Original Article

Omega 3 Fatty Acids and Cardiovascular Outcomes
Systematic Review and Meta-Analysis

Sradha Kotwal, BHB, MBChB, FRACP; Min Jun, BSc (Hons), MSc; David Sullivan, MBBS, FRACP, FRCPA; Vlado Perkovic, MBBS, PhD, FRACP; Bruce Neal, MBChB, PhD, FRACP

Background—Early trials evaluating the effect of omega 3 fatty acids (ω-3 FA) reported benefits for mortality and cardiovascular events but recent larger studies trials have variable findings. We assessed the effects of ω-3 FA on cardiovascular and other important clinical outcomes.

Methods and Results—We searched MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials for all randomized studies using dietary supplements, dietary interventions, or both. The primary outcome was a composite of cardiovascular events (mostly myocardial infarction, stroke, and cardiovascular death). Secondary outcomes were arrhythmia, cerebrovascular events, hemorrhagic stroke, ischemic stroke, coronary revascularization, heart failure, total mortality, nonvascular mortality, and end-stage kidney disease. Twenty studies including 63 030 participants were included. There was no overall effect of ω-3 FA on composite cardiovascular events (relative risk [RR]=0.96; 95% confidence interval [CI], 0.90–1.03; *P*=0.24) or on total mortality (RR=0.95; 95% CI, 0.86–1.04; *P*=0.28). ω-3 FA did protect against vascular death (RR=0.86; 95% CI, 0.75–0.99; *P*=0.03) but not coronary events (RR=0.86; 95% CI, 0.67–1.11; *P*=0.24). There was no effect on arrhythmia (RR=0.99; 95% CI, 0.85–1.16; *P*=0.92) or cerebrovascular events (RR=1.03; 95% CI, 0.92–1.16; *P*=0.59). Adverse events were more common in the treatment group than the placebo group (RR=1.18, 95% CI, 1.02–1.37; *P*=0.03), predominantly because of an excess of gastrointestinal side effects.

Conclusions—ω-3 FA may protect against vascular disease, but the evidence is not clear-cut, and any benefits are almost certainly not as great as previously believed. (***Circ Cardiovasc Qual Outcomes*. 2012;5:00-00.**)

Key Words: cardiac outcomes ■ cardiovascular disease ■ fatty acids ■ meta-analysis ■ systematic review

Some decades ago, the Inuit people of Greenland were noted to have a low rate of cardiovascular disease,[1] and this was attributed to their high intake of oily fish. Early trials testing this hypothesis found a beneficial effect of fish oil on mortality,[2,3] with subsequent recommendations developed for the use of omega 3 fatty acids (ω-3 FA) for the primary and secondary prevention of cardiovascular disease. More recent trials have, however, failed to replicate these initial positive results, with several large studies reporting null effects. Systematic reviews of the accumulating data[4–8] done during the last decade have also delivered variable findings. In part, this is because more recent overviews have included new data from large neutral trials,[9,10] and in part it is because different overviews have sought to address particular questions for specific patient groups.[4,7,8] This is the first overview to include all recent trials, systematically address the effects on all-important outcomes, and fully explore the potentially different effects achieved with particular interventions in major patient subgroups and in primary and secondary prevention. With several large trials completed in the past 18 months, we sought to more precisely and reliably define the effects of ω-3 FA on a broad range of clinical outcomes, overall and in major patient subsets.

Methods

Data Sources and Searches

The study was undertaken according to the PRISMA statement[11] for overviews of intervention studies. Randomized, controlled trials were identified without language restriction by searching Medline via Ovid (from 1946 to March 2011), EMBASE (from 1966 through March 2011), and the Cochrane Central Register of Controlled Trials (until March 2011). Reference lists of relevant trials and review articles were also hand searched. The MeSH terms used were the following: fish oils, omega fatty acids, omega 3, fatty acids, α linolenic acid, docosahexaenoic acids, eicosapentaenoic acid, cardiovascular disease, heart failure, cardiovascular death, myocardial infarction, revascularization, stroke, coronary disease, arrhythmia, sudden death, cardiovascular outcome, mortality, chronic kidney failure, renal insufficiency, kidney failure, kidney disease, renal failure, renal outcome, albuminuria, serum creatinine, exp creatinine, and cancer. All terms were not used in every database, but all spellings of the terms were used as needed. Subject headings were exploded and truncated where necessary.

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From the George Institute for Global Health, University of Sydney, Sydney, Australia (S.K., M.J., V.P., B.N.); and University of Sydney, Sydney, Australia (D.S.).

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Correspondence to Sradha Kotwal, BHB, MBChB, FRACP, the George Institute for Global Health, University of Sydney, PO Box M201, Missenden Rd, Sydney, NSW 2050, Australia. E-mail skotwal@georgeinstitute.org.au

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WHAT IS KNOWN

- On the basis of the positive results of early trials, various clinical guidelines recommend the use of omega 3 fatty acid supplements to reduce mortality and cardiovascular risk.
- Several recent large trials have reported no benefit of omega 3 acids on cardiovascular outcomes; however, the recommendations for their use remain.

WHAT THIS ARTICLE ADDS

- This meta-analysis, which includes 20 trials and >60 000 patients, summarizes the entire body of evidence on this subject including all the recent trials.
- The results of this meta-analysis report that omega 3 fatty acids protect against vascular death, but there is no clear effect on total mortality, sudden death, stroke, or arrhythmia.
- The beneficial effects of omega 3 fatty acids are not as large as previously implied and recommendations for widespread use should be tempered.

Study Inclusion Criteria

Studies were included if they were done in adults, were randomized or quasirandomized (trials using methods not completely random for patient allocation, eg, sequential allocation, etc), reported effects on 1 or more of the primary or secondary outcomes, included a comparison between ω-3 FA (delivered as either a dietary supplement or as dietary modification) and control, and recorded ≥100 patient years or more of follow-up per randomized group. Trials with a crossover design were excluded, as were trials done in pregnant women or children.

Data Extraction and Quality Assessment

Two investigators (S.K. and M.J.) reviewed all abstracts independently for eligibility according to the prespecified inclusion criteria. A third investigator (V.P.) resolved any discrepancies. For selected studies, the full text articles were reviewed and data were extracted from each qualifying study into a standard form by 2 independent investigators, with discrepancies resolved by reviewing the original data or with the assistance of a third investigator as necessary. Data extracted included the baseline characteristics of the trial participants (age, sex, history of hypertension, history of diabetes mellitus, history of prior cardiovascular disease, mean systolic and diastolic blood pressure levels, baseline and end trial lipid levels, smoking status, body mass index, and medication use), type of ω-3 FA supplementation used, dose of ω-3 FA, nature of intervention (dietary change or supplementation), follow-up duration, outcome events, compliance, and adverse events. The quality of the studies was assessed by the application of a modified version of the Jadad criteria, which is a quality assessment tool to assess the methodological quality of clinical trials[12] with additional recording of the use of intention-to-treat analysis methods. A higher Jadad score indicates higher methodological quality.

Outcomes

The primary outcome was a composite of cardiovascular events (myocardial infarction, stroke, and cardiovascular death, or, as defined by the authors of the contributing trials) (Table 1). Secondary outcomes were vascular death (death from myocardial infarction, stroke, sudden death), myocardial infarction, cerebrovascular events (recorded separately for hemorrhagic and ischemic stroke where reported), coronary revascularization (percutaneous coronary interventions and coronary artery bypass grafting), arrhythmia (atrial fibrillation, ventricular fibrillation, or ventricular tachycardia), total mortality, nonvascular mortality, and end-stage kidney disease. Wherever reported, medication adherence rates and total adverse events (which mostly comprised gastrointestinal side effects) were recorded.

Data Synthesis and Analysis

Overall estimates of effect were estimated using random effects models to calculate relative risks (RR) with 95% confidence intervals (CIs). In each case, the numerator was the number of patients with an event and the denominator the total number of patients randomized. Where there were no events recorded in 1 randomized group in a trial, 0.5 was added to the numerator and denominator to enable the trial to be included in the analysis.[13] The I^2 statistic was used to quantify heterogeneity in the results of studies contributing to each overview analysis, with sensitivity analyses excluding individual trials done to explore the heterogeneity. Subgroup analyses and univariate meta-regressions were used to explore the association between the primary outcome and study characteristics, including median age of patients, proportion with hypertension, proportion with diabetes mellitus, mean baseline lipid levels (triglycerides, low-density lipoprotein, high-density lipoprotein, and total cholesterol), proportion using lipid lowering agents, dietary modification versus supplementation, dose of free fatty acids (high versus low dose), median follow-up time, every 5-year increase in publication year, study size, trial setting, and Jadad score. The presence of publication bias was investigated and quantified using Egger test and Begg funnel plots of the natural log of the RR versus its standard error[14] for composite cardiovascular outcomes and all cause mortality. $P<0.05$ was considered unlikely to have arisen by chance, and all analyses were done using Stata version 11.1 (Stata, College Station, TX).

Results

Search Results

Initial search identified 2362 possibly eligible studies, of which 201 were duplicates, leaving 2161 abstracts that were reviewed by the 2 investigators. Two thousand, one hundred sixteen were excluded on the basis that they did not evaluate an intervention of interest, did not report an outcome of interest, were nonrandomized studies, were trials done in a pediatric or pregnant population, included <100 patient years of follow-up per arm, were repeat publications from the same trial or were crossover designs. Full text reports were obtained for the 47 remaining studies, and on further review another 27 were excluded. One study was excluded subsequently on the basis of strong suspicion of fraud.[15] The recent ORIGIN trial[16] has also been included yielding a total of 20 studies being included for the meta-analysis (Figure 1).

Characteristics of Included Studies

The 20 studies randomized a total of 62 851 patients with 31 456 assigned to active treatment and 31 395 to control (Table 1). The total sample size of contributing trials ranged from 106 to 18 645 participants, and the follow-up duration from 6 months to 6 years. The median age of the participants was 61 years, and 50% of the participants were male despite several studies being conducted exclusively in men.[2,17,18] Seventeen were multicenter trials,[2,3,9,10,16–28] and 2 were exclusively studies of primary prevention.[18,19] The trials were variously conducted in the United States, the United Kingdom, Europe, and Japan.

Three trials assessed the effect of dietary advice[2,17,24] and the remainder, the effects of fish oil supplements.[3,9,10,16,18–23,25–31] Fourteen used supplements comprising a combination of eicosapentaenoic acid and docosahexaenoic acid,[3,10,16,18,20–23,25,27–30]

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AQ13 **Table 1. Baseline Characteristics of Included Studies**

Study	Inclusion Criteria	Treatment Group	Placebo	Design/ Country of Origin	Mean Follow-Up, y	No. of Patients	Mean Age, y	Male, %	Hypertension, %	Diabetes mellitus, %	Primary or Secondary Prevention	No. of Composite CV Events	No. of All Cause Mortality	No. of Coronary Events
DART study (1989)[2]	Men<70 post acute AMI	Dietary advice	No dietary advice	Randomized, UK	2	2033	56.55	100	24	NR	Secondary	276	224	NR
Lyon Diet heart Study (1994)[24]	Men and women <70 post AMI within past 6 mo	Dietary advice	No dietary advice	Randomized, France	1.25	605	53.5	91	NR	NR	Secondary	NR	28	22
IgA nephropathy (1994)[20]	Biopsy proven IgA nephropathy, urinary protein excretion of ≥1 g/d, serum Cr≤3.0 mg/dL and survival >2 y	EPA/DHA 1680/970	Placebo	Randomized, US	3	106	37	91	58	NR	Secondary	NR	NR	NR
CART study (1999)[29]	Patients for elective coronary angioplasty	EPA/DHA 900/780	Corn oil as Placebo	Randomised, Norway	0.5	500	59.7	77.6	34	8.6	Secondary	NR	4	NR
GISSI-Prevenzione (1999)[3]	Patients with recent AMI	EPA/DHA 850/882	Placebo	Randomized, Italy	3.5	5664	59.4	85	35	15	Secondary	584	529	NR
Effect of Dietary Omega-3 fatty acids on coronary atherosclerosis (1999)[31]	Patients hospitalised for coronary angiography	Fish oil, 1650–3300 mg	Placebo	Randomized, Germany	2	223	52.35	80	49	NR	Secondary	9	NR	4
High dose n-3 fatty acids introduced early after AMI (2001)[30]	Patients post AMI	EPA/DHA 1700/1764	Corn oil as Placebo	Randomized, Norway	1.5	300	64	79	24	10	Secondary	78	46	NR
Dietary advice to men with angina (2003)[17]	Men<70 with angina	Dietary advice	Sensible eating	Randomized, UK	6	1528	61.1	100	49	12	Secondary	NR	250	NR
Fish oil Supplementation and risk of VT and VF in patients with implantable defibrillators (2005)[25]	Patients receiving ICD for VT/VF not because of AMI	Fish oil, EPA/ DHA 756/540	Placebo	Randomized, US	1.97	200	62.5	86	51	24	Secondary	NR	14	4
FAATI (2005)[26]	Patients with ICD at high risk for fatal ventricular arrhythmias	EPA 2600 mg	Placebo	Randomized, US	1	402	65.5	83	NR	NR	Secondary	NR	25	NR
SOFA trial (2006)[27]	Men and women with 1 true spontaneous VT or VF in past 3 mo and either had or were receiving ICD	Fish oil EPA/ DHA 464/335	Placebo	Randomized, Europe	0.9753	546	61.5	84	51	16	Secondary	NR	22	4
OPACH study group (2006)[21]	Patients with CVD and stablished on HD for 6 mo	EPA/DHA 765/638	Placebo	Randomized, Denmark	1.53	206	67	65	78	24	Secondary	121	64	17
JELIS trial (2007)[19]	Patients with hypercholesterolemia	EPA 1800 mg and statin	Placebo and statin	Randomized, Japan	4.6	18645	61	31	35	16	Primary and secondary	586	551	145

(*Continued*)

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Table 1. (Continued)

Study	Inclusion Criteria	Treatment Group	Placebo	Design/ Country of Origin	Mean Follow-Up, y	No. of Patients	Mean Age, y	Male, %	Hypertension, %	Diabetes mellitus, %	Primary or Secondary Prevention	No. of Composite CV Events	No. of All Cause Mortality	No. of Coronary Events
GISSI-Prevenzione HF (2008)[22]	Men and women >18 with clinical evidence of heart failure	EPA/DHA 850–882 mg	Placebo	Randomized, Italy	3.9	7046	67	78	54	28	Secondary	3322	1969	236
Omega (2010)[10]	Men and women >18 with acute STEMI or NSTEMI	EPA/DHA 460/380	Placebo	Randomized, Germany	1	3851	64	74	66	27	Secondary	331	158	NR
Efficacy and safety of prescription N-3 FA for the prevention of recurrent symptomatic AF (2010)[28]	Patients>18 with persistent or paroxysmal AF	EPA/DHA 1860/1500	Placebo	Randomized, US	0.5	663	60.5	56	NR	NR	Secondary	NR	2	NR
Alpha Omega (2010)[9]	Men and women, 60–80 y of age, with MI in past 10 y	EPA/DHA/ALA	ALA and Placebo	Randomized, Netherlands	3.4	4837	69	78	90	21	Secondary	671	NR	NR
SU.FOL.OM3 (2010)[23]	Men and women aged 45–80 y who had an acute coronary or cerebral ischemic events within last 12 mo	EPA/DHA 1200/600	Placebo	Randomized, France	4.7	2501	60.9	79	NR	NR	Secondary	157	117	60
Diet and Omega 3 Intervention trial (2010)[18]	Survivors from a population of healthy men with hypercholesterolemia from the OSLO Diet & Antismoking study	EPA/DHA 1176/840	Placebo	Randomized, Norway	3	563	70.1	100	28	14	Primary	68	38	NR
n-3 Fatty Acids and Cardiovascular Outcomes in Patients with Dysglycemia (2012)[16]	Patients with impaired fasting glucose, impaired glucose tolerance or diabetes mellitus	EPA/DHA 465/375	Olive oil as placebo	Randomized, International	6.2	12611	63.5	65	79	100	Primary and secondary	2051	1915	660

EPA indicates eicosapentaenoic acid, DHA, docosahexaenoic acid.

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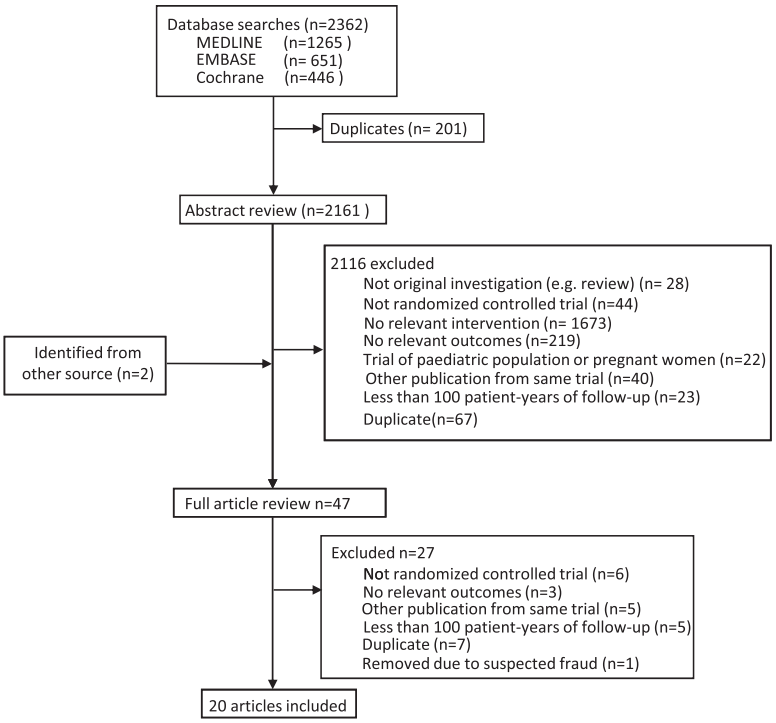

Figure 1. Flow of papers.

with the daily doses of eicosapentaenoic acid/docosahexaenoic acid ranging between 464 to 1860 mg and 335 to 1500 mg, respectively,[27,28] compared with recommended dietary intakes of 250 to 2000 mg/d for each.[32] The placebo composition varied and included control,[19,21–23,31] corn oil,[18,28–30] and olive oil.[10,16,25,26]

The reporting of trial methodology was variable (Table 2), with the earlier studies reporting less information about their methods of randomization, allocation concealment, and completeness of follow-up. Nine studies scored 4 on the Jadad scale,[9,16,18,21,23,25,27,28,31] 5 studies scored 3,[19,20,22,24,26] 3 studies scored 2,[3,10,30] 1 study scored 1,[2] and 2 studies scored zero.[17,29]

Effects of ω-3 Fatty Acids on Clinical Outcomes

Composite Cardiovascular Outcome

For the primary composite cardiovascular outcome, 12 studies involving 57 936 participants[2,3,9,10,16,18,19,21–23,30,31] recorded 8254 events (Figure 2). There was no clear effect of ω-3 FA (RR=0.96; 95% CI, 0.90–1.03; *P*=0.24) on this outcome. There was, however, moderate heterogeneity in the effects of treatment across the included studies (I^2=47.2%; *P*=0.04). Sequentially excluding individual studies as part of a sensitivity analysis did not identify a single trial responsible for the heterogeneity. The definition of the composite cardiovascular outcome differed somewhat between studies with the majority comprising cardiovascular death, myocardial infarction, and sudden death but not all including stroke outcomes.

Vascular Death and Sudden Death

Thirteen studies reported 3776 heart disease deaths, stroke deaths, or sudden deaths that occurred among 54 834 randomized participants.[2,3,9,16–19,22,24–27,30] Of these studies, 8 separately reported 1496 sudden deaths among 49 971 participants.[3,10,16,17,19,22,24,25] Treatment with ω-3 FA protected against vascular death (Figure 3; RR=0.86; 95% CI, 0.75–0.99; *P*=0.03) but not against sudden death (RR=1.00; 95% CI, 0.75–1.33; *P*=0.99). There was substantial heterogeneity (I^2=60.7%, *P*=0.001) across the results of the 12 trials contributing to the analysis of vascular death and across the 8 trials that evaluated sudden death (I^2=77.0%, *P*<0.0001). No individual trial was able to explain a substantial proportion of the heterogeneity for the vascular death or the sudden death outcome.

Total Mortality and Nonvascular Mortality

Seventeen studies done in 57 671 participants[2,3,10,16–19,21–30] reported 5956 deaths from any cause, and 5 studies reported 723 deaths of nonvascular origin that occurred among 13 913 individuals.[3,18,20,22,24] There was no evidence that ω-3 FA reduced total mortality (Figure 3; RR=0.95; 95% CI, 0.86–1.04; *P*=0.28) or nonvascular mortality (RR=0.97; 95% CI, 0.84–1.11; *P*=0.65). The heterogeneity across the individual trial results for total mortality (I^2=52.1%; *P*=0.007) was significant but once again it was hard to identify specific trials that caused this.

Coronary Events and Revascularization

One thousand, two hundred thirty-four coronary events were reported by 10 studies among 44 470 participants[2,16,19,21–25,27,31] and 3537 occurrences of cardiac revascularization in 8 studies and 38 429 participants.[10,16,19,21,23,25,30,31] There was no evidence of benefit for coronary events (Figure 3; RR=0.86; 95% CI, 0.67–1.11, *P*=0.24) and no significant benefit for revascularization (RR=0.95; 95% CI, 0.89–1.00; *P*=0.07). There was moderate heterogeneity for the coronary outcome (I^2=60.6%, *P*=0.07).

Cerebrovascular Events

Only 7 studies done among 46 750 participants[3,16,19,21–23,31] reported on stroke outcomes. There were a total of 1369

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Table 2. Quality Assessment of Trials Included in the Systematic Review and Meta-Analysis

Study	Randomization Process Described	Randomization Process Achieved	Allocation Concealment Described	Allocation Concealment Adequately Achieved	Similarity of Baseline Characteristics	Eligibility Criteria Described	Double-Blinding Described	Completeness of Follow-Up/ Loss to Follow-Up Described	Intention-To-Treat Described	Completion Rate (Treatment/ Placebo)	Jadad Score
DART study (1989)[2]	No	Yes	No	NR	Yes	Yes	No	Yes	Yes	6.8/6.9	1
Lyon Diet heart Study (1994)[24]	No	Yes	No	NR	Yes	Yes	Yes	Yes	Yes	NR	3
IgA nephropathy (1994)[20]	No	Yes	No	NR	Yes	Yes	Yes	Yes	Yes	71%	3
CART study (1999)[29]	Yes	Yes	Yes	NR	Yes	Yes	No	Yes	No	78%	0
GISSI-Prevenzione (1999)[3]	Yes	Yes	No	NR	Yes	Yes	No	No	Yes	Reported	2
Effect of Dietary Omega-3 fatty acids on coronary atherosclerosis (1999)[31]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	4
High dose n-3 fatty acids introduced early after AMI (2001)[30]	No	NR	No	NR	Yes	Yes	Yes	No	Yes	NR	2
Dietary advice to men with angina (2003)[17]	No	No	No	NR	No	Yes	No	No	Yes	NR	0
Fish oil Supplementation and risk of VT and VF in patients with implantable defibrillators (2005) [25]	Yes	Yes	No	NR	Yes	Yes	Yes	Yes	Yes	98%/94%	4
FAATI (2005)[26]	Yes	Yes	No	NR	Yes	Yes	No	Yes	Yes	86%	3
SOFA trial (2006) [(27)]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	89%/91%	4
OPACH study group (2006)[21]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	74%/78%	4
JELIS trial (2007)[19]	Yes	Yes	Yes	NR	Yes	Yes	No	Yes	Yes	71%/73%	3
GISSI-Prevenzione HF (2008)[22]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	99%/99%	3
Omega (2010)[10]	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No	NR	2
Efficacy and safety of prescription n-3 FA for the prevention of recurrent symptomatic AF (2010)[28]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	88%	4
Alpha Omega (2010)[9]	Yes	Yes	No	NR	Yes	Yes	Yes	Yes	Yes	90%/92%	4
SU.FOL.OM3 (2010)[23]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	90%/90%	4
Diet and Omega 3 Intervention trial (2010)[18]	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	94%	4
ORIGIN Trial[16]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	88%	4

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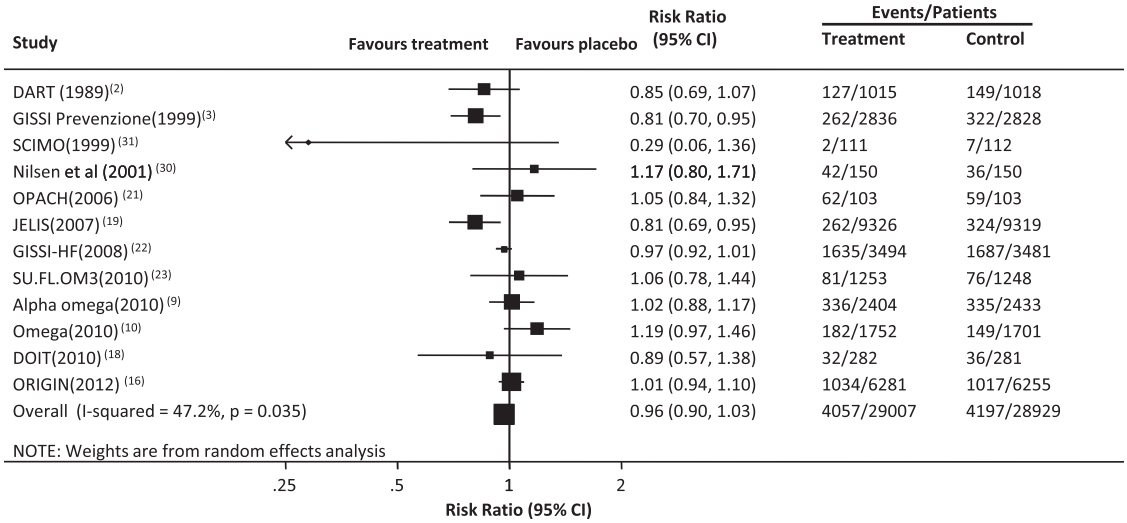

Figure 2. Effect of ω-3 fatty acids on composite cardiovascular outcomes. CI indicates confidence interval.

events. Of these 6 studies, 3 provided a further subclassification into strokes of ischemic and hemorrhagic origin.[19,22,31] Overall, there was no clear effect of ω-3 FA on all cerebrovascular events (Figure 3; RR=1.03; 95% CI, 0.92–1.16; *P*=0.59), although the point estimate of effect was just to the right side of unity. The trend toward harm was stronger for hemorrhagic stroke (RR=1.28; 95% CI, 0.88–1.85; *P*=0.20) than ischemic stroke (RR=1.04; 95% CI, 0.76–1.41; *P*=0.80).

Arrhythmia

This outcome was reported in 5 studies involving 10 097 participants[9,10,25,27,28] and recorded 758 events with no treatment effect identified overall (Figure 3; RR=0.98; 95% CI, 0.82–1.18; *P*=0.84) or for the subset of 3 trials that included patients with a confirmed prior history of atrial fibrillation, ventricular tachycardia, or ventricular fibrillation.[25,27,28] There was evidence of moderate heterogeneity across the included trials (I^2=53.5%; *P*=0.07) but no 1 trial was clearly responsible for this.

Other Outcomes

Two thousand, six hundred fifty heart failure admissions were reported by 3 studies of 19 711 participants.[16,22,25] The overall estimate of effect was a RR of 0.99 (Figure 3; 95% CI, 0.93–1.06; *P*= 0.78). Renal outcomes were reported by 1 study[20] of 106 participants with IgA nephropathy, in which the use of fish oil protected renal function. A further longer-term follow-up of these same patients confirmed this result,[33] although the long-term data were not included in our meta-analysis.

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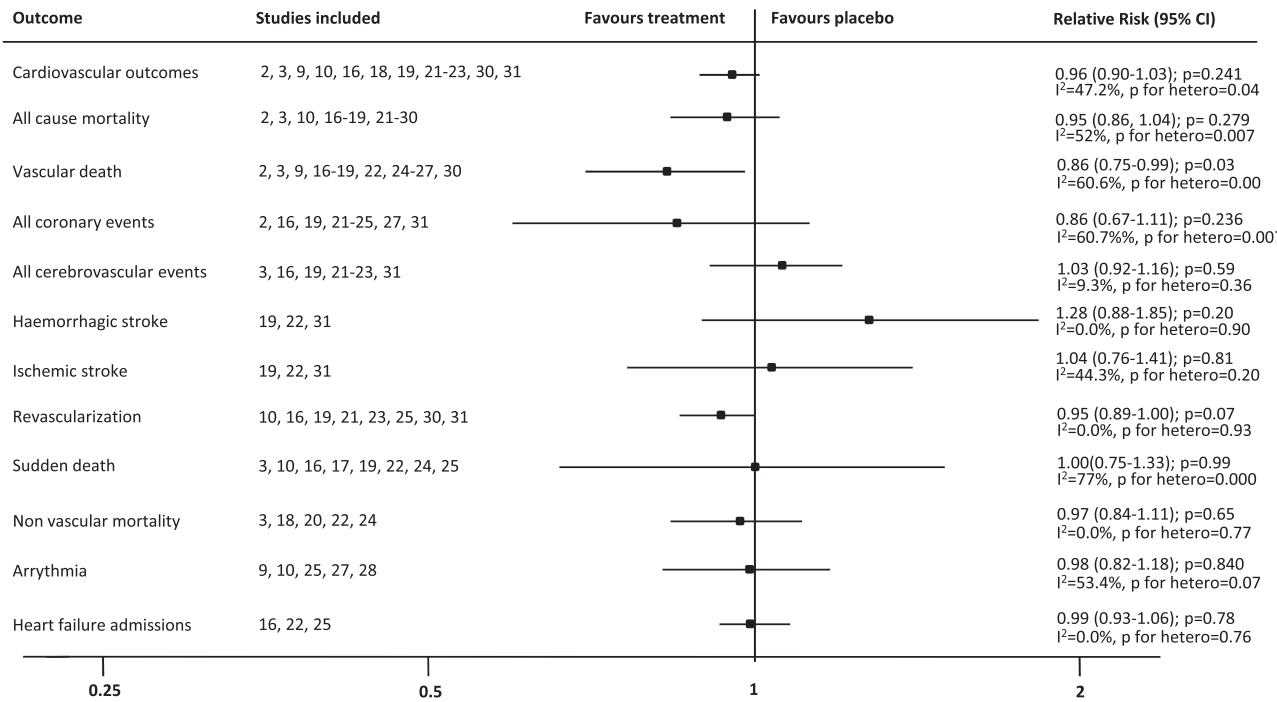

Figure 3. Effect of ω-3 fatty acids on all outcomes. CI indicates confidence interval.

Subgroup Analysis

We undertook a large number of subgroup analyses according to the baseline characteristics of patients and design features of the trials (Figure 4). These analyses identified greater protection against the composite cardiovascular outcomes in trials of younger patients, in trials with fewer hypertensive patients, and in trials in which patients had higher baseline triglyceride levels. There was no difference in effect based on era of publication, study size, or trial setting or when trials were separated into those that used dietary advice compared with those that used dietary supplementation. Univariate meta-regression, hypertension, diabetes mellitus, achieved cholesterol reduction, year of publication, and Jadad score were associated with the likelihood of benefit from ω-3 FA (Table 3) with these variables being well distributed to allow us to estimate the change in proportional risk.

Side Effects

Thirteen studies reported adverse effects among a total of 52 213 participants.[9,10,16,18,19,21–23,25,27–29,31] The use of ω-3 supplements compared with placebo showed an increased risk of side effects (RR=1.18; 95% CI, 1.02–1.37; *P*=0.03). The majority were gastrointestinal and comprised nausea, diarrhea, and other mild gastrointestinal disturbances. Eight studies[9,10,18,19,22,23,25,27] also reported rates of malignancies during the study period with no significant association between the use of ω-3 FA and the incidence of cancer detected (RR=1.10, 95% CI 0.98–1.23, *P*=0.10).

Publication Bias

We found evidence of publication bias (online only Data Supplement Figures I and II) as our funnel plots show an asymmetrical distribution of data. The majority of the studies are located at the base of the plots.

Discussion

The findings of this large systematic review, that includes data from 20 trials, >60 000 individuals and >6000 major cardiovascular events raises important questions about the use of fish oil for the prevention of cardiovascular disease. Recommendations for the use of fish oil supplements are included in a number of guidelines,[34,35] but the neutral outcomes of recent large trials[9,10,16] have served to weaken rather than strengthen the evidence base. Although it remains possible that fish oil supplements will produce health benefits through the prevention of vascular complications, the size of these gains are probably smaller than previously believed, and both physician and patient expectations may need to be reset.

A key strength of this overview is the attempt to extract data on all commonly reported vascular outcomes from all trials and to systematically report the summary estimates of effect in each case. The impact of this approach has been to move the focus of attention from the positive or negative findings for particular outcomes identified in individual studies or overviews, to the overall estimates of effect across

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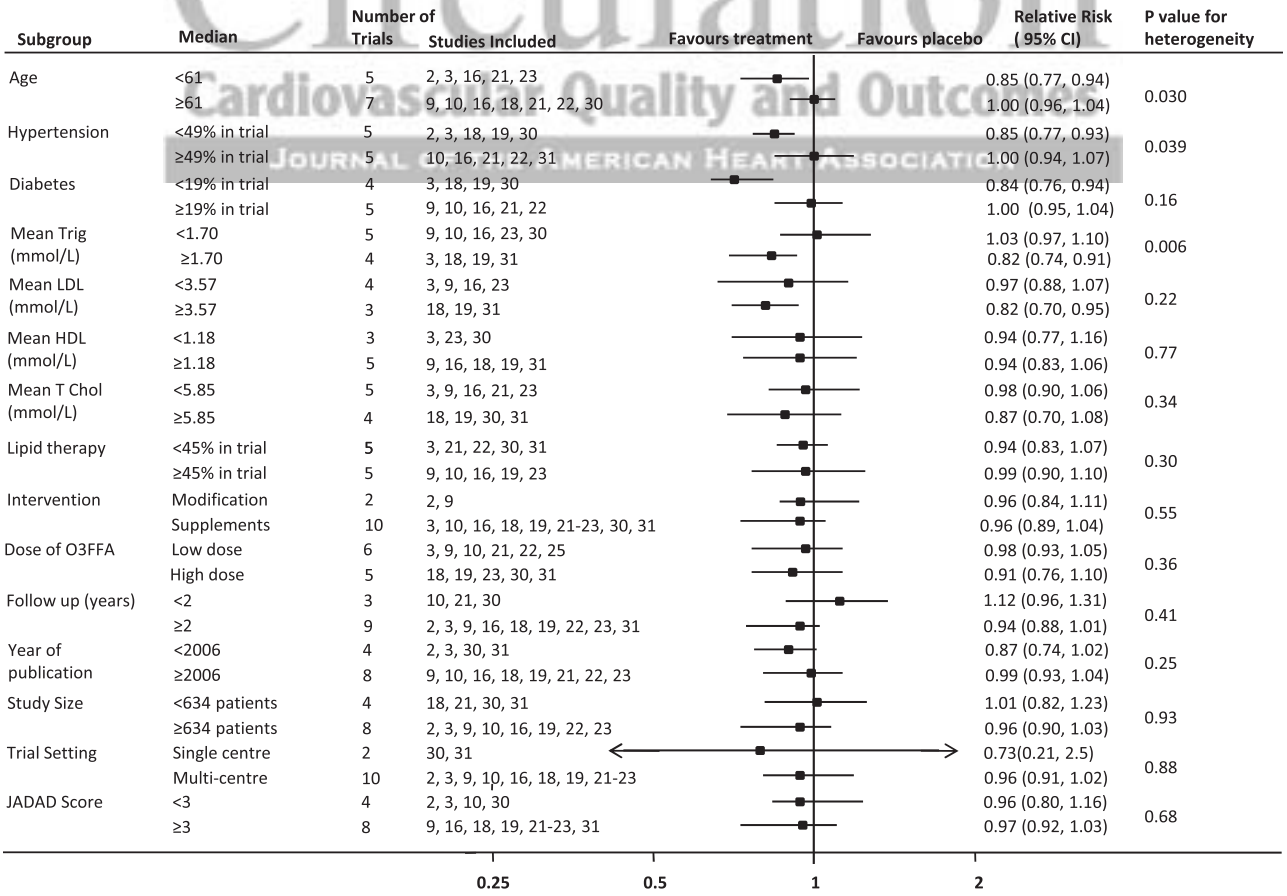

Figure 4. Subgroup analysis for the effect of ω-3 free fatty acids on cardiovascular outcomes. CI indicates confidence interval.

Table 3. Univariate Meta-Regression

Variable	Scale	RR	95% CI		No. of Studies
Age	Every 5 y	1.08	0.90	1.26	12
Male, %	Every 10% increase	0.99	0.92	1.06	12
HTN	Every 10% increase	1.09	1.04	1.13	10
DM	Every 10% increase	1.07	1.05	1.08	8
Mean baseline TRIG	Every 1 mmol/L increase	0.50	–0.56	1.55	6
Mean baseline LDL	Every 1 mmol/L increase	0.76	0.51	1.02	5
Mean baseline HDL	Every 1 mmol/L increase	1.00	0.98	1.03	6
Mean baseline cholesterol	Every 1 mmol/L increase	0.84	18.00	19.68	7
TRIG difference: TX1 vs TX2	Every 0.1 mmol/L difference	0.89	0.62	1.17	3
HDL difference: TX1 vs TX2	Every 0.02 mmol/L reduction	1.04	0.88	1.20	3
CHOL difference: TX1 vs TX2	Every 0.1 mmol/L increase	0.93	0.92	0.95	3
Drug dose (composite cv outcomes)	Every 200 mg increase	0.97	0.92	1.02	11
Follow-up (y)	Every 1 y	1.04	0.97	1.11	12
Year of publication	Every 5 y	1.09	1.01	1.18	12
Study size	Every 100 participants	1.00	1.00	1.00	12
Jadad score	Every 1 point increase	1.12	1.02	1.23	12

HTN indicates hypertension; RR, risk ratio, CI, confidence interval, DM, diabetes mellitus; TRIG, triglycerides; LDL, low-density lipoprotein, HDL, high-density lipoprotein; and CHOL, cholesterol.

the entire body of evidence. This attempt to apply greater objectivity to the analysis of the data has not, however, been without its challenges. In part because the reporting of outcomes across studies is inconsistent and in part because there is significant heterogeneity between the trials' results for several of the outcomes studied. This heterogeneity may also contribute to the absence of positive findings in this meta-analysis.

The heterogeneity in results between trials was large for several analyses and is unlikely to simply reflect the play of chance. Although not easy to explain in every case, the analyses of trial subgroups suggest a number of explanations based on plausible biological phenomena and correlations in the data. Greater average effects on the primary outcome were observed in the studies that used higher doses of ω-3 FA[3,18,19,22,23,30,31] and trials done in patients with higher baseline levels of triglycerides.[3,19,31] These findings are similar to those reported for fibrates, which is notable given that both classes of agents have similar effects on lipid profiles, and especially on triglyceride levels.[36] We also observed greater average effects in those with younger average ages,[3,23,31] and in trials with lower proportions of hypertensives[2,3,18,19,30] and lower proportions of diabetes mellitus.[3,18,19,30] These differences between subgroups are difficult to explain on the basis of physiology, although there are also animal data that suggest a mechanism of action for lesser effects in patients with diabetes mellitus.[37] The subgroup findings also seem to be heavily influenced by the characteristics and results of a few large trials. The GISSI-Prevenzione trial,[3] for example, studied mostly younger individuals who were nonhypertensive, and was reported before the year 2000. As a major contributor of events to all 3 of these subgroup analyses, it is easy to see how the heterogeneity of effects by these trial characteristics arises even if it is not entirely explained. The neutral findings of the more recent trials might also be associated with underlying levels of marine oil intake, but with background consumption data reported by only 7 trials[3,9,10,17,24,29,30] that used very different definitions this was difficult to robustly investigate. Variation in the composition of the placebo compound may also contribute to the neutrality of the findings, although a subgroup analysis based on the use of an inactive control compared with corn oil or olive oil identified significant heterogeneity.

Vascular death was the only outcome for which a significant benefit was observed. This result does not seem to have been driven by an effect on sudden death or arrhythmia, both of which had more moderate and nonsignificant estimates of effect. The JELIS trial[19] as well as the GISSI-Prevenzione trial[3] however, found a reduction in major cardiovascular events. The absence of benefit in the more recent trials raises the possibility that the effects of ω-3 FA are determined by some as yet unquantified external factor.

The overview identified no effect of fish oil on the overall risk of stroke, although there was a trend toward harm for intracerebral hemorrhage. This is an effect that might be anticipated on the basis of the known effects of ω-3 FA on bleeding time and platelet aggregation.[38–40]

The conduct of the analyses on tabular data extracted from the original trial reports was a limitation of our study design. Access to the original trial datasets would likely uncover additional outcome events from trials that did not publish data on each of the outcomes we studied. This would increase the power of the analyses by raising the number of events available as well as permitting analyses based on more directly comparable definitions than has been possible here. Analyses done on individual participant data would also allow for much more sophisticated exploration of the effects in different patient subgroups, and provide a better understanding of the sources of heterogeneity in the trial findings. A notable deficit in the current data are the systematic reporting

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of side effects. Total adverse events, although mostly fairly benign, were clearly higher with fish oil, and if the benefits are smaller than previously believed the risk-benefit trade-off will require more careful evaluation. Therapies that ameliorate cardiovascular risk, such as antihypertensives, statins, and antiplatelet agents have become prevalent and potent over time and, therefore, trials, such as the ORIGIN trial that include patients with moderate cardiovascular risk at baseline, are likely to comprise patients that are on these therapies. This might further dilute the detectable effect of ω-3 FA. Finally, the generalizability of the overview findings may be questioned, given that aside from a handful of trials,[18,19] the data derive entirely from the secondary prevention setting and white populations.

In conclusion, these results raise further uncertainty about the net effects of ω-3 fish oil therapy and reinforce the importance of the forthcoming ASCEND[41] and R&P[42] trials. Although it is probably reasonable for patients with existing vascular disease who are currently using fish oil to continue to do so, better evidence is required to support the more widespread promulgation of this strategy, particularly among lower risk patients. Individuals with high triglyceride levels or IgA nephropathy may be especially worthy of investigation, and higher rather than lower doses seem more likely to produce benefit. Further research in the primary prevention setting would be welcome given the potential implications of evidence about fish oil intake to dietary advice about fish consumption in the general population.

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