of cardiovascular death, all-cause mortality, and nonfatal cardiovascular events. However, those meta-analyses[35-37] included randomized trials with a control group that did not use placebo. Most important, although several additional large randomized controlled trials[30-33] have been published since 2009, no meta-analysis of those trials has been reported to date. The objective of the present study was to investigate the preventive effect of omega-3 fatty acid supplements (EPA and DHA) against CVD among patients with existing CVD (defined in this study as secondary prevention) using a meta-analysis of randomized, double-blind, placebo-controlled trials. Ethical approval was not required for the meta-analysis.

METHODS

LITERATURE SEARCH

We searched PubMed (January 1, 1976, through April 30, 2011), EMBASE (January 1, 1985, through April 30, 2011), and the Cochrane Library (January 1, 1987, through April 30, 2011) using common keywords related to omega-3 fatty acids and CVD. The keywords included the following: *omega-3 fatty acid*, *eicosapentaenoic acid* or *EPA*, *docosahexaenoic acid* or *DHA*, *cardiovascular disease*, *angina*, *myocardial infarction*, and *sudden cardiac death*. We reviewed the bibliographies of relevant articles for additional publications. The language of publication was restricted to English.

SELECTION CRITERIA

We included trials that met the following 4 criteria: (1) the trial studied adult patients (male or female aged ≥18 years) with a history of CVD; (2) the patients had used omega-3 fatty acid supplements for at least 1 year; (3) the design was a randomized, double-blind, placebo-controlled trial; and (4) the trial reported outcome measures like angina, unstable angina, CVD or events, sudden cardiac death, cardiovascular death, all-cause mortality, congestive heart failure, transient ischemic attack and stroke, or fatal or nonfatal myocardial infarction.

Two of us (S.M.K. and S.-K.M.) independently evaluated the eligibility of all studies retrieved from the databases according to the selection criteria. Disagreements between evaluators were resolved by discussion or in consultation with another of us (Y.J.L.). If data were duplicated or shared in more than 1 study, the first published or larger study was included in the analysis.

ASSESSMENT OF METHODOLOGICAL QUALITY

We assessed the methodological quality of the included studies using the scale by Jadad et al,[38] which is the most widely used assessment tool in meta-analyses. Scores range from zero (very poor) to 5 points (rigorous). The scale measures the following characteristics of randomized controlled trials: randomization (1 point if the trial is randomized and an additional point if a table of random numbers or computer-generated randomization is used), double-blind design (1 point if it is a double-blind trial and an additional point if masking, such as identical placebo, is used), and follow-up reporting (1 point if the trial states the numbers and reasons for withdrawal in each study group). We classified the trials as those with a score of 4 or less vs 5 because the mean score on the scale by Jadad et al[38] among all 14 trials was 4.4 points. We then performed subgroup analyses.

MAIN AND SUBGROUP ANALYSES

The main analysis was the association between omega-3 fatty acid supplementation and overall cardiovascular events. Overall cardiovascular events included the following: angina, sudden cardiac death, cardiovascular death, congestive heart failure, peripheral vascular disease, transient ischemic attack and stroke, fatal and nonfatal myocardial infarction, and nonscheduled cardiovascular interventions (ie, coronary artery bypass surgery or angioplasty).

We performed the following subgroup analyses: history of CVD, geographic area (inland vs coastal), duration of treatment (<2 vs ≥2 years), dosage of EPA or DHA (<1.7 vs ≥1.7 g/d), use of fish oil supplementation only as treatment, type of placebo material in the trial (oil vs nonoil), methodological quality of the trial (≤4 vs 5 points), country (United States, Asia, Western Europe, or Northern Europe), and concomitant medication use (lipid-lowering agents, no lipid-lowering agents, or use of antiplatelet agents only).

STATISTICAL ANALYSIS

We performed statistical analyses with 2×2 tables on the basis of an intent-to-treat analysis. To estimate heterogeneity, we used I^2, which measures the percentage of total variation across trials.[39] I^2 was calculated as follows: $100.0\% \times (Q-df)/Q$, where Q is Cochran heterogeneity statistic. Negative I^2 values are defined as zero so that I^2 ranges between 0.0% (no observed heterogeneity) and 100.0% (maximal heterogeneity). An I^2 value exceeding 50.0% was considered indicative of substantial heterogeneity.

We pooled relative risk (RR) (95% CI) using random-effects model. We assessed publication bias using Begg funnel plot and Egger test. If publication bias exists, Begg funnel plot is asymmetric or Egger test $P<.05$. We used commercially available software (STATA SE, version 10.0; StataCorp LP) for all statistical analyses.

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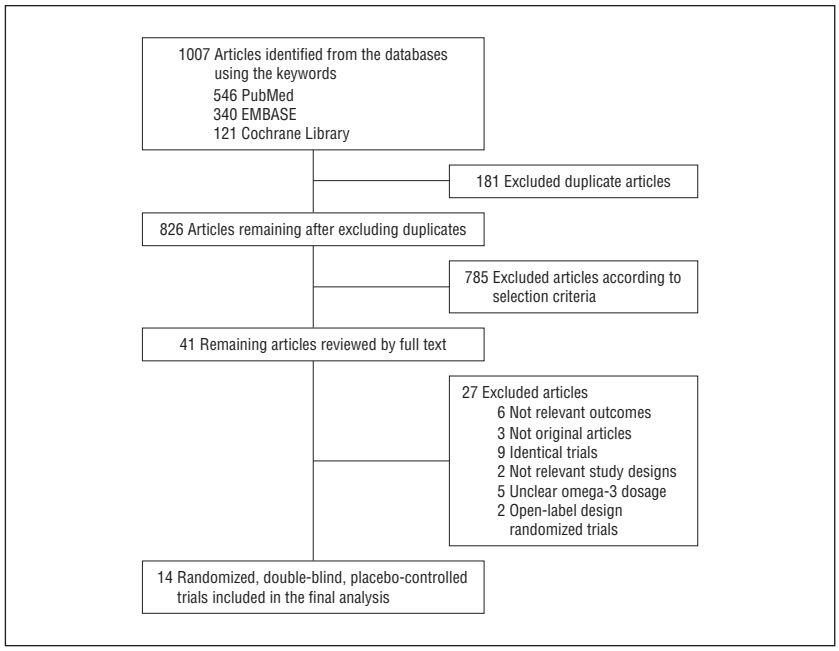

Figure 1. Identification of relevant randomized, double-blind, placebo-controlled trials.

RESULTS

Figure 1 shows how we identified relevant randomized, double-blind, placebo-controlled trials. A total of 1007 articles were retrieved by searching 3 databases and by reviewing relevant bibliographies. We excluded 181 duplicate articles and an additional 785 articles that did not fulfill the selection criteria. After reviewing the full text of the remaining 41 articles, 27 articles were excluded because of several reasons, as shown in the figure. We included 14 randomized, double-blind, placebo-controlled trials[20-33] in the final analyses.

Among 14 randomized, double-blind, placebo-controlled trials, we identified 20 485 patients with a history of CVD, 10 226 randomized to an intervention group and 10 259 randomized to a placebo group. Among the trials in which patient age and sex were reported, the mean age of participants was 63.4 years (age range, 40-80 years), and 78.5% of participants were male. **Table 1** summarizes general characteristics of 14 randomized, double-blind, placebo-controlled trials in the final analyses. The included trials were reported from June 1995 through November 29, 2010. Among the trials, the daily dose of EPA or DHA ranged from 0.4 to 4.8 g/d (mean [SD], 1.7 [1.2] g/d), and the follow-up period ranged from 1.0 to 4.7 years (mean [SD], 2.0 [1.2] years). The trials investigated the secondary preventive effect of omega-3 fatty acid supplements against CVD in patients with stable coronary heart disease (2 trials[20,23]), after myocardial infarction (4 trials[21,24,32,33]), with implanted cardioverter defibrillator (3 trials[25-27]), with congestive heart failure (1 trial[29]), and with other CVDs (4 trials[22,28,30,31]). Placebo groups received vegetable oils (olive oil,[20,25,26,28,33] sunflower oil,[22,27] and corn oil[24]), mixed fatty oil,[23,32] and other "inert" or ill-defined substances (aluminum hydroxide[21] and unspecified placebo[29-31]).

Among the trials, the mean score on the scale by Jadad et al[38] was 4.4 points (**Table 2**): scores were 5 points for 6 trials,[23,25,26,28,29,31] 4 points for 7 trials[20-22,27,30,32,33] that used inappropriate randomization methods, and 3 points for 1 trial[24] that did not describe the loss to follow-up. Publication bias was not observed in the trials (ie, Begg funnel plot is symmetric and Egger test $P = .53$) (**Figure 2**).

As shown in **Figure 3**, omega-3 fatty acid supplementation did not reduce the risk of overall cardiovascular events (RR, 0.99; 95% CI, 0.89-1.09; $I^2 = 27.1\%$). No statistically significant effect of omega-3 fatty acid supplementation was observed for most other outcome measures, including the following: all-cause mortality, sudden cardiac death, myocardial infarction, fatal myocardial infarction, nonfatal myocardial infarction, angina and unstable angina, congestive heart failure, and transient ischemic attack and stroke (**Table 3**).

However, omega-3 fatty acid supplementation significantly reduced cardiovascular death (RR, 0.91; 95% CI, 0.84-0.99). When we excluded the trial by Singh et al,[21] in which there was a significant difference in the proportions with a history of angina between the fish oil intervention group vs the placebo group (14.7% vs 25.4% [$P < .05$]), no preventive effect was found for cardiovascular death (RR, 0.92; 95% CI, 0.35-1.01). Among the trials, there was no significant difference in the occurrence of adverse events, such as gastrointestinal troubles or gastrointestinal bleeding, between the intervention and placebo groups.

Table 4 summarizes results of the subgroup analyses. There was no significant preventive effect of omega-3 fatty acid supplements against overall cardiovascular events, as measured by the following: duration of treatment (<2 vs ≥2 years), dosage of EPA or DHA (<1.7 vs ≥1.7 g/d), methodological quality of the trial (≤4 vs 5 points), use of fish oil supplementation only as treatment, country location (United States, Asia, Western Europe, or Northern Europe), geographic area (inland vs coastal), history of CVD, concomitant medication use (lipid-lowering agents, no lipid-lowering agents, or antiplatelet agents only), and type of placebo material in the trial (oil vs nonoil).

In subgroup analyses by concomitant medication use, no preventive effect was observed regardless of the use of lipid-lowering agents, while a minimal preventive effect (RR, 0.71; 95% CI, 0.50-1.00) was associated with the use of antiplatelet agents only (eg, aspirin) (Table 4). However, when we excluded the trial by Singh et al,[21] in which there was a significant difference in the proportions with a history of angina between the fish oil intervention group vs the placebo group, no preventive effect was found (RR, 0.71; 95% CI, 0.34-1.47).

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Table 1. Characteristics of 14 Randomized, Double-blind, Placebo-Controlled Trials Included in the Meta-analysis

Source (Country Location)	Participants (Follow-up Period)	Intervention vs Control	Primary Outcome Measures in the Trial	Main Outcome Measures Used in the Present Meta-analysis	RR (95% CI)	No./Total No. (%)			
						Intervention Group		Placebo Group	
						Event Rate	Lost to Follow-up	Event Rate	Lost to Follow-up
Sacks et al,[20] 1995 (United States)	59 Patients with angiographically documented CHD (2.3 y)	Omega-3 FA (6 g/d), DHA (2.88 g/d), and EPA (1.92 g/d) (n = 31) vs placebo olive oil capsules (n = 28)	Change in minimal diameter of atherosclerotic coronary arteries	Cardiovascular events (nonfatal MI, PCI, UA, CHF, coronary death, stroke)	0.90 (0.36-2.25)	7/31 (22.6)	10/31 (32.3)	7/28 (25.0)	11/28 (39.3)
Singh et al,[21] 1997 (India)	240 Patients with suspected AMI (1.0 y)	Omega-3 FA (1.8 g/d), EPA (1.08 g/d), and DHA (0.72 g/d) (n = 122) vs aluminum hydroxide capsules (n = 118)	Total cardiac events (nonfatal MI, cardiac death)	Total cardiac events (nonfatal MI, cardiac death)	0.71 (0.48-1.05)	30/122 (24.6)	4/122 (3.3)	41/118 (34.7)	6/118 (5.1)
Leng et al,[22] 1998 (Scotland)	120 Patients with stable lower limb atherosclerosis (1.0 y)	EPA (0.18 g/d) and GLA (1.12 g/d) for first 2 wk, followed by EPA (0.27 g/d) and GLA (1.68 g/d) (n = 60) vs sunflower capsules (n = 60)	Change in cholesterol, lipoprotein, and hemostatic variables	Cardiovascular death	1.00 (0.15-6.87)	2/60 (3.3)	21/60 (35.0)	2/60 (3.3)	24/60 (40.0)
von Schacky et al,[23] 1999 (Germany)	223 Patients with angiographically proven CHD (2.0 y)	Omega-3 FA (3.4 g/d), EPA, and DHA for first 3 mo, followed by omega-3 FA (1.7 g/d) for 21 mo (n = 112) vs mixed fatty oil (nonmarine omega-3 FA) capsules (n = 111)	Change in diameter of atherosclerotic coronary arteries	Cardiovascular events (SCD, fatal or nonfatal MI, CHF, stroke)	0.28 (0.06-1.33)	2/112 (1.8)	31/112 (27.7)	7/111 (6.3)	30/111 (27.0)
Nilsen et al,[24] 2001 (Norway)	300 Patients with AMI (1.5 y)	Omega-3 FA (3.4 g/d) and EPA-DHA (1:2) (n = 150) vs corn oil capsules (n = 150)	Cardiac events and serum lipid levels	Fatal or nonfatal cardiac events (cardiac death, resuscitation, recurrent MI, UA)	1.17 (0.80-1.71)	42/150 (28.0)	NA	36/150 (24.0)	NA
Raitt et al,[25] 2005 (United States)	200 Patients with ICD and a recent episode of sustained VT or VF (2.0 y)	Omega-3 FA (1.3 g/d), EPA (0.76 g/d), and DHA (0.54 g/d) (n = 100) vs olive oil capsules (n = 100)	Time to first episode of ICD, treatments for VT or VF	Cardiac death	0.40 (0.08-2.01)	2/100 (2.0)	2/100 (2.0)	5/100 (5.0)	6/100 (6.0)
Leaf et al,[26] 2005 (United States)	402 Patients with ICD (1.0 y)	Omega-3 FA (2.6 g/d), EPA, and DHA (n = 200) vs olive oil capsules (n = 202)	Time to first episode of ICD treatments for VT or VF	Cardiac death	1.01 (0.21-2.50)	9/200 (4.5)	NA	9/202 (4.5)	NA
Brouwer et al,[27] 2006 (Europe)	546 Patients with ICD and prior malignant VT or VF (1.0 y)	Omega -3 FA (0.96 g/d), EPA (0.46 g/d), and DHA (0.33 g/d) (n = 273) vs sunflower oil capsules (n = 273)	All-cause death or ICD intervention for VT or VF	Cardiac death	0.46 (0.18-1.20)	6/273 (2.2)	29/273 (10.6)	13/273 (4.8)	25/273 (9.2)
Svensson et al,[28] 2006 (Denmark)	206 Patients with stable heart disease for ≥6 mo and established CVD (2.0 y)	Omega-3 FA (1.7 g/d), EPA, and DHA (n = 103) vs olive oil capsules (n = 103)	Cardiovascular events or death	Cardiovascular events (AMI, angina, stroke, TIA, PVD) or death	1.05 (0.84-1.32)	62/103 (60.2)	28/103 (27.2)	59/103 (57.3)	23/103 (22.3)
Tavazzi et al,[29] 2008 (Italy)	6975 Patients with CHF New York Heart Association class II-IV (3.9 y)	Omega-3 FA (0.85 g/d), EPA, and DHA (n = 3494) vs placebo capsules (n = 3481)	Time to death or admission to hospital for cardiovascular reasons	Cardiovascular death	0.93 (0.85-1.02)	712/3494 (20.4)	69/3494 (2.0)	765/3481 (22.0)	82/3481 (2.4)

(continued)

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Table 1. Characteristics of 14 Randomized, Double-blind, Placebo-Controlled Trials Included in the Meta-analysis (continued)

Source (Country Location)	Participants (Follow-up Period)	Intervention vs Control	Primary Outcome Measures in the Trial	Main Outcome Measures Used in the Present Meta-analysis	RR (95% CI)	No./Total No. (%)			
						Intervention Group		Placebo Group	
						Event Rate	Lost to Follow-up	Event Rate	Lost to Follow-up
Garbagnati et al,[30] 2009 (Italy)	72 Stroke survivors (1.0 y)	Omega-3 FA (0.5 g/d), EPA (0.25 g/d), and DHA (0.25 g/d) ± antioxidant supplements (n = 38) vs placebo capsules ± antioxidant supplements (n = 34)	Improvement in functional status	Cardiovascular death	0.10 (0.01-1.79)	0/38	6/38 (15.8)	4/34 (11.8)	10/34 (29.4)
Galan et al,[31] 2010 (France)	2501 Patients with a history of MI, UA, and ischemic stroke within 12 mo (4.7 y)	Omega-3 FA (0.6 g/d), EPA, and DHA ± vitamin B (n = 1253) vs placebo capsules ± vitamin B (n = 1248)	Major cardiovascular events (nonfatal MI, stroke, cardiovascular death)	Major cardiovascular events (nonfatal MI, stroke, cardiovascular death)	1.06 (0.78-1.44)	81/1253 (6.5)	134/1253 (10.7)	76/1248 (6.1)	145/1248 (11.6)
Kromhout et al,[32] 2010 (the Netherlands)	4837 Patients with a history of MI (3.3 y)	Omega-3 FA (0.4 g/d), EPA (0.23 g/d), and DHA (0.15 g/d) ± ALA (n = 2404) vs placebo margarine ± ALA (n =2433)	Major cardiovascular events (fatal or nonfatal cardiovascular events, PCI, CABG)	Major cardiovascular events (fatal or nonfatal cardiovascular events, PCI, CABG)	1.02 (0.89-1.17)	336/2404 (14.0)	766/2404 (31.9)	335/2433 (13.8)	638/2433 (26.2)
Rauch et al,[33] 2010 (Germany)	3851 Patients with AMI (1.0 y)	Omega-3 FA (1 g/d), EPA (0.46 g/d), and DHA (0.38 g/d) (n = 1925) vs olive oil (n = 1893)	SCD	Major cardiovascular events (total mortality, reinfarction, stroke)	1.20 (0.98-1.48)	182/1919 (9.5)	6/1919 (0.3)	149/1885 (7.9)	8/1885 (0.4)

Abbreviations: ALA, α-linolenic acid; AMI, acute myocardial infarction; CABG, coronary artery bypass surgery; CHD, coronary heart disease; CHF, congestive heart failure; CVD, cardiovascular disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FA, fatty acid; GLA, γ-linolenc acid; ICD, implanted cardioverter defibrillator; MI, myocardial infarction; NA, not available; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; RR, relative risk; SCD, sudden cardiac death; TIA, transient ischemic attack; UA, unstable angina; VF, ventricular fibrillation; VT, ventricular arrhythmia.

Table 2. Methodological Quality of 14 Trials According to Scores on the Scale by Jadad et al[38]

Source	Score on the Scale by Jadad et al[38]					
	Randomization	Description of Randomization Methods	Double-blind Design	Use of Identical Placebo	Follow-up Reporting	Total
Sacks et al,[20] 1995	1	0	1	1	1	**4**
Singh et al,[21] 1997	1	0	1	1	1	**4**
Leng et al,[22] 1998	1	0	1	1	1	**4**
von Schacky et al,[23] 1999	1	1	1	1	1	**5**
Nilsen et al,[24] 2001	1	0	1	1	0	**3**
Raitt et al,[25] 2005	1	1	1	1	1	**5**
Leaf et al,[26] 2005	1	1	1	1	1	**5**
Brouwer et al,[27] 2006	1	0	1	1	1	**4**
Svensson et al,[28] 2006	1	1	1	1	1	**5**
Tavazzi et al,[29] 2008	1	1	1	1	1	**5**
Garbagnati et al,[30] 2009	1	0	1	1	1	**4**
Galan et al,[31] 2010	1	1	1	1	1	**5**
Kromhout et al,[32] 2010	1	0	1	1	1	**4**
Rauch et al,[33] 2010	1	0	1	1	1	**4**

COMMENT

Our meta-analysis showed insufficient evidence of a secondary preventive effect of omega-3 fatty acid supplements against overall cardiovascular events. Likewise, we found no beneficial effect of omega-3 fatty acid supplements on other cardiovascular events, such as sudden cardiac death, myocardial infarction (fatal or nonfatal), angina and unstable angina, congestive heart failure, and transient ischemic attack and stroke, or on all-cause mortality. Furthermore, no significant preventive effect was observed in subgroup analyses by

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the following: history of CVD, country location, geographic area, duration of treatment, dosage of EPA or DHA, concomitant medication use, methodological quality of the trial, type of placebo material in the trial, or use of fish oil supplementation only as treatment.

Two large randomized controlled trials (the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico [GISSI]–Prevenzione trial[18] and the Japan EPA Lipid Intervention Study[19]) were not included in the present analysis because they had an open-label study design without the use of placebo. Results of the GISSI-Prevenzione trial,[18] which involved 11 324 patients who had survived recent myocardial infarction, indicated that the use of omega-3 fatty acid supplements (1 g/d) for more than 3½ years significantly reduced the risk of death, nonfatal myocardial infarction, and nonfatal stroke. Findings of the JELIS[19] among 18 645 Japanese participants who had hypercholesterolemia and were taking statins showed that supplementation with EPA (1.8 g/d) lowered the incidence of major coronary events. However, an open-label study design is liable to performance bias (ie, differential behavior of participants between the intervention and control groups or differential care provided by prescribing physicians).[18,36] As mentioned in the JELIS,[19] a preventive effect of EPA might be due to biases in some of the physician-initiated end points, such as hospital treatment for unstable angina and coronary revascularization. Also, participants who knew they were in the intervention group might have experienced placebo effects of EPA. When we performed a meta-analysis with the GISSI-Prevenzione trial[18] and the JELIS[19] in addition to the 14 trials included in the present study, a preventive effect of omega-3 fatty acid supplementation was not observed (RR, 0.95; 95% CI, 0.87-1.03; I^2 = 35.5%) (data not shown).

With respect to the type of placebo material used in the trial, results of the meta-analysis by Marik and Varon[37] indicated that the use of olive oil as a control in several trials[20,25,26] might have disguised the "true" benefit of omega-3 fatty acid supplementation because olive oil has beneficial effects on lipoprotein metabolism, glucose metabolism, and the risk of other CVDs. However, when we performed subgroup analyses, no significant preventive effect was found regardless of the type of placebo material in the trial, including olive oil, sunflower oil, corn oil, or nonoil (inert or ill-defined substances).

Although it has been suggested that omega-3 fatty acids may have several beneficial cardiovascular effects, such as antiarrhythmic properties, antiatherothrombotic influences, plaque stabilization, vasodilation, and lipid level reduction,[4-8] this remains unproven. Some researchers have insisted that the benefits of omega-3 fatty acids are their antithrombotic effects,[6,40] while others have emphasized their strong antiarrhythmic action, which would explain a limited effect of fish oils on fatal myocardial infarction and sudden cardiac death.[18,35,41] However, recent clinical trials and meta-analyses[25-27,42] among patients with an implanted cardioverter defibrillator who were at high risk of arrhythmia found that fish oil supplementation did not reduce the risk of fatal ventricular arrhythmia or sudden cardiac death and was harmful to some patients. Our meta-analysis found no significant protective effect of omega-3 fatty acid supplements

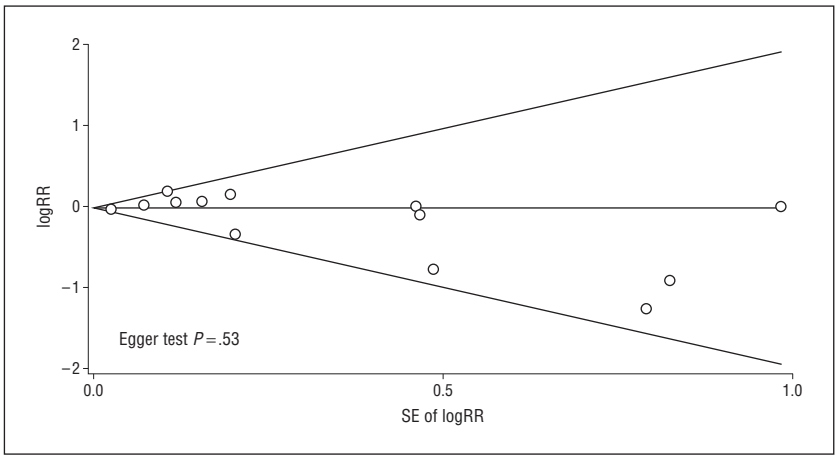

Figure 2. Begg funnel plot and Egger test *P* value for identifying publication bias in a meta-analysis of 13 trials. RR indicates relative risk. Because the study by Garbagnati et al[30] resulted in a zero outcome, it was excluded in funnel plot analysis by the STATA program.

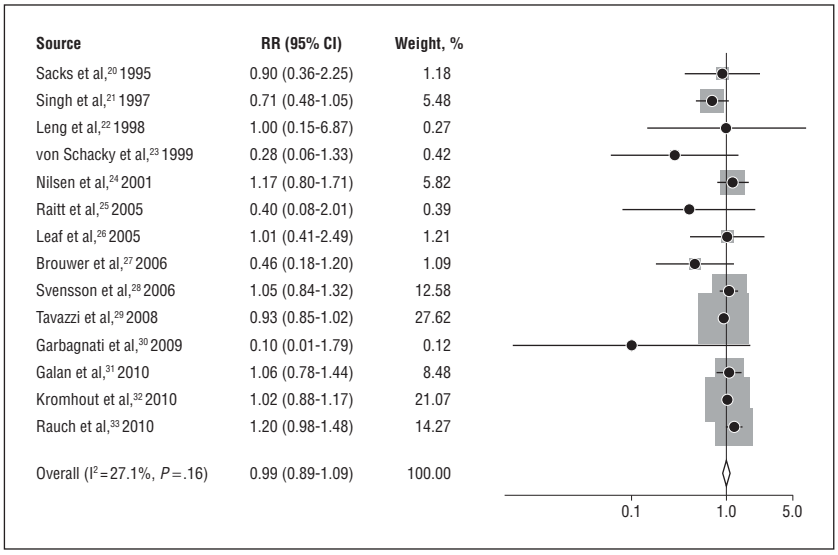

Figure 3. Efficacy of omega-3 fatty acid supplements in the secondary prevention of overall cardiovascular events in a random-effects meta-analysis of 14 randomized, double-blind, placebo-controlled trials. RR indicates relative risk. Horizontal lines indicate 95% CIs; gray boxes, the weight of each study. The box area is proportional to the weight of each study.

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Table 3. Efficacy of Omega-3 Fatty Acid Supplements Against the Risk of Overall Cardiovascular Events

Variable	No. of Trials	RR (95% CI)	I^2 Value, %
Cardiovascular events			
Overall	14 Trials[20-33]	0.99 (0.89-1.09)	27.1
Excluding Tavazzi et al,[29] 2008	13 Trials[20-28,30-33]	1.09 (0.89-1.14)	21.8
All-cause mortality	13 Trials[20,22-33]	0.96 (0.90-1.02)	0.0
Sudden cardiac death	5 Trials[21,25,26,29,33]	0.93 (0.66-1.30)	23.7
Cardiovascular death			
Overall	11 Trials[20-27,29,30,32]	0.91 (0.84-0.99)	0.0
Excluding Singh et al,[21] 1997	10 Trials[20,22-27,29,30,32]	0.92 (0.35-1.01)	0.0
Myocardial infarction	11 Trials[20-25,27-29,31,32]	0.81 (0.65-1.01)	24.9
Fatal	5 Trials[20,23,29,31,32]	0.87 (0.67-1.13)	0.0
Nonfatal	7 Trials[20-24,29,31]	0.86 (0.65-1.14)	24.3
Angina and unstable angina	7 Trials[20-22,24,25,27,28]	0.77 (0.50-1.18)	45.2
Congestive heart failure	6 Trials[20,21,25-27,29]	0.92 (0.73-1.17)	20.1
Transient ischemic attack and stroke	7 Trials[20,22,23,25,28,29,31]	1.13 (0.77-1.66)	31.1
Adverse events			
GI troubles[a]	8 Trials[22,23,25,27-29,31,32]	1.19 (0.95-1.49)	31.7
GI bleeding	1 Trial[28]	1.60 (0.54-4.73)	0.0

Abbreviations: GI, gastrointestinal; RR, relative risk.
[a] Include diarrhea, flatulence, nausea, vomiting, and abdominal pain.

Table 4. Subgroup Analyses of the Efficacy of Omega-3 Fatty Acid Supplements Against the Risk of Overall Cardiovascular Events

Variable	No. of Trials	RR (95% CI)	I^2 Value, %
Duration of treatment, y			
Short, <2	7 Trials[21,22,24,26,27,30,34]	0.95 (0.70-1.26)	46.0
Long, ≥2	7 Trials[20,23,25,28,29,31,32]	0.96 (0.90-1.03)	0.0
Dosage of EPA or DHA, g/d			
Low, <1.7	7 Trials[25,27,29-33]	1.00 (0.87-1.14)	48.2
High, ≥1.7	7 Trials[20-24,26,28]	0.97 (0.81-1.16)	5.9
Methodological quality of the trial, No. of points on the scale by Jadad et al[38]			
5	7 Trials[23,25-29,31]	0.95 (0.83-1.08)	16.8
≤4	7 Trials[20-22,24,30,32,33]	1.03 (0.87-1.21)	29.7
Use of fish oil supplementation only as treatment	11 Trials[20-29,33]	0.97 (0.85-1.12)	31.9
Country location			
United States	3 Trials[20,25,26]	0.85 (0.47-1.54)	0.0
Asia	1 Trial[21]	0.71 (0.48-1.05)	. . .
Western Europe	8 Trials[22,23,27,29-33]	0.99 (0.87-1.14)	45.6
Northern Europe	2 Trials[24,28]	1.08 (0.89-1.32)	0.0
Geographic area			
Inland	3 Trials[21,23,33]	0.83 (0.48-1.45)	75.5
Coastal	9 Trials[20,22,24-26,28-30,32]	0.97 (0.90-1.04)	0.0
History of CVD			
Stable CVD[a]	5 Trials[20,22,23,28,31]	1.03 (0.86-1.23)	0.0
Unstable CVD[b]	9 Trials[21,24-27,29,30,32,33]	0.97 (0.85-1.12)	45.2
Cardiac disease	10 Trials[20,21,23-27,29,32,33]	0.97 (0.85-1.10)	38.6
Coronary heart disease[c]	6 Trials[20,21,23,24,32,33]	1.01 (0.84-1.21)	42.5
Prior myocardial infarction	4 Trials[21,24,32,33]	1.04 (0.87-1.24)	49.5
Implanted cardioverter defibrillator	3 Trials[25-27]	0.65 (0.35-1.18)	0.0
Concomitant medication use			
Lipid-lowering agents	8 Trials[24,25,27-29,31-33]	1.02 (0.92-1.12)	24.8
No lipid-lowering agents	5 Trials[20-23,26]	0.74 (0.54-1.03)	0.0
Antiplatelet agents only	4 Trials[20-23]	0.71 (0.50-1.00)	0.0
Antiplatelet agents only, excluding Singh et al,[21] 1997	3 Trials[20,22,23]	0.71 (0.34-1.47)	0.0
Type of placebo material in the trial			
Oil	11 Trials[20-28,32,33]	1.05 (0.95-1.16)	2.3
Olive oil	5 Trials[20,25,26,28,33]	1.11 (0.96-1.29)	0.0
Sunflower oil	2 Trials[22,27]	0.54 (0.23-1.26)	0.0
Corn oil	1 Trial[24]	1.17 (0.80-1.71)	0.0
Nonoil	4 Trials[21,29-31]	0.91 (0.75-1.10)	37.9

Abbreviations: CVD, cardiovascular disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; RR, relative risk.
[a] Includes stable coronary heart disease, stable peripheral vascular disease, and stable hemodialysis.
[b] Includes prior myocardial infarction, implanted cardioverter defibrillator, congestive heart failure, and recent stroke.
[c] Includes coronary heart disease and myocardial infarction.

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against sudden cardiac death or angina and unstable angina.

Our findings differ from the results of a previous systematic review[37] and meta-analysis[35] on this topic. Marik and Varon[37] suggested that dietary supplementation with omega-3 fatty acids should be considered in the secondary prevention of cardiovascular events based on their results of a meta-analysis of 11 trials. Although the authors stated that they performed a meta-analysis of prospective, randomized, placebo-controlled clinical trials, they included 2 large open-label trial (the GISSI–Prevenzione trial[18] and the JELIS[19]). When we performed a meta-analysis of the remaining 9 trials after excluding those 2 open-label studies, no significant preventive effect was observed, with the following results similar to those of the present meta-analysis: cardiovascular death (RR, 0.91; 95% CI, 0.83-0.99), sudden cardiac death (RR, 0.94; 95% CI, 0.81-1.09), all-cause mortality (RR, 0.93; 95% CI, 0.86-1.00), and nonfatal cardiovascular events (RR, 0.96; 95% CI, 0.92-1.01). In another meta-analysis of 11 trials by Bucher et al,[35] the use of omega-3 fatty acid supplementation reduced overall mortality, fatal myocardial infarction, and sudden cardiac death in patients with coronary heart disease. However, these authors did not differentiate dietary omega-3 fatty acid intake (eg, fish) from omega-3 fatty acid supplement use and included as a the control group both patients consuming a control diet and patients receiving placebo.

Although the main findings herein are not consistent with those of the meta-analyses[35,37] published before 2010, they correspond well with the results of the randomized controlled trials[31-34] published in 2010, which reported no significant effects of supplementary omega-3 fatty acids on cardiovascular death or on major cardiovascular events. Kromhout et al[32] suggested that the lack of an effect of omega-3 fatty acid supplements in their trial could be the result of improvements in cardioprotective drug treatment, such as statin use. For example, in the GISSI-Prevenzione trial,[18] only 5% of patients were receiving statins at baseline, while 85% of participants in the trial by Kromhout et al[32] used statins. Additional use of omega-3 fatty acid supplements in patients receiving cardioprotective agents like statins might not be beneficial in preventing CVD.

Our study has several limitations. First, our findings are limited to the secondary prevention of omega-3 fatty acid supplementation against CVD among patients with a history of CVD, not in healthy individuals. We were unable to investigate the primary preventive effects because only 1 trial,[34] in which 28% of participants had overt CVD at baseline, reported on primary prevention. Second, we initially had planned to conduct subgroup analyses by the type of funding source because the study results might have been affected by who had funded the trial (ie, investigator-initiated trial vs industry-initiated trial). However, almost all the trials included in our study were funded by pharmaceutical companies. Third, our findings are limited to Western populations because of a paucity of data for Eastern populations. Fourth, we only used published information on outcomes like nonfatal or fatal myocardial infarction. Therefore, we are unable to exclude information bias, if any. Fifth, most trials included in the present meta-analysis had a small sample size of 59 to 500 participants and a short duration of treatment of less than 2 to 3 years. Further larger trials are needed.

In summary, we performed a meta-analysis among 14 randomized, double-blind, placebo-controlled trials investigating the beneficial cardiovascular effects of omega-3 fatty acid supplementation. Our results showed insufficient evidence of a secondary preventive effect of omega-3 fatty acid supplements against overall cardiovascular events among patients with a history of cardiovascular disease.

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Correspondence: Seung-Kwon Myung, MD, Center for Cancer Prevention and Detection, National Cancer Center, 323 Ilsan-Ro, Ilsan-dong-Gu, Goyang-Si, Gyeonggi-Do, Ilsan 410-769, Republic of Korea (msk@ncc.re.kr).
Author Contributions: Dr Myung had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Kwak and Myung. *Acquisition of data:* Kwak and Myung. *Analysis and interpretation of data:* Kwak, Myung, Lee, and Seo. *Drafting of the manuscript:* Kwak, Myung, Lee, and Seo. *Critical revision of the manuscript for important intellectual content:* Kwak, Myung, Lee, and Seo. *Statistical analysis:* Kwak and Myung.
Group Information: The Korean Meta-analysis Study group members are Seung-Kwon Myung, MD; Woong Ju, MD, PhD; Seung Won Oh, MD; Ji-Hyun Bae, DDS, PhD; Young-Kyun Kim, DDS, PhD; Chang-Hae Park, MD; Young-Jee Jeon, MD; Eun-Hyun Lee, MD; Yoon Jung Chang, MD, PhD; Sang Min Park, MD, PhD; Chun Sik Eom, MD; Yeon Ji Lee, MD; Hyun-Suk Jung, MD; and Sang Mi Kwak, MD.
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INVITED COMMENTARY

Omega-3 Fatty Acids and Secondary Prevention of Cardiovascular Disease—Is It Just a Fish Tale?

Omega-3 fatty acids are among the most extensively studied nutrients for their potential cardiovascular benefits. There are 2 major classes of omega-3 fatty acids. The first is α-linolenic acid, an essential fatty acid derived from plant sources, such as flaxseed, walnut, soybean, and canola oils. The second class includes long-chain omega-3 fatty acids, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), which are derived primarily from fatty fish. α-Linolenic acid can be converted to EPA and DHA in the human body, although the efficiency of such conversions seems to be low.[1] A large body of evidence from experimental, clinical, and epidemiologic research has demon-

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