Chapter 4. Discussion

In this chapter, we discuss the main findings related to the general and cardiovascular disease (CVD) key questions addressed by this evidence report. We also describe limitations of the studies reviewed for the report and future research needs.

Overview

This report summarizes scientific evidence regarding the effects of dietary or supplemental omega-3 fatty acids on CVD outcomes including mortality (e.g., all-cause mortality, sudden death, and deaths due to myocardial infarction and stroke), and summarizes evidence of associations between omega-3 fatty acids and CVD outcomes. To assess the role of omega-3 fatty acids in reducing CVD outcomes, we reviewed the clinical literature on primary and secondary prevention. We analyzed the third National Health and Nutrition Examination Survey (NHANES III) database to assess the dietary intake of omega-3 fatty acids in the US population, and to determine whether there is a difference in the mean intake of omega-3 fatty acids between various sub-populations and between adults with and without CVD. To evaluate adverse events and potential drug interactions associated with omega-3 fatty acids, we reviewed studies that reported any occurrences of these events.

We screened over 7,464 abstracts and retrieved 768 full text articles. We found and analyzed 39 unique studies that reported mortality or CVD clinical outcomes and that had a follow-up duration of 1 year or longer. These studies include 12 randomized controlled trials (RCTs) and 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 the fish or omega-3 fatty acid intake — including fish oil or alpha linolenic acid (ALA, 18:3 n-3) supplements — and assessed the effects of their consumption on CVD outcomes in the general (primary prevention) or CVD (secondary prevention) populations. Our analyses of adverse events and potential drug interactions are based on a review of 148 articles that reported these events.

Main Findings

The main findings of our analyses are presented below. Findings related to the dietary intake of omega-3 fatty acids in the US population are discussed first, followed by findings related to the effects of omega-3 fatty acids on CVD outcomes and adverse events associated with omega-3 fatty acid supplements.

Dietary Intake of Omega-3 Fatty Acids in the US

We analyzed the data from a single 24-hour dietary recall from the NHANES III database to determine the average US population intake of ALA, linoleic acid (LA, 18:2 n-6),

eicosapentaenoic acid (EPA, 20:5 n-3), and docosahexaenoic acid (DHA, 22:6 n-3). These analyses showed that the average intake of LA is 14 g/d (5.79 %kcal/d), of ALA is 1.33 g/d (0.55 %kcal/d), of EPA is 0.04 g/d (0.02 %kcal/d), and of DHA is 0.07 g/d (0.03 %kcal/d). Only 25% of the US population reported any amount of daily EPA or DHA intake. These results are similar to the estimates reported in the Multiple Risk Factor Intervention (MRFIT) study in the late 1970s, which estimated that the average intake of LA was 14.6 g/d, of ALA was 1.69 g/d, and of EPA+DHA+docosapentaenoic acid (DPA, 22:5 n-3) was 0.18 g/d. Intake estimates of ALA and EPA+DHA for the US population are much lower than estimates for the Japanese population (which has significantly fewer CVD events). Average Japanese intake in 1985 for ALA was 2.08 g/d, while the intake of EPA+DPA+DHA was 1.56 g/d [52].

Additional analyses of the NHANES III database showed that there are significant variations in the dietary intake of omega-3 fatty acids among different US sub-populations. Corrected for energy intake, men consume significantly less ALA than women, adults consume more ALA than youths, and subjects with a history of CVD consume less ALA than those without CVD. People who had a Poverty Index Ratio index (PIR) of ≤ 1.3 consumed less ALA and LA than people who had a PIR >1.3. Non-Hispanic whites, non-Hispanic blacks, and Mexican Americans all had a significantly higher intake of both ALA and LA compared to other groups.

Effects of Consumption of Omega-3 Fatty Acid from Fish or Overall Diet, or from Supplements of Fish Oil or ALA, on Cardiovascular Disease Outcomes

CVD outcomes of secondary prevention studies. We reviewed 11 RCTs and 1 prospective cohort study that reported outcomes in CVD populations. The trials lasted between 1.5 to 5 years and, together, included over 16,000 patients (mostly outside the US).

Five trials used fish oil (EPA+DHA) supplements with a dose ranging between 0.27 and 4.8 g/d. The largest trial reported that fish oil significantly reduces all-cause mortality (risk ratio [RR] = 0.79, 95% confidence interval [CI] = 0.66-0.93) and CVD outcomes, but has no effect on stroke [35]. Other trials that evaluated fish oil supplements reported similar results on CVD and stroke outcomes. One multi-arm trial compared fish oil, mustard oil (ALA), and non-oil placebo [38]. In this trial, both fish oil and mustard oil were efficacious in reducing CVD outcomes, although no difference was seen between the 2 oils. The methodological quality of 4 RCTs for EPA+DHA[34-37] was generally good (summary quality grade A or B), but the multi-arm trial from India [38] was of poor quality (grade C).

The other 6 trials, involving about 4,000 patients, were diet/dietary advice trials. The duration of these trials ranged from 2 to 5 years. Four of the dietary studies reported estimates of the amount of ALA consumed (1.8 to 6.3 g/d) in the intervention arms [42-44 45]. All of the trials were of poor quality. The applicability of these trials ranged from CVD-I (highly applicable) to CVD-III (limited applicability). The subjects were mostly MI survivors or those at significant CVD risk. The 2 largest ALA trials included over 600 patients each and reported reductions in all-cause mortality and CVD events [43,44]. The study by Singh 2002 was conducted among patients in India. Two-thirds of the participants were vegetarians, which limits the applicability of the study results to the US population. The smallest ALA trial, which had a duration of 2 years, reported a very low all-cause or CVD mortality event rate (0.6%) and found no beneficial effect from increased ALA intake[45]. An early trial [42], which included 412 post MI patients

randomized to diet and control groups, experienced a significantly lower combined incidence of fatal/non fatal MI and sudden death.

Two all-male trials from the UK reported estimates of EPA intake[41,47] of 2.4 g and 2.7 g, respectively. Both of these trials were rated as poor quality studies (grade C), and their applicability was rated CVD-II (relevant subgroups). The first trial[47] found significant reduction of all-cause mortality with a relative risk of 27%. However, the 10-year follow-up to this study found no long-term benefit of fish advice in the same group of patients taking a similar amount of EPA [48]. The second, more recent, trial [41] found that those taking fish oil supplements had an increased sudden death risk.

The single prospective cohort study [46] also reported an at least 50% relative risk reduction of all cause mortality with any amount of fish intake compared with subjects who consumed no fish.

CVD outcomes of primary prevention studies. Twenty-two prospective cohort studies and 1 RCT reported data on outcomes in general populations. Among the cohort studies, there were considerable differences in the populations studied, the diet of the study populations, and the estimates of fish or omega-3 fatty acids consumed. The duration of the cohort studies ranged from 4 to 30 years. The number of subjects in the studies ranged from 272 to as many as 223,170. The cohort studies have been conducted worldwide, including in the US, China, Japan, the UK, and Scandinavian and Mediterranean countries. Eight cohort studies were conducted in the US. Most of the large cohort studies found that fish consumption reduced all-cause mortality and CVD events, although several studies reported no significant or negative results. Many of the studies that found significant CVD benefit also reported a statistically significant inverse association with fish intake. A significant benefit for ischemic stroke was reported in only 1 study [63]. The only RCT that evaluated ALA in a large general population lasted 1 year and yielded no significant results. This lack of significance is possibly due to high background omega-3 fatty acids, but there is no evidence available to explain absence of effect. The authors of this study reported that the mortality event rates observed in the study were lower than expected when compared with the general population [49].

The largest relative reduction of CVD outcomes was seen in trials that reported on sudden death. The relative risk of CVD events in these studies ranged from 0.06 to 0.55. An inverse association between estimated fish or fish oil consumption and a reduction in sudden death events was also reported in several prospective cohort studies [56,58,60]. One study reported on the effects of fried fish or fish sandwich consumption on CVD outcomes. This study found a trend of increased numbers of arrhythmic death with increased consumption [60].

Overall, the evidence supports the hypothesis that consumption of omega-3 fatty acids (EPA, DHA, or ALA) from fish or from supplements of fish oil reduces all-cause mortality and various CVD events, although the evidence is strongest for fish and fish oil supplements.

Adverse Events Associated with Consumption of Omega-3 Fatty Acid

The FDA has ruled that up to 3g of EPA+DHA is safe to be included in the food supply of Americans without fear of adverse events[86].

Gastrointestinal symptoms associated with fish oil or ALA supplements are the most commonly reported adverse events in RCTs and non-randomized comparison studies. These symptoms may require dose reduction or discontinuation of the agent in some individuals.

Clinical bleeding is a theoretical concern, but there was no difference in the overall number of bleeding events between the supplement groups and the control groups. Overall, adverse events related to consumption of fish oil or ALA supplements appear to be minor.

Limitations

Our analyses and estimates of omega-3 fatty acids from the NHANES III database are based on a single 24-hour dietary recall. The dietary method is less than optimal for estimating intake of omega-3 fatty acids from foods that are not consumed on a daily basis, such as seafood. Given large variations in intake from day to day, multiple 24-hour recalls are considered to be best suited for most nutrition monitoring [9]. Two additional 24-hour recalls were completed by NHANES III participants age 50 years and older. While it would have been ideal to adjust for the within-person day-to-day variations in dietary intake using all 24-hour recalls [23], we did not have access to the additional data due to resource limitations. We also did not consider additional estimates of omega-3 fatty acid intake developed by other studies, particularly those that focused on the intake of omega-3 polyunsaturated fatty acids (PUFAs) from seafood, in large part because they do not represent national samples.

Overall, the methodological quality of the RCTs was from fair to poor whereas the quality of prospective cohort studies for omega-3 fatty acids was generally graded as good. However, the studies demonstrate a number of limitations, which are highlighted below:

- Almost all of the evidence for the health benefits of omega-3 fatty acids for the general population (i.e., for primary prevention) was derived from cohort studies, whereas almost all the evidence for secondary prevention was derived from RCTs of limited duration. Given the recent observation that flawed assessments of the health benefits of hormone replacement therapy were based on observational studies that were not later verified by RCTs, we propose that recommendations regarding omega-3 fatty acids as a dietary supplement should be developed using RCT evidence.

- The data for secondary prevention appear to be reliable but they are derive from 1 very large study [35]. Data on women are limited. Data on the exact interventions that are effective (and relative efficacy of different preparations) are very limited. The specific effects on different CVD outcomes (especially MI and stroke) are uncertain.

- The single RCT for primary prevention that evaluated ALA supplements in the general population [49] lasted only 1 year and the study subjects had a lower mortality event rate than the general population. Although this was a large study with over 13,000 subjects, the results were not particularly useful given the short trial duration and the small number of clinical events. The finding of no effect might be explained by high background EPA+DHA in the native populations; however, we have no data to show that is the case. Future RCTs should incorporate sufficient study duration into their design.

- Many of the studies on fish intake do not report the type of fish and the method of preparation. Such information is important, since different types of fish have different amounts of EPA+DHA and the method of preparation may affect the fish oil content.

- The data on the effect of ALA on CVD outcomes is limited. There is only 1 comparative trial of ALA and fish oil and its findings are highly suspect.

- Most of the evidence for primary prevention was derived from prospective cohort studies that examined fish intake, not fish oil supplements.

- The studies included in this evidence review were heterogeneous with regard to the methods of estimating fish or omega-3 fatty acid intake, background diets, settings, and the methods of reporting results. For these reasons, the validity of applying the results of studies conducted in countries outside of the US to the US population is uncertain, and methods used to assess background diet and fish consumption must be improved and standardized.

- Data are limited concerning the effects and associations of omega-3 fatty acids with CVD outcomes in different subpopulations.

Research Recommendations

- In general, future studies of omega-3 fatty acid should include the following:

  - Omega-6/omega-3 ratio should always be estimated and reported

  - Attempts should 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)

  - Future prospective cohort studies and diet trials on fish consumption should place special emphasis on collecting data on fish consumed, type of fish, and method of preparation

- Well-designed, multi-center RCTs are needed to assess the effect of omega-3 fatty acid consumption on CVD outcomes in primary and secondary prevention settings. The trial design should include a period of long-term follow-up for 3 to 5 years so that long-term effects of omega-3 fatty acids can be monitored.

- Additional research should address questions about the effect of omega-3 fatty acid consumption on CVD outcomes in specific populations, including patients with diabetes and other chronic diseases.

- The potential effect of ALA is unknown. Current data sets are of poor quality and are too limited for adequate assessment. More trials are needed to confirm or report the effect of ALA, separate from fish or fish oil, on CVD outcomes. We need to know more about the potential interaction of ALA with EPA+DHA.

- The relative effect of ALA versus fish oil is not well defined. Comparative trials between these 2 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 change in US dietary patterns.