



# Effects of Omega-3 Fatty Acids on Cardiovascular Disease

## Summary

### Introduction

Since the first cross-cultural epidemiological studies in the 1970s<sup>1,2</sup> the body of evidence supporting a role for omega-3 fatty acids in the prevention of cardiovascular disease (CVD) has continued to increase. However, the beneficial effects of omega-3 fatty acids are not consistently observed in all epidemiological studies.

In this report, we review information from experimental and observational studies that investigate the effect of dietary or supplemental omega-3 fatty acids on clinical outcomes. More specifically, we examine how dietary or supplemental omega-3 fatty acids affect particular CVD outcomes such as myocardial infarction and stroke, and investigate whether omega-3 fatty acids can play a role in primary and secondary prevention of these outcomes. In addition, we examine evidence of adverse events and drug interactions associated with omega-3 fatty acids. The report also includes an analysis of dietary intake of omega-3 fatty acids based on the third National Health and Nutrition Examination Survey (NHANES III) database.<sup>3,4</sup> Using NHANES III data, we have determined the mean intake of omega-3 fatty acids in the U.S. population and various subpopulations and whether there is a difference in the mean intake of omega-3 fatty acids between adults with and without cardiovascular disease.

This evidence report is one of three reports prepared by the Tufts-New England Medical Center (Tufts-NEMC) Evidence-based Practice Center (EPC) concerning the health benefits of omega-3 fatty acids on cardiovascular diseases. These reports are among several that address

topics related to omega-3 fatty acids, and that were requested by the Office of Dietary Supplements, National Institutes of Health, through the EPC Program at the Agency for Healthcare Research and Quality (AHRQ). Three EPCs—the Tufts-NEMC EPC, the Southern California/RAND EPC, and the University of Ottawa EPC—each produced evidence reports. To ensure consistency of approach, the three EPCs collaborated on selected methodological elements, including literature search strategies, rating of evidence, and data table design.

### Methods

#### Key Questions

Key questions addressed by this report include one general question and three questions specific to CVD:

##### General Question

1. What are the mean and median intakes of docosahexaenoic acid (DHA, 22:6 n-3), eicosapentaenoic acid (EPA, 20:5 n-3), docosapentaenoic acid (DPA, 22:5 n-3), alpha linolenic acid (ALA, 18:3 n-3), fish, fish oil, and omega-6 fatty acids, and what is the mean and median omega-6 to omega-3 fatty acid ratio, in the U.S. population?
  - a. Do consumption levels differ among subpopulations?

##### Cardiovascular Disease Questions

1. What is the efficacy or association of omega-3 fatty acids (DHA, EPA or ALA supplements, and fish consumption) in reducing CVD events (including all-cause mortality, CVD



mortality, non-fatal CVD events, and new diagnosis of CVD)?

- a. What is the efficacy or association of omega-3 fatty acids in preventing incident CVD events in people without known CVD (primary prevention) and with known CVD (secondary prevention)?
  - b. How does the efficacy or association of omega-3 fatty acids in preventing incident CVD events differ in subpopulations, including men, pre-menopausal women, post-menopausal women, and different age groups?
  - c. What are the effects of potential confounders—such as lipid levels, body mass index, blood pressure, diabetes, aspirin use, hormone replacement therapy, and cardiovascular drugs—on associations found in prospective cohort studies?
  - d. What is the relative efficacy of omega-3 fatty acids on different CVD outcomes? Can the CVD outcomes be ordered by strength of treatment effect of omega-3 fatty acids?
2. Omega-3 fatty acid variables and modifiers:
- a. What is the efficacy or association of specific omega-3 fatty acids (DHA, EPA, ALA), and different ratios of omega-3 fatty acid components in dietary supplements, on CVD outcomes?
  - b. Does the ratio of omega-6 to omega-3 fatty acid intake affect the efficacy or association of omega-3 fatty acid intake on CVD outcomes?
  - c. How does the efficacy or association of omega-3 fatty acids on CVD outcomes differ by source (e.g., dietary fish, dietary oils, dietary plants, fish oil supplement, flax seed supplement)?
  - d. How does the efficacy or association of omega-3 fatty acids on CVD outcomes differ by different ratios of DHA, EPA, and ALA?
  - e. Is there a threshold or dose-response relationship between omega-3 fatty acids and CVD outcomes?
  - f. How does the duration of intervention or exposure affect the treatment effect of omega-3 fatty acids on CVD outcomes?
  - g. Are treatment effects or association of omega-3 fatty acids on CVD events sustained after the intervention or exposure stops?
  - h. What is the effect or association of baseline dietary intake of omega-3 fatty acids on the efficacy of omega-3 fatty acid supplements on CVD outcomes?
  - i. Does the use of medications for CVD and/or CVD risk factors (including lipid lowering agents and diabetes medications) affect the efficacy or association of omega-3 fatty acids?

3. Adverse events and drug interactions:

- a. What adverse events related to omega-3 fatty acid dietary supplements are reported in studies of CVD outcomes and markers?
- b. What adverse events related to omega-3 fatty acid dietary supplements are reported specifically among diabetics and people with CVD in studies of CVD outcomes and markers?
- c. What interactions between omega-3 fatty acid dietary supplements and medications are reported in studies of CVD outcomes and markers?
- d. What interactions between omega-3 fatty acid dietary supplements and medications are reported specifically among diabetics and people with CVD in studies of CVD outcomes and markers?

### **Method to Assess the Dietary Intake of Omega-3 Fatty Acids in the U.S. Population**

Data from the NHANES III database were analyzed using SAS<sup>®</sup>-callable SUDAAN<sup>®</sup>, version 7.5.6 (Research Triangle Institute, Research Triangle Park, NC). All analyses incorporated sampling weights that adjusted for unequal sampling probabilities. Variance estimations were made with the WR (sampling with replacement) method. Each denominator has 49 degrees of freedom. Simple linear regression was used to test the significance of the differences in the daily intake of the polyunsaturated fatty acids between groups. The adjusted means for categorical covariates in the regression model were calculated with the least square method. Statistical significance of the correlation between the dependent variables (e.g., intake of ALA) and independent variables (e.g., sex groups, age groups, CVD groups) were calculated with the Wald chi-square statistics.

### **Literature Search for Omega-3 Fatty Acids and Cardiovascular Disease**

To address the three key questions related to CVD, we conducted a comprehensive literature search and used the Ovid search engine for all preliminary searches on the MEDLINE<sup>®</sup> database. The final searches used six databases, including MEDLINE<sup>®</sup> from 1966 to week 2 of February 2003, PreMEDLINE<sup>®</sup> February 7, 2003, EMBASE from 1980 to week 6 of 2003, Cochrane Central Register of Controlled Trials 4th quarter of 2002, Biological Abstracts 1990-December 2002, and Commonwealth Agricultural Bureau Health from 1973 to December 2002. Additional publications were identified from reference lists and review and primary articles, and from domain experts, the Technical Expert Panel (TEP), and the other two EPCs.

## Selection Criteria and Screening Process

**Abstract and full article screening.** All abstracts identified through the literature search were screened using eligibility criteria developed in conjunction with the TEP. We included all English language original experimental or observational studies that evaluated any potential source of omega-3 fatty acids in at least five human subjects regardless of the study outcomes reported in the abstract. In addition, we excluded abstracts that clearly included only subjects who had a non-CVD-related condition (e.g., cancer, schizophrenia, or organ transplant). Reports published only as letters or as abstracts in proceedings were also excluded. All abstracts were categorized to one or more of the key questions or as rejects.

Articles that passed the abstract screening process were retrieved and the full articles were screened for eligibility. We accepted randomized controlled trials (RCTs) or prospective cohort studies with a minimum of 1-year followup to address CVD outcome questions. We also accepted case-control studies and cross-sectional studies that assessed the prevalence of CVD in populations with varying levels of omega-3 fatty acid consumption.

**Selection of studies for adverse events and drug interactions.** Human studies that were analyzed for clinical outcomes (for this report) or for risk factors (for the accompanying report, *Effects of Omega-3 Fatty Acids on Cardiovascular Risk Factors and Intermediate Markers of Cardiovascular Disease*) were reviewed for data on adverse events and drug interactions.

We looked for studies that evaluated potential interactions between omega-3 fatty acid supplements and commonly used drugs, including but not limited to hormone replacement therapy, diabetes medications, aspirin, and anticoagulants. In the studies that reported serious adverse events such as clinical bleeding, we note the concurrent medications that the subjects were taking.

**Data extraction process.** From each qualified study, we extracted information about the study design, population demographics, the intervention of exposure, and outcomes. For randomized controlled trials, we extracted information about randomization and blinding status to assess methodological quality. For prospective cohort studies, we extracted data on the estimates of various levels of fish or fish oil consumption and the associated effect.

## Results

### Population Intake of Omega-3 Fatty Acids in the United States

The intake of omega-3 fatty acids in the population varies. Corrected for energy intake, men consume significantly less ALA than women, adults more than youths, and subjects with

a history of CVD less than those without CVD. Based on analyses of a single 24-hour dietary recall in NHANES III, only 25 percent of the U.S. population reported any amount of daily EPA or DHA intake.

### Effects of Omega-3 Fatty Acid Supplements or Fish Consumption on Cardiovascular Disease Outcomes

We screened over 7,464 abstracts that were indexed as English language articles concerning humans. Based on this initial review, we retrieved and screened 768 full text articles for potentially relevant human data. We subsequently examined 118 articles that passed our screen for studies that might have CVD clinical outcome data, identifying 39 unique studies that fulfilled our inclusion criteria for reporting mortality or CVD clinical outcomes with a followup duration of 1 year or longer (interim reports or articles reporting different outcomes from the same overall study were counted as a single study).

The 39 studies included 12 RCTs, 22 prospective cohort studies of at least 1 year in duration, 4 case-control studies, and 1 cross-sectional study. All of these studies quantified or estimated the intake of fish or omega-3 fatty acids (including fish oil or ALA supplements) and assessed the effects of their consumption on CVD outcomes in the general (primary prevention) or CVD (secondary prevention) populations.

**Secondary prevention studies.** We reviewed 11 RCTs and one prospective cohort study that reported outcomes on CVD populations. Together, the trials included over 16,000 patients and each lasted between 1.5 to 5 years.

Four trials used fish oil (EPA+DHA) supplements in a dosage that ranged from 0.27 to 4.8 g/d.<sup>5-8</sup> The methodological quality was generally good. The largest trial<sup>9</sup> reported that fish oil (EPA + DHA) reduces all-cause mortality and CVD outcomes but does not affect stroke. Other trials that evaluated fish oil supplements reported similar results on CVD and stroke outcomes. A fifth RCT, which was the only multi-arm RCT identified,<sup>9</sup> directly compared mustard seed oil (containing ALA), fish oil, and non-oil placebo. It found that both oil treatments were efficacious in reducing CVD outcomes compared to placebo but found no difference between the two supplements; however, the methodological quality of this study was poor.

Six trials were diet or fish dietary advice trials. Four of the dietary studies generally of poor quality reported estimates of the amount of ALA consumed (1.8 to 6.3 g/d)<sup>10-13</sup> and two reported an estimate of EPA (2.4 to 2.7 g/week) consumed. Two large ALA trials reported reduction of all-cause mortality and CVD events.<sup>11,12</sup> Another study, the smallest ALA trial,<sup>13</sup> had a very low all-cause or CVD mortality event rate (0.6 percent) over the 2-year study duration and found no beneficial effect from increased ALA intake.

Six RCTs<sup>5,9,11,12,14,15</sup> reported data on sudden death. Four of the six studies reported a significant or near-significant large reduction of this outcome (risk ratio [RR] = 0.06 to 0.55).<sup>5,9,11,12</sup> The reduction of sudden death was observed in both the fish oil group as well as in the ALA group. However, the quality of the ALA trials was poor.<sup>9,11,12</sup> A new report by Burr et al. found that those taking fish oil supplements experienced an increase in sudden death risk. The methodological quality of this trial was also poor.<sup>15</sup>

Six trials reported contradictory data on stroke. The control groups reported that strokes occurred in 0 percent to 3 percent of the subjects during the study. The three omega-3 fatty acid supplements trials<sup>5,7,8</sup> reported trends of increased strokes, whereas the three diet/dietary advice trials<sup>11-13</sup> reported trends of fewer strokes. No result from these studies was statistically significant.

One study consistently reported no beneficial effect of omega-3 fatty acid on any of the CVD outcomes.<sup>6</sup> It randomized a total of 300 patients to 1.7 g/d of EPA+DHA or an equivalent amount of corn oil and followed subjects for 1.5 years.

The single prospective cohort study<sup>16</sup> also reported an at least 50 percent relative risk reduction of all cause mortality with any amount of fish intake compared with subjects who consumed no fish.

**Primary prevention studies.** Twenty-two prospective cohort studies, four case-control studies, one cross-sectional study, and one RCT<sup>17</sup> reported data on outcomes in general populations. These studies were conducted in many parts of the world including the United States, China, Japan, and countries in the Mediterranean and Northern Europe. The methodological quality of most of the studies within their study design category was good. Most of the cohorts had several thousand subjects and study duration ranged from 4 to 30 years. Most of the large cohort studies found that fish consumption reduces all-cause mortality and CVD events, although several studies reported no significant or negative results. A significant benefit for stroke was reported in only one study.<sup>18</sup> The only RCT,<sup>17</sup> which evaluated ALA in a large general population, lasted 1 year and yielded no significant results. Presumably, subjects in this study had high background omega-3 fatty acid levels because of characteristically large consumption of fish in their native lands.

For each study, outcomes in terms of CVD deaths, cardiac deaths, and myocardial infarction (MI) were similar. Most of the large cohort studies reported significant reduction of clinical events. Among the large studies, only the Physicians' Health Study<sup>19</sup> consistently reported no beneficial effect from fish consumption.

Two prospective cohort studies<sup>19,20</sup> reported data on sudden death. These studies provided estimates of both fish and fish oil consumption. The Physicians' Health Study, which followed

20,551 subjects for 12 years, reported an approximately 50 percent overall relative risk reduction even with a small amount of fish intake (>0.3g of fish oil per month or eating fish once a month).<sup>19</sup> A smaller study also found significant reduction of arrhythmic deaths at higher levels of fish intake. However, in the same study, opposite results were observed with consumption of fried fish or fish sandwiches.<sup>20</sup> A case-control study of 827 subjects in the United States also reported a significant inverse association of sudden death with increasing fish intake.<sup>21</sup>

Nine prospective cohort studies and one case-control study provided data on stroke. Five of the cohort studies estimated the amount of fish oil consumed and eight estimated fish intake. These studies included the large U.S. cohorts of the Nurses' Health Study,<sup>22</sup> Health Professionals Study,<sup>18</sup> and the Physicians' Health Study<sup>23</sup> which followed subjects for 14, 12, and 4 years, respectively. Together, these three studies comprised a total of about 145,000 men and women. Only the Health Professionals Study reported a significant reduction of ischemic strokes with any level of fish consumption above the lowest quintile. In the Nurses' Health Study, there was a non-significant trend of decreased strokes with increasing fish consumption. Other studies showed a weak benefit, no benefit, or an increased risk of strokes. The fish oil estimates and fish estimates gave similar results.

Overall, the evidence from the primary and secondary prevention studies supports the hypothesis that consumption of omega-3 fatty acids (EPA, DHA, ALA), fish, and fish oil reduces all-cause mortality and various CVD outcomes such as sudden death, cardiac death (coronary or MI death), and MI, although the evidence is strongest for fish or fish oil.

**CVD question 1a.** We identified one RCT and 22 prospective cohort studies that provided data on primary prevention. Eleven RCTs and one prospective cohort study provided data on secondary prevention. These studies were summarized in previous sections.

**CVD question 1b.** CVD question 1b. concerns the efficacy or association of omega-3 fatty acids and prevention of incident CVD events in selected subpopulations. There were no subgroup data from RCTs to address differences between men and women. However, the proportion of women in RCTs was small, four cohort studies and one case-control study reported data on men and women separately. Overall, these studies found no consistent difference in the effect of omega-3 fatty acids on CVD outcomes between men and women.

A report based on NHANES I that separately analyzed data for men and women found a trend of decreased stroke with increasing fish consumption for women between ages 45 and 74, but not for men.<sup>24</sup>

The Adventist Health Study, which grouped subjects into those who ate fish less than once a week and those who ate more, did not find a beneficial effect of fish intake on all-cause

or coronary-disease mortality. There were also no differences between men and women.<sup>25</sup> Osler et al. reported a similar finding.<sup>26</sup> However, Nagata et al. followed a cohort of 13,355 men and 15,742 women in Japan for 7 years and reported that the association between soy intake and all-cause mortality was significant in women (trend  $P = 0.04$ ) and marginally significant (trend  $P = 0.07$ ) in men, and the association between fish oil intake and all-cause mortality was significant for women (trend  $P = 0.01$ ) and non-significant for men (trend  $P = 0.38$ ).<sup>27</sup> Results from a cross-sectional study reported that ALA intake was inversely associated with the prevalence odds ratio of coronary artery disease using age and energy-adjusted quintiles of ALA.<sup>28</sup> Significant trends were found for men and women after adjusting for multiple variables.

The Nurses' Health Study, a large prospective cohort study of women, reported no subgroup analyses based on menopausal status or age groups.<sup>29,30</sup> The Adventist Health Study found no difference in all-cause mortality between fish intake of less than or greater than once a week in a subgroup of 603 oldest old ( $\geq 84$  years old) subjects.<sup>31</sup>

**CVD question 1c.** Key question 1c. asks about the effects of potential confounders on associations found in prospective cohort studies. Because only summary data about potential confounders was available (and this data was insufficiently detailed), we were unable to analyze the effect of confounders across studies. To fully answer question 1c. would require a meta-analysis of the original data from the cohort studies.

Only one study addressed the potential confounding effect of a specific variable (i.e., aspirin treatment).<sup>32</sup> Iso et al. analyzed subgroups of women in the Nurses' Health Study who took aspirin regularly versus those who did not.<sup>30</sup> Stroke events were reduced in both groups at most levels of fish intake, and a statistically significant trend with increasing fish consumption was found in women who did not take aspirin regularly.

**CVD question 1d.** There is limited evidence from RCTs and cohort studies to answer question 1d. regarding the relative efficacy or association of omega-3 fatty acids on different CVD events. Because of large heterogeneity across studies and inconsistent reporting of outcomes, it is difficult to compare the magnitude of outcomes across studies. Evidence from RCTs is strongest for all-cause mortality and sudden death, while evidence from the cohort studies is strongest for all-cause mortality, cardiac mortality, MI, and stroke. All the prospective cohort studies showed a similar order; however, the effect on total mortality (assuming benefits are restricted to CVD) were directly dependent on the proportion of all deaths due to CVD. Given the inconsistent effects in RCTs on stroke, and less consistent effects in cohort studies, the relative effect of omega-3 fatty acids on stroke is uncertain.

**CVD question 2a.** Question 2a. asks about the efficacy of different omega-3 fatty acids and ratios of omega-3 fatty acid components on CVD outcomes. This question is difficult to

answer since data on specific omega-3 fatty acids are very limited. The only RCT that directly compared ALA (at 2.9 g/d) with fish oil (EPA+DHA at 1.8 g/d) found that total cardiac deaths, nonfatal MI, and CVD events in the fish oil group were significantly lower compared to placebo. There were no differences in CVD outcomes between the two supplements.<sup>9</sup>

**CVD question 2b.** To determine whether the ratio of omega-6 to omega-3 fatty acid intake affects the efficacy of omega-3 fatty acid intake on CVD events, we identified two cohort studies<sup>33,34</sup> and one cross-sectional study<sup>28</sup> that reported associations between omega-3/omega-6 ratios and CVD outcomes.

Using data from the Multiple Risk Factor Intervention study, Dolecek divided omega-3/omega-6 ratios into five quintiles and reported near significant trends ( $P < 0.1$ ) for reduction of CVD and all-cause mortality. The mean omega-3/omega-6 ratio for the entire cohort was 0.133, the lowest quintile was 0.086 and the highest was 0.199.<sup>34</sup> Djousse et al. analyzed the association of omega-6/omega-3 ratios with quintiles of ALA intake on the prevalence odds ratio of coronary artery disease.<sup>28</sup> They reported a near significant association in the lowest tertile of omega-6/omega-3 ratio (higher ALA intake) with higher levels of ALA intake (trend  $P = 0.06$ ). Near significant reduction of the prevalence odds ratio of coronary artery disease was also found for the combination of the highest tertile of linoleic acid (LA, 18:2 n-6) and highest tertile of ALA.

In another study, Hu et al. stratified the omega-6/omega-3 ratio into two groups (low ratio group, median = 5.9; high ratio group, median = 9.2) and compared the effect of increasing amounts of omega-3 fatty acids (ALA, EPA, DHA). They reported that the inverse association with risk of CVD appeared to be somewhat stronger in the high ratio group compared to the low-ratio group, but a test for interaction was not statistically significant.<sup>29</sup>

**CVD question 2c.** Question 2c. asks how the efficacy or association of omega-3 fatty acids on CVD events differs by source (e.g., dietary fish, dietary oils, dietary plants, fish oil supplement, and flax seed supplement). To address this question, we needed to compare the efficacy of different sources of omega-3 fatty acids; however, the available studies were too heterogeneous in terms of study design, duration, background diet, methods of assessment, and outcomes to allow even indirect comparisons that were meaningful. Overall, fish oil is more efficacious than ALA. In the Nurses' Health Study, Hu performed primary analyses of ischemic heart disease outcomes using ALA intake quantified from all sources and repeated the same analyses using ALA from plant sources only.<sup>35</sup> Results for fatal ischemic heart disease outcomes were similar for the two ALA estimates.

**CVD question 2d.** Comparative efficacy of different ratios of DHA, EPA, and ALA can be reliably assessed only by

concurrent multi-arm comparisons in a randomized trial setting. No data were found to answer this question.

**CVD question 2e.** Question 2e. asks whether there is a threshold or dose-response relationship between omega-3 fatty acids and CVD events. To answer this question we identified several RCTs that reported beneficial effects from fish oil at a relatively low daily dose. The GISSI-Prevention trial used a fish oil (EPA+DHA) dose of 0.85 g/d and reported significant beneficial effects on CVD outcomes. Leng et al. showed that no beneficial effect was observed with a daily EPA dosage of 0.27 g/d in a 2-year trial involving 120 CVD patients.<sup>7</sup> Nilsen et al. used 1.7 g/d EPA+DHA which showed no effects on CVD outcomes.<sup>6</sup> Two ALA diet trials<sup>11,12</sup> which estimated a daily ALA intake of 1.8 or 1.9 g/d, reported significant or near-significant beneficial effects on CVD outcomes compared with control diets with estimated ALA intakes of 0.67 or 0.8 g/d, respectively.

**CVD question 2f.** To address this question about how the duration of intervention or exposure affects the treatment effect of omega-3 fatty acids on CVD events, we examined the duration of the RCTs in the CVD population and found that it ranged from 1.5 to 5 years. The largest RCT (13,000 subjects), which had a 1-year duration in the non-CVD population, found no effect on any of the CVD outcomes.<sup>17</sup> The duration of the prospective cohort studies ranged from 4 to 30 years. Among the cohort studies, those that followed subjects for less than 6 years demonstrated no significant benefit for clinical effects. The Physicians' Health Study reported no significant effect on CVD outcomes after 4 years of followup.<sup>23</sup>

**CVD question 2g.** Only one study,<sup>36</sup> which is the 10-year followup to the Diet and Reinfarction (DART) study, addressed the question of whether treatment effects of omega-3 fatty acids on CVD events were sustained after the intervention stopped. This study showed no long-term benefit from being in the fish advice group in the DART study.

**CVD question 2h.** Question 2h. asks about the effect or association of baseline dietary intake of omega-3 fatty acid supplements on CVD events. We found only a few dietary RCTs that provide some information about the benefits of adding omega-3 fatty acids to baseline intake. Two ALA diet trials,<sup>11,12</sup> each of 2-years duration, estimated daily ALA intake at 1.8 or 1.9 g/d and reported significant or near-significant beneficial effects on multiple CVD outcomes compared to control diets with an estimated ALA intake of 0.67 or 0.8 g/d. In an RCT of dietary fish advice, Burr et al. estimated the amount of EPA in the control group (0.6 g/week) and the interventional group (2.4 g/week).<sup>37,38</sup>

**CVD question 2i.** None of the RCTs were specifically designed to determine whether the addition of CVD risk factor

medications (lipid lowering agents or diabetes medications) affects the efficacy of omega-3 fatty acids. Similarly, none of the cohort studies specifically adjusted for CVD risk factor medications.

## Adverse Events Associated With Omega-3 Fatty Acid Consumption

We reviewed 395 human clinical articles for reports of adverse events associated with omega-3 fatty acid consumption. We rejected 247 articles because they did not provide adverse event information and two additional articles that were duplicate publications. Of the remaining 148 articles in the general and CVD populations, a variety of adverse events were reported in 71 studies, but 77 RCTs and non-randomized comparison studies reported no adverse events.

One hundred and forty-two articles provided data on about 20,000 subjects, about one-half of whom were exposed to different forms and dosages of omega-3 fatty acid for durations ranging from 1 to 364 weeks. The majority of the studies evaluated a few dozen subjects for less than 6 months. The GISSI-Prevention trial, that had over 11,000 subjects and a followup duration of 182 weeks, reported the largest number of adverse events.<sup>5</sup> This trial contributed about one-third of the total number of gastrointestinal complaints (in both the omega-3 fatty acid arm and the control arm) from all the studies combined, and also contributed almost all the withdrawals due to adverse events (although the reasons for withdrawals were not given). This discordance suggests that most other studies did not adequately report adverse event data, especially concerning withdrawals.

None of the serious adverse events that were reported associated omega-3 fatty acid consumption with events such as death, life-threatening illness, or significant disability or handicap, although two studies reported that some important bleeding occurred with fish oil combined with aspirin or warfarin.<sup>39,40</sup>

## Discussion

Overall, a number of studies offer evidence to support the hypothesis that fish, fish oil, or ALA supplement consumption reduces all-cause mortality and various CVD outcomes, although the evidence is strongest for fish or fish oil.

The overall methodological quality of the studies included in this evidence review was graded as good for fish oil (EPA+DHA), but RCT data for ALA was poor. The adverse events due to fish oil or ALA supplement consumption appear to be minor.

However, there is an imbalance in the design of studies available. Almost all of the evidence for health benefits of

omega-3 fatty acid in the general population (primary prevention studies) derives from cohort studies, whereas almost all the evidence, however limited, for secondary prevention derives from RCTs. The data for secondary prevention mostly derives from one very large study, and data on women are limited. The specific effects on different CVD outcomes (especially MI and stroke) are uncertain.

In addition, the studies were heterogeneous with regard to the methods of estimating fish or omega-3 fatty acid intake, background diets, background risk for heart disease, settings, and the methods of reporting results. For these reasons, the validity of applying the results of studies conducted in countries outside of the United States to the U.S. population is uncertain. Moreover, dietary intervention trials, such as DART,<sup>38</sup> the Lyon Heart,<sup>11</sup> and the Indian Experiment of Infarct Survival,<sup>12</sup> are limited by multiple and complex dietary changes in the trials that do not permit easy differentiation among components and make it difficult to determine which specific components or combinations of these diets are most beneficial. Furthermore, the optimal quantity and type of omega-3 fatty acid, and the optimal ratio of omega-3 to omega-6 fatty acid, if any, still remain undefined. Finally, different types of fish and the method of food preparation may cause different effects.

Therefore, future research needs to address all these lingering issues. Well-designed multinational trials that assess the effect of EPA+DHA on CVD outcomes during a long followup period are especially needed. RCTs should be performed in the general population since there is still a gap in information about the general versus CVD population. They should not only confirm the pharmacological approach of the GISSI-Prevention trial in countries with different background habits and risk, but should also explore in parallel the various mechanistic hypotheses. In addition, studies must adequately assess background diet and fish consumption, particularly the type of fish and method of preparation. Attempts should always be made to determine the effect of higher fish intake on the consumption of other foods in the diet, specifically meat and cheese (sources of saturated fat). In addition, the omega-3/omega-6 ratio should always be estimated and reported.

The potential effect of ALA is unknown. Current data sets are too limited for adequate assessment. To address this issue, a cardioprotective diet rich in ALA should be included in a comprehensive strategy to decrease cardiovascular morbidity and mortality, and more trials are needed to confirm the effect of ALA, independent of fish oil and fish intake, on the secondary prevention of CVD outcomes. The relative effect of ALA versus fish oil is also unknown and should be explored in the future studies.

The relative effect of ALA versus fish oil is not well defined. Comparative trials between these two supplements should be conducted. Given the abundance of soybean and canola oils

relative to fish in the diet, it would be useful to understand the economic and ecological impact of increased fish intake and the potential to initiate changes in the U.S. dietary patterns.

Our evidence review also indicates that there is little data concerning the needs of different high-risk subpopulations. Additional research should address questions about the effect of omega-3 fatty acid on CVD outcomes in specific populations, including people at high risk of sudden death or with diabetes, congestive heart failure, or other chronic diseases.

## Availability of the Full Report

The full evidence report from which this summary was taken was prepared for the Agency for Healthcare Research and Quality (AHRQ) by the Tufts-New England Medical Center Evidence-based Practice Center, Boston, MA, under Contract No. 290-02-0022. The full report is expected to be available in March 2004. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 94, *Effects of Omega-3 Fatty Acids on Cardiovascular Disease*. In addition, Internet users will be able to access the report and this summary online through AHRQ's Web site at [www.ahrq.gov](http://www.ahrq.gov).

## Suggested Citation

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