PS and viscous fiber may be used in combination, but there are few studies that have administered them together to investigate their combined influences on atherogenic cholesterol. Both PS and viscous fibers reduce atherogenic cholesterol, in part, by reducing cholesterol absorption.[98,119] Viscous fibers also lower bile acid re-absorption.[119] Therefore, there is uncertainty regarding whether their effects are fully additive. PS products should not be used in combination with a cholesterol absorption inhibitor drug (ezetimibe) because both work through interference with cholesterol absorption and the addition of PS to ezetimibe therapy did not have an incremental effect on the LDL-C response.[123]

Long-chain omega-3 fatty acids

The long-chain polyunsaturated fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), both derived from marine sources, as well as the essential fatty acid, ALA, derived from plant sources, have been of scientific interest for decades. The history of the marine-derived omega-3 fatty acids dates back to the first studies conducted with Greenland Eskimos that reported that a low death rate from CHD was associated with a very high intake of seafood (around 400 g/day).[124,125] Recommendations for EPA and DHA are based on epidemiological and RCTs of both primary and secondary prevention of CVD and have evaluated both fish/seafood and omega-3 fatty acid supplements/fortified foods. The recommendation for ALA is based on the precept of meeting nutrient adequacy.

Evidence from prospective observational studies and some randomized clinical trials suggests that, compared with little or no intake, consumption of 250 to 550 mg/day of EPA and DHA is associated with a 36% lower risk of CHD death and reduced total mortality by 17% (summarized by Mozaffarian and Rimm[126]). Harris et al.[127] conducted a pooled analysis of observational studies and reported that the highest (approximately 566 mg/day) vs lowest intake of EPA + DHA was associated with approximately a 37% reduction in CHD mortality. These collective analyses formed the basis for the current dietary recommendations for EPA and DHA for the primary prevention of coronary disease.

The 2010 DGA recommended 250 mg/day of EPA and DHA[19] and the Academy of Nutrition and Dietetics recommends 500 mg/day.[128] The DGAC 2010 concluded:[19]

> "Moderate evidence shows that consumption of two servings of seafood per week (4 oz per serving), which provide an average of 250 mg per day of long-chain n-3 fatty acids, is associated with reduced cardiac mortality from CHD or sudden death in persons with and without CVD. An increase in seafood intake to two servings per week at 4 oz per serving is advised for high-risk (those with CVD) and average-risk persons, especially as the first presentation of CVD (MI, stroke) is frequently fatal or disabling. The quantity and frequency of seafood consumption is important, but the type of seafood (those providing at least 250 mg of long-chain n-3 fatty acids per day) also is critical."[19]

The recommendation for increased seafood intake can be met by consuming both farm-raised and wild-caught seafood, because, as a result of current aquaculture practices, they now contain approximately the same amounts of omega-3 fatty acids.[23]

The AHA issued 2020 Impact Goals to improve the cardiovascular health of all Americans, which included a primary dietary recommendation for fish: ≥ two 3.5-oz. servings per week (preferably oily fish).[129]

Secondary prevention

For secondary prevention of CHD, Harris et al.[130] noted that there have been 9 large randomized trials with omega-3 fatty acid supplements, of which 4 reported positive (favorable) results,[131–134] 4 were neutral,[135–138] and 1 study was negative (i.e., suggested an adverse effect).[139] The positive trials were conducted between the 1980s through the early 2000s and showed that EPA and DHA intakes between 0.85 and 1.8 g/day were associated with reduced risk for CVD events. The trials with neutral results were reported between 2010 and 2012 and provided 376 to 840 mg/day of EPA and DHA. Five systematic reviews and meta-analyses have been conducted evaluating omega-3 long-chain PUFA intake for the secondary prevention of CHD. Two of these meta-analyses were published before 2010[140,141] and reported evidence of benefits in patients with existing CHD; however, the 3 meta-analyses published after 2010 did not report benefits.[142–144] The Rizos et al.[144] meta-analysis has been criticized because the authors used a critical value for declaring statistical significance of 0.006 to account for multiple comparisons instead of the traditional P value of 0.05. As noted by Harris,[145] "Without this statistical maneuver, their data led to the conclusion that fish oil supplementation significantly reduced risk for cardiac death by 9% [RR of 0.91; 95% CI 0.85–0.98; $P = .01$]."

Several possible reasons for the lack of an effect in the most recent trials have been put forth.[145] First, it may be that EPA and DHA are not effective, although there is considerable evidence that argues against this possibility. Second, increased consumer awareness of the benefits of fish and fish oil have increased background intakes and an additional 1 g of supplemental omega-3 fatty acids daily may not confer any further benefit. Notably, no measures of omega-3 status, such as plasma or red blood cell levels of omega-3, were included in most of the large-scale trials. Thus, it is not possible to determine whether a subset of patients with low omega-3 status might have benefitted. Third, in more recent clinical trials of higher risk subjects, standards of medical care were different from those in earlier decades, resulting in large percentages of study