

## n-3 Long-chain polyunsaturated fatty acids reduce risk of coronary heart disease death: extending the evidence to the elderly<sup>1,2</sup>

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In terms of its potential impact on health in the Western world, the “omega-3” story may someday be viewed as one of the most important in the history of modern nutritional science. The readers of this Journal are no doubt familiar with the seminal investigations of Bang and Dyerberg (1) that suggested a link between the Eskimo intake of n-3 long-chain polyunsaturated fatty acids (LC-PUFAs) and a reduced risk of acute myocardial infarction. The outcomes of randomized trials testing the vitamin E-coronary heart disease (CHD) hypothesis were disappointing because they succeeded strong data from epidemiologic, pathophysiologic, animal, and human surrogate-endpoint studies that had made clinical benefit in CHD almost a foregone conclusion. In contrast, the evidence for a clinical benefit of n-3 LC-PUFAs on CHD is becoming stronger with each new report. Perhaps the most compelling evidence to date for both the inefficacy of vitamin E and the efficacy of n-3 LC-PUFAs has come from the GISSI-Prevenzione study (2). In this trial, 11 324 post-myocardial infarction patients were randomly assigned to receive eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) ethyl esters (850 mg/d), vitamin E (300 mg/d), both, or neither and were followed for 3.5 y. Although no statistically significant benefit was observed with vitamin E, the n-3 LC-PUFA group experienced significant decreases in risks of total mortality (20%), cardiovascular mortality (30%), and sudden death (45%). The evidence base for a cardioprotective effect of n-3 LC-PUFAs grows even richer with the report in this issue of the Journal by Lemaitre et al (3). In this case-control study nested in the Cardiovascular Health Study, the authors found a highly significant relation between serum phospholipid n-3 LC-PUFA concentrations and risk of fatal ischemic heart disease. A 1-SD increase above the mean serum phospholipid EPA+DHA concentration (ie, from 3.3% to 4.1% of total fatty acids) was associated with a 68% reduction in the relative risk of fatal ischemic heart disease. Lemaitre et al also found a significant 48% reduction in the relative risk of fatal CHD with the plant-derived, short-chain n-3 PUFA  $\alpha$ -linolenic acid (ALA). Because the average age of the participants in this study was 78 y, the Cardiovascular Health Study now extends to older Americans the findings reported for men a generation younger in the Physicians’ Health Study, in which whole-blood n-3 fatty acid concentrations were associated with a marked reduction in risk of sudden cardiac death (4). Thus, we now have supportive data across a wide age range in the primary prevention setting for a cardioprotective role for n-3 LC-PUFAs.

Compared with the evidence for a benefit of n-3 LC-PUFAs, the issue of benefit from ALA is far less clear, and the supporting data are largely epidemiologic. Two randomized, double-blind, placebo-controlled, prospective intervention trials examined the

effects on CHD endpoints of supplementation with oils rich in ALA. The Norwegian Vegetable Oil Experiment of 1965–1966 (5) was a primary prevention trial in which > 13 000 men aged 50–59 y were randomly assigned to receive a daily dose of 10 mL of either linseed or sunflower oil. The former provided 5.5 g ALA/d, whereas current US intake is  $\approx$ 1.4 g ALA/d (6). After 1 y, no significant difference between the groups was found for any cardiovascular endpoint. However, it is possible that the generally high fish oil intake of the Norwegian population (unfortunately not assessed in this study) afforded all the “omega-3-related” protection that was possible, and no further benefit could have been achieved. In the Indian Experiment of Infarct Survival (7), 360 patients admitted to the Moradabad Medical Hospital with suspected myocardial infarction were randomly assigned to receive either placebo, fish oil (1.8 g EPA+DHA/d), or mustard oil (2.9 g ALA/d) and were followed for 1 y. The authors reported significant benefits for several CHD endpoints in both the fish oil and mustard oil groups. However, the extremely high event rates in this study,  $\approx$ 10-fold greater than those observed after 1 y in the GISSI-Prevenzione study (8), cast some doubt on the findings. Finally, the Lyon Heart Study (9) suggested a possible link between ALA and reduced CHD risk. Unfortunately, there were many differences between the control and the ALA-enriched Mediterranean diets, rendering it impossible to ascribe the observed benefit to ALA alone. Because alternative explanations may apply in all of these studies, none has shown an unambiguous link between ALA supplementation and reduced risk of CHD.


The rationale for expecting a benefit from ALA is that it is the metabolic precursor of EPA and DHA. The extent of its conversion is controversial, however, even among investigators using similar tracer technologies. Emken et al (10) reported that  $\approx$ 15% of ALA is converted to EPA+DHA, whereas Pawlosky et al (11) published a radically different estimate of 0.2%. Further work is clearly needed to determine how much ALA is converted to EPA and DHA in adults *in vivo*.

The growing evidence supporting the view that n-3 LC-PUFAs reduce the risk of death from CHD can no longer be ignored. The dietary recommendation from the American Heart Association to consume 2 fish meals (preferably fatty fish) per week (12, 13) is well supported. Patients with documented CHD

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may need to go further, however. A target of 1 g EPA+DHA per day is both safe and prudent, but that amount can only with difficulty and persistence be obtained from fish alone. Fish oil capsules or foods fortified with n-3 LC-PUFAs may be needed to bridge the gap. Several questions remain, however. What is the role of ALA compared with n-3 LC-PUFAs in CHD risk reduction? What is the optimal dose and ratio of EPA and DHA? What is the mechanism by which these fatty acids modulate risk? Should the laboratory assessment of blood n-3 fatty acid concentrations be included as part of a 21st century CHD risk panel? And, perhaps most important, can n-3 LC-PUFA supplementation reduce the risk of death from CHD in a primary prevention population? 

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