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## n-3 Fatty Acids and Cardiovascular Events

**TO THE EDITOR:** In the Alpha Omega Trial, as reported by Kromhout et al. (Nov. 18 issue),<sup>1</sup> supplementation with a combination of n-3 eicosapentaenoic acid (EPA) and n-3 docosahexaenoic acid (DHA), n-3 alpha-linolenic acid (ALA), or both EPA-DHA and ALA did not significantly reduce the rate of major cardiovascular events among patients who had had a myocardial infarction and who were receiving conventional state-of-the-art therapy. In contrast to the Alpha Omega trial, the Lyon Diet Heart Study (LDHS), which also involved patients who had had a myocardial infarction, was stopped early because a clinical benefit from a margarine intervention

had been demonstrated.<sup>1,2</sup> In the LDHS, a canola-based margarine that was high in n-3 fatty acids, low in n-6 fatty acids, and high in n-9 fatty acids was the only study-supplied intervention. As in the Alpha Omega trial (Fig. 1 in the Supplementary Appendix, available with the full text of the article by Kromhout et al. at NEJM.org), the higher intake of n-3 ALA in the LDHS also increased the level of EPA.

In the Alpha Omega trial, the four study groups should have been reported separately, since in the comparison of ALA with and without EPA-DHA, intergroup differences were reduced owing to the increases in ALA-derived EPA. Moreover, the margarine in the Alpha Omega trial had 2.3 times as much n-6 linoleate as the margarine in the LDHS, which probably further weakened the power to demonstrate benefit.<sup>3</sup> Paraphrasing from a previous editorial: “only omega-3 trials that also reduced n-6 polyunsaturates found reductions in cardiovascular and all-cause mortality.”<sup>4</sup>

Plant-based ALA is abundant, increases EPA levels, and may well have contributed to the reduced incidence of arrhythmias in the Alpha Omega trial<sup>2,4,5</sup> (and Fig. 3 in the Supplementary Appendix of the article by Kromhout et al.). A subsequent trial with a (canola-rapeseed) margarine that is naturally low in n-6 fatty acids and high in n-3 ALA would avoid the confusing results of the Alpha Omega trial.

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No potential conflict of interest relevant to this letter was reported.

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**TO THE EDITOR:** In the Alpha Omega trial, the doses of fatty acids used were low (particularly the dose of EPA-DHA, which was 376 mg per day) and differed substantially from those in previous studies that showed a benefit with EPA-DHA (1 g per day in the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico [GISSI]-Prevenzione trial<sup>1</sup> and 1.8 g per day in the Japan Eicosapentaenoic Acid [EPA] Lipid Intervention Study [JELIS; ClinicalTrials.gov number, NCT00231738]<sup>2</sup>). In the latter study, patients were receiving concurrent statin therapy and had had a myocardial infarction more than 6 months previously (similar to patients in the Alpha Omega trial), but also had higher consumption of fish.

In addition, any potential benefit (such as that mediated by ALA and supported by findings in a recent epidemiologic study<sup>3</sup>) would be diminished when the outcomes of subjects taking the n-3 fatty acid supplements are compared with those of subjects taking the combination of placebo and an alternative fatty acid, instead of with the outcomes of subjects taking placebo alone. Furthermore, possible confounding effects of the intake of saturated and trans fatty acids on the development of atherosclerosis and its consequences<sup>4</sup> have not been excluded, despite randomization.

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No potential conflict of interest relevant to this letter was reported.

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**THE AUTHORS REPLY:** Both Vos et al. and Heazlewood et al. point out that we should have reported the results of the four study groups in the Alpha Omega trial separately. As we described in the Methods section of our article, the data were analyzed according to a prespecified analysis plan (see the Protocol, available with the article at NEJM.org). The first step in the analysis was to determine the incidence ratios for all four randomly assigned treatments. The primary and secondary outcomes did not differ among the four treatment groups, as shown by the Kaplan–Meier curves for the primary outcome of major cardiovascular events (Fig. 1), and therefore we proceeded with two-way comparisons.

Vos et al. mentioned as one of the reasons for the negative results of the Alpha Omega trial and the positive results of the LDHS<sup>1</sup> the higher content of linoleate (also known as linoleic acid) in the diet of the patients in the Alpha Omega

trial. In the Netherlands, the average intake of linoleic acid among patients who have had a myocardial infarction is approximately 5% of total energy intake. A similar level was found in the Health Professionals Follow-up Study.<sup>2</sup> In that study, EPA–DHA and ALA reduced the risk of coronary heart disease, with little influence from linoleic acid. This makes competition of linoleic-acid intake with ALA an unlikely explanation for the differing results of the Alpha Omega trial and the LDHS. More likely explanations are differences in the diet other than differences in ALA alone (e.g., the amounts of saturated fat and of fruits and vegetables) in the LDHS<sup>2</sup> and the much higher use of medication<sup>3</sup> for cardiovascular risk factors in the Alpha Omega trial than in the LDHS.

Heazlewood et al. compared the results of the Alpha Omega trial with those of the GISSI-Prevenzione and the JELIS trials and concluded that the low dose of EPA–DHA (376 mg per day) could be the explanation for the lack of an effect on major cardiovascular events in the Alpha Omega trial. Another explanation could be the higher level of medication use among the patients in the Alpha Omega trial.<sup>3</sup> They also suggested that there may have been confounding effects of the intake of saturated and trans fatty acids. Although we did not check the levels of saturated and trans fat in the diet of our patients, it is unlikely, given the successful randomization (as shown in Table 1 of the article), that there were confounding effects of these fatty acids.

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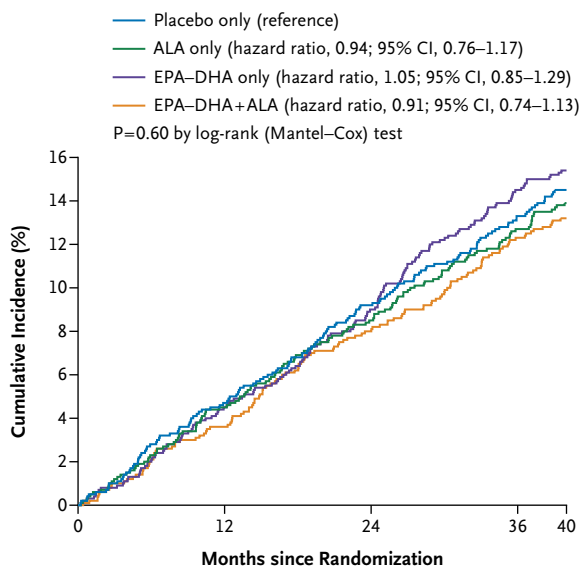
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Since publication of their article, the authors report no further potential conflict of interest.

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**Figure 1. Kaplan–Meier Curve for the Primary End Point of Major Cardiovascular Events, According to n–3 Fatty Acid Supplementation.**

A Kaplan–Meier curve is shown for the cumulative incidence of major cardiovascular events (the primary end point) among 4837 patients who had had a myocardial infarction and were assigned to receive a study margarine containing supplemental eicosapentaenoic acid (EPA) combined with docosahexaenoic acid (DHA), a margarine containing alpha-linolenic acid (ALA), a margarine containing both EPA–DHA and ALA, or a placebo margarine. CI denotes confidence interval.