N-3 Fatty Acids
Priority for Post-Myocardial Infarction Clinical Trials
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A large body of data points to potential benefits of N-3 polyunsaturated fatty acids in reducing the risk of cardiovascular disease (CVD). Available data suggest that higher intakes of N-3 fatty acids will reduce various forms of CVD, especially sudden cardiovascular death. These data derive from laboratory animal studies, epidemiological data, metabolic studies, and smaller clinical trials. The literature also contains other evidence that N-3 fatty acids may help to prevent or treat several non-cardiovascular diseases. This editorial nonetheless will limit itself to the cardiovascular system.

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N-3 polyunsaturated fatty acids are principally of 2 types: (1) a long-chain, 18-carbon atom fatty acid with 3 double bonds (α-linolenic acid), and (2) very long chain polyunsaturated fatty acids of 20 carbon atoms and 5 double bonds (eicosapentaenoic acid [EPA]) and of 22 carbon atoms and 6 double bonds (docosahexaenoic acid [DHA]). α-linolenic acid comes largely from plant oils; the primary sources of EPA and DHA are fish oils. The human body can convert a portion of dietary α-linolenic acid into EPA and DHA. The latter are labeled “essential” fatty acids because they are required for normal development and function of the retina and brain. Most putative health benefits of N-3 fatty acids are thought to derive from EPA and DHA. Nonetheless, adequate intakes of α-linolenic acid allow for formation of enough EPA and DHA to meet normal requirements.

N-3 fatty acids undoubtedly modify biochemical function in many systems. They enter membrane phospholipids and may alter membrane function there. They decrease the arachidonic acid content of cell membranes, which reduces eicosanoid production. Consequently, N-3 fatty acids can inhibit the synthesis of proinflammatory cytokines, eg, tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and IL-2; these in turn may destabilize atherosclerotic lesions. Moreover, N-3 fatty acids reduce aggregational properties of blood platelets, thereby interfering with thrombosis formation. They further appear to modify the electrical activity of heart muscle, possibly reducing the tendency for arrhythmias. In addition, N-3 fatty acids may moderately reduce blood pressure and favorably modify vascular neuroeffector mechanisms. Finally, in high doses, they reduce serum triglyceride levels, which could further reduce risk for CVD. Thus, if N-3 fatty acids have a beneficial influence on CVD risk, multiple mechanisms could be involved.

Prospective epidemiological studies bolster the evidence that N-3 fatty acids offer protection against CVD. The article by Hu et al1 provides support for this evidence. These workers examined the association between intake of fish and N-3 fatty acids and CHD and total mortality in 5103 women with type 2 diabetes. Multivariate analysis of records of diet composition revealed that higher intakes of fish and N-3 fatty acids are associated with a lower incidence of CHD and a lower total mortality.

Epidemiological studies of this type led both the United States Government panel on Dietary Guidelines of America 20009 and the Institute of Medicine’s Dietary Reference Intake panel10 to look on dietary N-3 fatty acids favorably with respect to CVD prevention. Even so, recommended dietary increases for the public were relatively moderate. Of interest, many prospective epidemiological studies found an association between higher intakes of fish and lower rates of CVD.1 Recent guidelines1,8,9 therefore went further to recommend that the general public should regularly consume fish as part of a healthy diet. Whether fish consumption correlates highly with intakes of EPA and DHA, however, has not been documented with certainty. For the public, recommendations for consumption of more fish or more plant products containing α-linolenic acid seem safe and perhaps beneficial. Some concern has been expressed that high consumptions of fish may result in too much mercury intake, which could be harmful;11 otherwise, recommendations for a higher fish intake seem reasonable.

Several clinical trials have been preformed to determine whether relatively high intakes of N-3 fatty acids will reduce the risk for CVD. The moderately positive results of these trials have persuaded some investigators to advise routine prescription of supplemental N-3 fatty acids in the form of fish oil-containing capsules to patients at high risk for CVD. A brief review of recent clinical trials supporting this position may therefore be worthwhile.

In the Diet And Reinforcement Trial (DART),12 2033 men who had suffered a myocardial infarction (MI) were divided into 2 groups. Half were advised to reduce fat intake, increase dietary fiber, and increase fatty fish intake. The other half received no dietary advice. The prescribed diet was reported to provide about 500 to 800 mg/d of very long chain N-3 fatty acids. Patients consuming prescribed amounts of fatty fish had a 29% reduction in all-cause mortality over the period of

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study. Fatal MIs seemingly declined more than in non-fatal infarctions. This raises the possibility that the benefit of fish oil is mainly a reduction in fatal MI perhaps fewer fatal arrhythmias. Much of the apparent benefit was ascribed to diet’s higher content of N-3 fatty acids.

Another trial suggestive of the benefit of N-3 fatty acids was the Lyon Diet Heart Study. This secondary prevention trial in 605 subjects tested efficacy of a Mediterranean-type diet rich in α-linolenic acid for reducing recurrent CVD events in post-MI patients. Participants were randomized to control and therapeutic diets. After follow-up of 46 months, both fatal and non-fatal MIs fell significantly in the study group, as did secondary CVD endpoints (unstable angina, stroke, heart failure, and CV embolism). The authors again attributed much but not all of the observed benefit to the higher content of α-linolenic acid in the therapeutic diet.14

The Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto miocardico (GISSI)-Prevenzione study15 examined the efficacy of a fish-oil supplement (1g/d), rich in EPA and DHA, on major CVD events in post-MI patients. GISSI was a larger trial than prior trials of N-3 fatty acids. Patients were randomized to supplements of N-3 fatty acids (n = 2836), vitamin E 300 mg daily (n = 2830), both (n = 2830), or none (n = 2828). They were followed-up for 3.5 years. Vitamin E had no beneficial effect. In contrast, the fish oil supplement reduced risk for the primary combined endpoint (death, non-fatal MI, and stroke) by about 15%. Follow-up analysis of this trial revealed an early favorable effect of N-3 fatty acids for total mortality and sudden death.16 The trial results again raised the possibility that the benefit of N-3 fatty acids results from their antiarrhythmic action.

In a smaller trial, Singh et al17 tested supplements of fish oil and mustard oil (rich in α-linolenic acid) on outcomes over 1 year in patients with recent MI. One hundred twenty-two patients received fish oil, 120 patients received mustard oil, and 118 patients received placebo. Although no benefit was observed for mustard oil, cardiac deaths in patients receiving fish-oil supplements were significantly lower than placebo.

These trials suggest efficacy of supplements (or high dietary intakes) of N-3 fatty acids in secondary prevention. Consequently, the National Cholesterol Education Program (NCEP)18 and a secondary prevention task force of the American Heart Association (AHA)19 listed use of fish-oil supplements in patients with established CHD as a therapeutic option. More recently, the AHA1 issued a stronger recommendation for supplemental N-3 fatty acids in patients with established CHD. Nonetheless, most clinical trialists would agree that the strength of this recommendation is much less robust than for other therapeutic recommendations for secondary prevention, namely, anti-platelet agents, cholesterol-lowering drugs, β-blockers, and angiotensin-converting enzyme inhibitors. Moreover, the medical profession is unlikely to embrace the recent AHA recommendation1 for supplemental fish oils without stronger clinical trial evidence of efficacy. The critical question therefore must be raised whether additional clinical trials are needed to test the efficacy of supplemental N-3 fatty acids in high-risk patients.

Several issues must be addressed before embarking on further randomized trials with fish oil supplements. The first is whether the evidence of efficacy to date justifies the investment. The best evidence on efficacy comes from the GISSI trial.15,16 It suggested that risk for major CVD events (CVD death, non-fatal MI, and non-fatal stroke) is reduced over a period of 3.5 years by about 20%. The greatest benefit seemingly occurred in cardiac death, coronary death, and sudden death.16 Reductions in these categories were in the range of 35% to 45%, and all were statistically significant. By contrast, only a modest, non-significant trend toward reduction in recurrent non-fatal MI was noted, with no reduction in non-fatal stroke.

Deeper analysis of the GISSI trial16 suggested that the greatest reduction in cardiac mortality occurred in the first 9 months after MI. Continued reduction thereafter was less pronounced. No benefit was observed in non-fatal MI during this time, implying that N-3 fatty acids are antiarrhythmic, but not plaque stabilizing or antithrombotic. This result is reminiscent of the benefits of β-blockers in post-MI patients. The findings of the GISSI trial seemingly support the need for a controlled clinical trial, but one that focuses on cardiac death and on the early period after MI.

The GISSI trial provides less support for a long-term, secondary prevention trial with supplemental N-3 fatty acids. Certainly, well-controlled short-term trials in the immediate post-MI period should be done first. The primary end-point should be cardiac death, and the trials should verify antiarrhythmic properties of N-3 fatty acids. Perhaps if such a trial(s) were strongly positive, consideration could be given to longer secondary prevention trials. Should longer trials eventually be contemplated, a model is the Heart Protection Study (HPS);20 this trial employed statin therapy in high-risk patients, ie, those with established CVD and/or with diabetes. This high risk gave it great statistical power to detect drug efficacy in a relatively small number of patients in subgroups. Still, GISSI results do not support a longer-term trial like HPS without prior results from a short-term trial. The next strongest trial after GISSI, DART,13 likewise supports a short-term trial of coronary mortality immediately after MI. Finally, the other clinical trials and even the prospective data, as indicated by Hu et al,8 seem to support a mortality benefit over a morbidity benefit.

Neither clinical trials nor prospective data at this time support a primary prevention trial with N-3 fatty acids. If the efficacy occurs mostly from antiarrhythmic properties, a primary prevention trial with a mortality end-point would simply require too many subjects treated for too long to attain a positive result. Priority for future trials seems best placed on shorter trials immediately after MI. Longer, secondary prevention trials with non-fatal endpoints are not a high priority, nor is a primary prevention trial.

In any short-term trial in post-MI patients, supplemental fish oil would have to be add-on therapy to other standard treatment, eg, antiplatelet drugs, β-blockers, cholesterol-lowering drugs, and angiotensin-converting enzyme inhibitors. All of these drugs may independently afford some benefit in reducing total mortality. They are well accepted as standard treatment; if N-3 fatty
acids are to be beneficial, their efficacy must exist over and above these accepted therapies.

Other issues should be addressed before N-3 supplements can be recommended as standard therapy. First, it is not known whether the efficacy, if any, of fish oil supplements resides with EPA or DHA. Second, the quality of current supplements of N-3 fatty acids available in the United States is not controlled by the Food and Drug Administration. Neither the efficacy nor safety of current supplements available to the public can be assured. Finally, there is the question of supply of N-3 supplements. If N-3 fatty acids were to prove to be a required therapy for standard of care, the need for their use could increase dramatically. At that point, availability of product and quality control of preparation would become major issues.

In summary, use of N-3 fatty acids in preventive cardiology is at a crossroads. Expert opinion in the dietary field\(^9\),\(^10\) now favors moderate increases in intakes of plant-derived \(\alpha\)-linolenic acid based on epidemiological evidence of benefit for CVD risk reduction. The costs of such a clinical trial to confirm this reasonable recommendation would be prohibitive. The same is true for “increased fish intake,” which likewise is based on epidemiological evidence. At the least, both of these recommendations are consistent with general dietary guidelines about “healthy eating patterns.” The AHA’s recent guideline\(^1\) for using fish-oil supplements for healthy eating patterns. The same is true for confirm this reasonable recommendation would be prohibitive. Neither the efficacy nor safety of current supplements available to the public can be assured. Finally, there is the question of supply of N-3 supplements. If N-3 fatty acids were to prove to be a required therapy for standard of care, the need for their use could increase dramatically. At that point, availability of product and quality control of preparation would become major issues.

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The AHA’s recent guideline\(^1\) for using fish-oil supplements for patients with established CHD is more problematic. Available evidence is suggestive of benefit in the immediate post-MI period, but a solid recommendation cannot be made without more definitive controlled clinical trials.

References


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