Conclusions and recommendations from the symposium, Beyond Cholesterol: Prevention and Treatment of Coronary Heart Disease with n–3 Fatty Acids1–3

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ABSTRACT
After the symposium “Beyond Cholesterol: Prevention and Treatment of Coronary Heart Disease with n–3 Fatty Acids,” faculty who presented at the conference submitted manuscripts relating to their conference topics, and these are presented in this supplement. The content of these manuscripts was reviewed, and 2 conference calls were convened. The objective was to summarize existing evidence, gaps in evidence, and future research needed to strengthen recommendations for specific intakes of n–3 fatty acids for different conditions relating to cardiovascular disease. The following 2 questions were the main items discussed. What are the roles of n–3 fatty acids in primary versus secondary prevention of coronary heart disease? What are the roles of n–3 fatty acids in hypertriglyceridemia, in the metabolic syndrome and type 2 diabetes, and in sudden cardiac death, cardiac arrhythmias, and vulnerable plaque? Each area was summarized by using 2 general categories: 1) current knowledge for which general consensus exists, and 2) recommendations for research and policy. Additional references for these conclusions can be found in the articles included in the supplement. Am J Clin Nutr 2008;87(suppl):2010S–2S.

ROLE OF n–3 FATTY ACIDS IN PRIMARY VERSUS SECONDARY PREVENTION OF CORONARY HEART DISEASE

Current knowledge for which a general consensus exists

Consistent evidence indicates that n–3 fatty acids contribute substantially to lowering coronary heart disease (CHD) mortality risk attributable to reduced arrhythmic death in the primary prevention setting and after an initial cardiac event (secondary prevention). Relative risk reduction appears similar in both of these settings given similar findings of 2 secondary prevention randomized controlled trial (RCTs) and 15 prospective observational studies. Absolute risk reduction will be greater in populations at higher absolute risk. Thus, the benefits associated with secondary prevention are likely to be greater than those for primary prevention. Some evidence suggests that n–3 fatty acids may reduce nonfatal CHD events, particularly at higher doses of consumption, but this body of evidence is smaller than that for prevention of fatal events. Based on data summarized in the article by Mozaffarian in this supplement (1), a daily average intake of ≈250 mg of eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA) appears to be effective in decreasing risk of fatal cardiac events. Most investigations have studied the combination of EPA plus DHA (either dietary or supplements) for prevention and treatment of cardiovascular disease, and insufficient evidence exists to make strong conclusions about optimal relative amounts of each of these individual fatty acids (2). In the JELIS (Japan EPA Lipid Intervention Study), which showed benefits for nonfatal coronary events, highly purified EPA supplements (1.8 g/d) were used in a Japanese population already consuming high amounts of n–3 fatty acids but with very low rates of coronary death (3). Findings from this trial support similar effects on nonfatal events in primary and secondary prevention. Effects of increased α-linolenic acid, the plant-based n–3 fatty acid, on decreasing cardiovascular disease risk have been studied to a much lesser extent in both primary and secondary prevention settings; some evidence suggests potential benefit, but results have not always been consistent (4). The benefits of increasing EPA and DHA intakes to at least 250 mg/d may never be tested formally in a primary prevention RCT, but based on our experience with exercise and smoking cessation, neither of which has been tested with formal RCTs in primary prevention, reasonable recommendations can be made on the basis of the coherence and breadth of the existing evidence.

Recommendations for research and policy

- Consumption of 250 mg DHA and EPA per day, from either dietary or supplement sources, should be part of management for primary prevention of CHD death and after a coronary event to reduce risk of CHD death. Given the uncertainty of this estimated target intake and no evidence for...

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harm at higher intakes. A target of 250–500 mg/d EPA plus DHA is reasonable. Differences based on relative amounts of EPA versus DHA, if any, still need to be determined.

- Optimal doses and relative amounts of EPA and DHA, as well as intake durations, need to be determined for prevention of nonfatal coronary events.

- The effects of α-linolenic acid on coronary artery disease prevention require further study.

HYPERTRIGLYCERIDEMIA

Current knowledge for which a general consensus exists

All faculty agreed that marine n-3 fatty acids (ie, DHA and EPA) are effective in lowering elevated plasma triacylglycerol concentrations. However, the dose of n-3 fatty acid required to achieve these effects (3–4 g/d) is much higher than the doses (0.25–1 g/d) needed for reduction in coronary mortality in secondary and primary prevention (5). Also, there is little evidence that reducing elevated plasma triacylglycerol concentrations by any means will have a significant effect on cardiovascular disease mortality and morbidity. Of note, in both the GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto)-Prevenzione and JELIS trials, there were only relatively minor changes in plasma triacylglycerol concentrations and no changes in other lipoprotein fractions in the control compared with treatment group, but there were significant reductions in cardiac events (3, 6). Thus, the major mechanisms underlying the beneficial effects of n-3 fatty acids in the prevention and treatment of coronary artery disease appear to be distinct from effects on lowering plasma triacylglycerol concentrations.

Recommendations for research and policy

- Studies are required to determine whether the higher doses of long-chain n-3 fatty acids required for triacylglycerol-lowering effects (3–4 g/d) provide additional benefits in reducing adverse cardiovascular endpoints compared with lower doses (eg, 0.5–1 g/d), which do not substantially lower plasma triacylglycerol concentrations.

- Studies are required to determine whether n-3 fatty acid supplementation will provide equal or better efficacy and safety than supplementation with other triacylglycerol-lowering agents (eg, fibrates or niacin) when given either alone or in combination with statins.

- Studies are required to determine whether a combination of n-3 fatty acids and current cardiovascular drugs will improve the efficacy and safety of the latter.

- Studies are required to further characterize the dose-response relation between lowering of triacylglycerol concentrations and the total amounts of n-3 fatty acids.

- Studies are required to better establish the hypotriacylglyceremic mechanism(s) of action of EPA and DHA in humans.

METABOLIC SYNDROME AND TYPE 2 DIABETES

Current knowledge for which a general consensus exists

n-3 Fatty acids are effective in diminishing several risk factors associated with insulin resistance and the metabolic syndrome (7). Examples include lowering of blood triacylglycerol concentrations, modest decreases in systolic and diastolic blood pressures, and possible anti-inflammatory effects (7). Lowering of blood triacylglycerol concentrations can be associated with increasing HDL cholesterol levels and increased LDL particle size (but the latter does not typically manifest until triacylglycerol concentrations of <150 mg/dL are achieved) (7). There is little evidence that n-3 fatty acids (at doses of 3 g/d or below) affect insulin sensitivity, and there remain concerns that at higher doses it may somewhat worsen (7).

Recommendations for research and policy

- Dose-response studies are needed to determine the effects of n-3 fatty acids on cardiometabolic risk factors in patients with the metabolic syndrome and type 2 diabetes. Upper levels of intake for benefits of n-3 fatty acids need to be established for these conditions.

- Inclusion of n-3 fatty acids as an adjunct to treatment in insulin resistance should be considered along with other interventions, including diet, increasing physical activity, and medications.

- The effects of coadministration of n-3 fatty acids with drugs known to benefit the metabolic syndrome should be explored.

- Given these individuals’ high risk of cardiovascular disease, modest consumption of EPA plus DHA (250–500 mg/d) is still recommended to reduce the risk of cardiac death.

SUDDEN CARDIAC DEATH, CARDIAC ARRHYTHMIAS, AND VULNERABLE PLAQUE

Current knowledge for which a general consensus exists

There is a strong body of evidence showing that n-3 fatty acids are effective in reducing the risk for sudden cardiac death, of which cardiac arrhythmias are a major contributor both for primary and secondary events (8). Small clinical trials suggest that n-3 fatty acids may be less effective for recurrent ventricular arrhythmias in patients with implantable cardioverter-defibrillator devices, but these studies may have been underpowered, and the appropriateness of the population with implantable cardioverter-defibrillator devices for testing the antiarrhythmic hypothesis has been questioned (9, 10). Most cardiac arrhythmias are associated with underlying coronary pathological conditions, which predispose to arrhythmias. These include ischemic events, obstruction of coronary arteries, and other pathways associated with vulnerable atherosclerotic plaque. Many of the individual mechanisms that contribute to vulnerable plaque have been shown to respond in a beneficial direction to n-3 fatty acids in in vitro studies and studies in animals (11). Nevertheless, in terms of a role in acute and chronic myocardial insult, most of these individual pathways have not been studied in the context of an overall role of n-3 fatty acids in the prevention, stabilization, and reversal of vulnerable plaque. Nonfatal acute coronary syndromes including nonfatal myocardial infarction may be good proxies for vulnerable plaque. Although the results from clinical trials, such as the JELIS trial, suggest that n-3 fatty acids supplementation could be associated with plaque stabilization, the GISSI trial did not show a clinically significant reduction in nonfatal myocardial infarction (3, 6).
Recommendations for research and policy

- Whereas reduced sudden death and arrhythmias are apparent in prospective observational studies and secondary prevention trials, more study is needed on the role and dosages of n-3 fatty acids for potential plaque stabilization.
- More biological/mechanistic studies are needed to define the effects of n-3 fatty acids on the factors that contribute to plaque instability.
- Emphasis needs to be placed on determining the individual roles of EPA and/or DHA and their doses in reducing risk for plaque rupture, cardiac arrhythmias, and sudden cardiac death.

GENERAL CONCLUSIONS

- Consumption of 250–500 mg DHA and EPA per day, from either dietary or supplement sources, should be part of management for primary prevention of CHD death and after a coronary event to reduce risk of CHD death. Although some evidence supports the efficacy of EPA and DHA for reducing nonfatal coronary events, the evidence is not as robust as that for fatal CHD reduction.
- Whereas the evidence for cardioprotective effects is strong for EPA and DHA, the body of evidence supporting a similar effect for α-linolenic acid is smaller and less consistent. More research on α-linolenic acid is still required as its evidence base does not include enough well-designed randomized trials.
- Given potential nonlinear (threshold) effects of n-3 fatty acids, the background consumption of n-3 fatty acids and the duration of these intakes need to be considered in planning and assessing results of clinical trials and population studies. In a recent editorial (12) reviewing the use of medications in primary prevention of coronary artery disease, longer-term use was associated with better outcomes “...suggesting the importance of duration of therapy in determining outcome. Earlier initiation of therapy appears to have durably mitigated the atherosclerotic process.” Thus, habitual consumption of n-3 fatty acids may be more beneficial than short-term consumption. Importantly, n-3 fatty acids need not be considered as a monotherapy in prevention of and/or treatment for cardiovascular disease. Rather, higher n-3 fatty acid intakes need to be considered as a biologically active partner to lifestyle changes and to medications that are used to prevent and treat cardiovascular disease. When used in the primary and secondary prevention of CHD, n-3 fatty acids are likely to have significant clinical and public health benefits.

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