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

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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 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;5:808-818.)

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 data4–8 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.5,7,8 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 statement11 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, 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.
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 THE STUDY 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 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, nature of intervention (dietary change or supplement), control and, 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. 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. The I² 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 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. The recent ORIGIN trial 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. Seventeen were multicenter trials, and 2 were exclusively studies of primary prevention. The trials were variously conducted in the United States, the United Kingdom, Europe, and Japan.

Three trials assessed the effect of dietary advice and the remainder, the effects of fish oil supplements. Fourteen used supplements comprising a combination of eicosapentaenoic acid and docosahexaenoic acid,
Table 1. Baseline Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion Criteria</th>
<th>Treatment Group</th>
<th>Design/Location</th>
<th>Mean Follow-Up, y</th>
<th>No. of Patients</th>
<th>Mean Age, y</th>
<th>Male, %</th>
<th>Hypertension, %</th>
<th>Diabetes mellitus, %</th>
<th>Primary or Secondary Prevention</th>
<th>No. of Composite CV Events</th>
<th>No. of All Cause Mortality</th>
<th>No. of Coronary Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>DART study (1989)</td>
<td>Men &lt;70 post acute AMI</td>
<td>Dietary advice</td>
<td>Randomized, UK</td>
<td>2</td>
<td>2033</td>
<td>56.55</td>
<td>100</td>
<td>24</td>
<td>NR</td>
<td>Secondary</td>
<td>276</td>
<td>224</td>
<td>NR</td>
</tr>
<tr>
<td>Lyon Diet heart Study (1994)</td>
<td>Men and women &lt;70 post AMI within past 6 mo</td>
<td>Dietary advice</td>
<td>Randomized, France</td>
<td>1.25</td>
<td>605</td>
<td>53.5</td>
<td>91</td>
<td>NR</td>
<td>NR</td>
<td>Secondary</td>
<td>NR</td>
<td>28</td>
<td>22</td>
</tr>
<tr>
<td>IgA nephropathy (1994)</td>
<td>Biopsy proven IgA nephropathy, urinary protein excretion of ≥1 g/d, serum Cr≤3.0 mg/dL and survival &gt;2 y</td>
<td>EPA/DHA 1680/970</td>
<td>Placebo, US</td>
<td>3</td>
<td>106</td>
<td>37</td>
<td>91</td>
<td>58</td>
<td>NR</td>
<td>Secondary</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>CART study (1999)</td>
<td>Patients for elective coronary angioplasty</td>
<td>EPA/DHA 900/780</td>
<td>Corn oil as Placebo</td>
<td>0.5</td>
<td>500</td>
<td>59.7</td>
<td>77.6</td>
<td>34</td>
<td>8.6</td>
<td>Secondary</td>
<td>NR</td>
<td>4</td>
<td>NR</td>
</tr>
<tr>
<td>GISSI-Prevenzione (1999)</td>
<td>Patients with recent AMI</td>
<td>EPA/DHA 850/882</td>
<td>Placebo, Italy</td>
<td>3.5</td>
<td>5664</td>
<td>59.4</td>
<td>85</td>
<td>35</td>
<td>15</td>
<td>Secondary</td>
<td>584</td>
<td>529</td>
<td>NR</td>
</tr>
<tr>
<td>Effect of Dietary Omega-3 fatty acids on coronary atherosclerosis (1999)</td>
<td>Patients hospitalised for coronary angiography</td>
<td>Fish oil, 1650–3300 mg</td>
<td>Placebo, Germany</td>
<td>2</td>
<td>223</td>
<td>52.35</td>
<td>80</td>
<td>49</td>
<td>NR</td>
<td>Secondary</td>
<td>9</td>
<td>NR</td>
<td>4</td>
</tr>
<tr>
<td>High dose n-3 fatty acids introduced early after AMI (2001)</td>
<td>Patients post AMI</td>
<td>EPA/DHA 1700/1764</td>
<td>Corn oil as Placebo</td>
<td>1.5</td>
<td>300</td>
<td>64</td>
<td>79</td>
<td>24</td>
<td>10</td>
<td>Secondary</td>
<td>78</td>
<td>46</td>
<td>NR</td>
</tr>
<tr>
<td>Dietary advice for men with angina (2003)</td>
<td>Men &lt;70 with angina</td>
<td>Dietary advice</td>
<td>Sensible eating</td>
<td>6</td>
<td>1528</td>
<td>61.1</td>
<td>100</td>
<td>49</td>
<td>12</td>
<td>Secondary</td>
<td>NR</td>
<td>250</td>
<td>NR</td>
</tr>
<tr>
<td>FAATI (2005)</td>
<td>Patients with ICD at high risk for fatal ventricular arrhythmias</td>
<td>EPA 2600 mg</td>
<td>Placebo, US</td>
<td>1</td>
<td>402</td>
<td>65.5</td>
<td>83</td>
<td>NR</td>
<td>NR</td>
<td>Secondary</td>
<td>NR</td>
<td>25</td>
<td>NR</td>
</tr>
<tr>
<td>SOFA trial (2006)</td>
<td>Men and women with 1 true spontaneous VT or VF in past 3 mo and either had or were receiving ICD</td>
<td>Fish oil EPA/DHA 464335</td>
<td>Placebo, Europe</td>
<td>0.9753</td>
<td>546</td>
<td>61.5</td>
<td>84</td>
<td>51</td>
<td>16</td>
<td>Secondary</td>
<td>NR</td>
<td>22</td>
<td>4</td>
</tr>
<tr>
<td>OPACH study group (2006)</td>
<td>Patients with CVD and stabilized on HD for 6 mo</td>
<td>EPA/DHA 765/638</td>
<td>Placebo, Denmark</td>
<td>1.53</td>
<td>206</td>
<td>67</td>
<td>65</td>
<td>78</td>
<td>24</td>
<td>Secondary</td>
<td>121</td>
<td>64</td>
<td>17</td>
</tr>
<tr>
<td>JEUS trial (2007)</td>
<td>Patients with hypercholesterolemia</td>
<td>EPA 1800 mg and statin</td>
<td>Placebo and statin</td>
<td>4.6</td>
<td>18645</td>
<td>61</td>
<td>31</td>
<td>35</td>
<td>16</td>
<td>Primary and secondary</td>
<td>586</td>
<td>551</td>
<td>145</td>
</tr>
</tbody>
</table>
Table 1. (Continued)

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

EPA indicates eicosapentaenoic acid, DHA, docosahexaenoic acid.
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 \(\omega-3\) Fatty Acids on Clinical Outcomes

Composite Cardiovascular Outcome
For the primary composite cardiovascular outcome, 12 studies involving 57 936 participants2,3,9,10,16,18,19,21–23,30,31 recorded 8254 events (Figure 2). There was no clear effect of \(\omega-3\) 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.2,3,9,16,18,19,22–27,30 Of these studies, 8 separately reported 1496 sudden deaths among 49 971 participants.1,10,16,17,19,22,24,25 Treatment with \(\omega-3\) 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 participants2,3,10,16–19,21–30 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 of \(\omega-3\) FA reducing 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 participants2,16,19,21–25,31 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 participants3,16,19,21–23,31 reported on stroke outcomes. There were a total of 1369
Table 2. Quality Assessment of Trials Included in the Systematic Review and Meta-Analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Randomization Process Described</th>
<th>Randomization Process Achieved</th>
<th>Allocation Concealment Described</th>
<th>Allocation Concealment Adequately Achieved</th>
<th>Similarity of Baseline Characteristics</th>
<th>Eligibility Criteria Described</th>
<th>Double-Blinding Described</th>
<th>Completeness of Follow-Up/Loss to Follow-Up Described</th>
<th>Intention-To-Treat Described</th>
<th>Completion Rate (Treatment/Placebo)</th>
<th>Jadad Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>DART study (1989)</td>
<td>No</td>
<td>No</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>6.8/6.9</td>
<td>1</td>
</tr>
<tr>
<td>Lyon Diet heart Study (1994)</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
<td>3</td>
</tr>
<tr>
<td>IgA nephropathy (1994)</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
<td>3</td>
</tr>
<tr>
<td>CART study (1999)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>78%</td>
<td>0</td>
</tr>
<tr>
<td>GISSI-Prevenzione (1999)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Reported</td>
<td>2</td>
</tr>
<tr>
<td>Effect of Dietary Omega-3 fatty acids on coronary atherosclerosis (1999)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
<td>4</td>
</tr>
<tr>
<td>High dose n-3 fatty acids introduced early after AMI (2001)</td>
<td>No</td>
<td>NR</td>
<td>No</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>NR</td>
<td>2</td>
</tr>
<tr>
<td>Dietary advice to men with angina (2003)</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>NR</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td>Fish oil Supplementation and risk of VT and VF in patients with implantable defibrillators (2005)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>98%/94%</td>
<td>4</td>
</tr>
<tr>
<td>FAATI (2005)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>86%</td>
<td>3</td>
</tr>
<tr>
<td>SOFA trial (2006)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>89%/91%</td>
<td>4</td>
</tr>
<tr>
<td>OPACH study group (2006)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>74%/78%</td>
<td>4</td>
</tr>
<tr>
<td>JELUS trial (2007)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>99%/99%</td>
<td>3</td>
</tr>
<tr>
<td>GISSI-Prevenzione HF (2008)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>NR</td>
<td>2</td>
</tr>
<tr>
<td>Omega (2010)</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>88%</td>
<td>4</td>
</tr>
<tr>
<td>Efficacy and safety of prescription n-3 FA for the prevention of recurrent symptomatic AF (2010)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>88%</td>
<td>4</td>
</tr>
<tr>
<td>Alpha Omega (2010)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>90%/92%</td>
<td>4</td>
</tr>
<tr>
<td>SU.FOL.OM3 (2010)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>90%/90%</td>
<td>4</td>
</tr>
<tr>
<td>Diet and Omega 3 Intervention trial (2010)</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>94%</td>
<td>4</td>
</tr>
<tr>
<td>ORIGIN Trial</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>88%</td>
<td>4</td>
</tr>
</tbody>
</table>
events. Of these 6 studies, 3 provided a further subclassification into strokes of ischemic and hemorrhagic origin.\textsuperscript{19,22,23} 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\textsuperscript{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.\textsuperscript{25,27,28} There was evidence of moderate heterogeneity across the included trials (I\textsuperscript{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.\textsuperscript{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\textsuperscript{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,\textsuperscript{33} although the long-term data were not included in our meta-analysis.

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

**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. 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 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, but the neutral outcomes of recent large trials 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
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 compared with corn oil or olive oil identified significant deficit in the current data are the systematic reporting of the sources of heterogeneity in the trial findings. A more sophisticated exploration of the effects in different patient subgroups, and provide a better understanding of the sources of heterogeneity in the trial findings.

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 as well as the GISSI-Prevenzione trial 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.

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

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

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.
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, 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.

Acknowledgments

S. Kotwal, M. Jun, D. Sullivan, V. Perkovic, and B. Neal were responsible for the design of the study. S. Kotwal and M. Jun were responsible for data collection and analysis. All authors were responsible for interpretation and manuscript preparation. All authors contributed to data interpretation and critical revision of the publication. S. Kotwal had full access to all data in the study and takes responsibility for the integrity of the data and accuracy of the analysis.

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Disclosures

D. Sullivan reports educational and advisory consultancy to Pfizer, Merck Schering Plough, AstraZeneca, Abbott, Amgen, and Roche, as well as research projects involving Pfizer (2007), Merck Schering Plough (2010), Abbott (2005), Sanofi-Aventis (2010), and AstraZeneca (2009). V. Perkovic reports his employer has received grants for clinical trials from Baxter, Johnson and Johnson, Novartis, Roche, and Servier; lecture fees from Abbott, AstraZeneca, Roche, and Servier; serving on a grant review panel for Baxter and on a steering Committee for Abbott. B. Neal reports receiving consulting fees from Pfizer, Roche, and Takeda; grant support from Johnson and Johnson, Merck Schering Plough, Servier, and United Healthcare Group; lecture fees and travel reimbursements from Amgen, AstraZeneca, GlaxoSmithKline, Pfizer, Roche, Sanofi-Aventis, Servier, and Tanabe; and being a member of advisory boards for Pfizer and Roche. The other authors report no conflicts.

References

21. Svensson M, Schmidt EB, Jørgensen KA, Christensen JH; OPACH Study Group. N-3 fatty acids as secondary prevention against cardiovascular


Omega 3 Fatty Acids and Cardiovascular Outcomes: Systematic Review and Meta-Analysis
Sradha Kotwal, Min Jun, David Sullivan, Vlado Perkovic and Bruce Neal

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Supplementary Material

Search strategy:

Medline

1. Exp fish oils/
2. Exp fatty acids, omega-3/
3. (omega 3 fatty acids).tw
4. (fatty acids).tw
5. (Omega 3$).tw
6. (Fatty acid$).tw
7. Exp alpha linolenic acid/
8. Exp docosahexaenoic acids/
9. Exp eicosapentaenoic acid/
10. Or/1-9
11. Exp Clinical Trial/
12. Exp Random allocation/
14. Exp Double Blind Method/
15. (random$ adj5 allocation$).tw
16. (random$ adj5 trial$).tw
17. (blind$ adj5 method$).tw
18. Or/11-17
19. Exp Cardiovascular disease/
20. Exp Heart failure/
21. (Cardiovascular death).tw
22. Exp Myocardial infarction/
23. Exp Stroke/
24. Exp Coronary disease/
25. Revasculari$ation.tw
26. Exp Arrhythmia/
27. Exp Sudden death/
28. (cardiovascular outcome$).tw
29. Exp Mortality/
30. Mortali$tw
31. Exp Chronic kidney failure/
32. Exp Renal insufficiency/
33. Exp Kidney failure/
34. (kidney disease$).tw
35. (renal failure).tw
36. (renal outcome$).tw
37. Exp Albuminuria/
38. (serum creatinine).tw
39. Exp Creatinine/
40. Exp Cancer/
41. Or/19-40
42. 10 and 18 and 41
43. Limit 42 to all adults <19 plus years>
44. Limit 43 to human
Embase

1. Exp omega 3 fatty acid
2. Exp fish oil
3. Exp linolenic acid
4. docosahexaenoic acid
5. icosapentaenoic acid
6. clinical trial
7. Randomization
8. single blind procedure
9. double blind procedure
10. Randomized controlled trial
11. Cardiovascular disease
12. Heart failure
13. Heart infarction
14. Coronary artery disease
15. Revascularization
16. Heart arrhythmia
17. Sudden death
18. Stroke
19. Mortality
20. Chronic kidney disease
21. Chronic kidney failure
22. Kidney disease
23. Creatinine
24. Neoplasm
25. Kidney failure
26. 1 or 2 or 3 or 4 or 5
27. 6 or 7 or 8 or 9 or 10
28. Or/11-25
29. 26 and 27 and 29
30. Limit to humans and adult and aged

Cochrane Central Register of Controlled Trials

1. Exp fatty acids, Omega-3/
2. Exp fish oils/
3. Exp cardiovascular disease/
4. Exp Heart failure/
5. Exp myocardial infarction/
6. Exp stroke/
7. Exp coronary disease/
8. Exp myocardial revascularization/
9. Exp kidney failure/
10. Exp renal insufficiency/
11. Exp Albuminuria/
12. Exp neoplasms/
13. Exp mortality/
14. 1 or 2
15. Or/3-13
16. 14 and 15
Supplementary Figure 1 Begg’s funnel plot for the assessment of publication bias in studies examining the effects of omega 3 free fatty acids on cardiovascular outcomes (p=0.775)
Supplementary Figure 2: Begg’s funnel plot for the assessment of publication bias in studies examining the effects of omega 3 free fatty acids on all-cause mortality (p=0.325)