

# Usefulness of Omega-3 Fatty Acids and the Prevention of Coronary Heart Disease

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Clinical trial evidence exists that supports a role for the omega-3 polyunsaturated fatty acids in coronary heart disease prevention. However, the results from these clinical trials have varied and were conducted in diverse population groups using several different types of omega-3 polyunsaturated fatty acids, including eicosapentaenoic acid, docosahexaenoic acid, and alpha-linolenic acid (ALA). Thus, we systematically reviewed previously published reports assessing the different types of omega-3 polyunsaturated fatty acid interventions and cardiovascular outcomes. Fourteen randomized clinical trials were included in the review. Six trials were included with fish oil, with 1 large trial (10,000 patients) dominating the analysis. In aggregate, the fish oil trials demonstrated a reduction in total mortality and sudden death without a clinically significant reduction in nonfatal myocardial infarction. The 6 trials with ALA supplements or an ALA-enriched diet were of poorer design than the fish oil trials and had limited power. Many of the trials with ALA involved other changes in dietary components. In aggregate, the ALA trials demonstrated possible benefits in reducing sudden death and nonfatal myocardial infarction, but with wider confidence intervals than in the fish oil trials. In conclusion, the evidence suggests a role for fish oil (eicosapentaenoic acid, docosahexaenoic acid) or fish in secondary prevention because recent clinical trial data have demonstrated a significant reduction in total mortality, coronary heart disease death, and sudden death. The data on ALA have been limited by studies of smaller sample size and limited quality. © 2005 Elsevier Inc. All rights reserved. (Am J Cardiol 2005;96:1521–1529)

An inverse association between the intake of omega-3 polyunsaturated fatty acids (n-3 PUFAs) and coronary heart disease (CHD) mortality has been demonstrated in several prospective epidemiologic studies, but not in all.<sup>1–4</sup> Studies have used food diaries and biologic markers of dietary intake (i.e., percentage of serum fatty acids) to estimate dietary exposure and CHD risk. A recent review of prospective cohort epidemiologic studies has suggested that n-3 PUFA consumption correlates with a reduction in CHD death.<sup>5</sup> Additionally, clinical trial evidence exists that supports a role for the n-3 PUFA in CHD prevention. The results from these clinical trials have varied and were conducted in several different ethnic groups and with several varieties of omega-3 fatty acids. The purpose of this study was to review published data systematically to assess the different types of randomized controlled clinical trials involving different types of n-3 PUFA interventions and their effects on CHD morbidity and mortality.

## Methods

**Search strategy:** Studies were identified by searching MedLine, EMBASE, and Index Medicus from 1966 to June 2004, as well as the Cochrane Library of references and clinical trials. We included all languages. A search was done with key words, including, omega-3 fatty acids, fish oil, eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), alpha-linolenic acid (ALA), gamma-linolenic acid, polyunsaturated fatty acids (PUFAs), flax seed oil, dietary therapy, and cardiovascular disease.

**Inclusion criteria:** We used several criteria to select the studies. First, the trials had to be randomized, controlled trials, which included a control group or a placebo group. Second, trial end points had to include either significant cardiovascular disease end points, such as fatal myocardial infarction, nonfatal myocardial infarction, cardiovascular mortality, or total mortality. Third, trials were excluded if patients were not followed for  $\geq 1$  year. Finally, trials were excluded if they involved  $>1$  intervention unless in a prospective  $2 \times 2$  design.

**Data extraction and validity assessment:** Study quality was also assessed by a scoring system described by Jadad et al.<sup>6</sup> Scoring was based on the following: (1) randomization of patients; (2) blinding of patients and providers and those analyzing the data; (3) complete follow-up of those who withdrew from the study; (4) the presence of concealed

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randomization; and (5) the presence of double blinding and a placebo group.

**Data synthesis:** The studies were divided into those with plant-based n-3 PUFAs (ALA), fish-based n-3 PUFAs (DHA and EPA), and those that used whole food changes, such as increased fish consumption or increased margarine consumption. The data were organized into tabular form and then divided by more specific cardiac end points. A formal meta-analysis was not performed due to the heterogeneity of the studies, limited number of studies, general poor study quality, and diversity of the interventions.

## Results

**Identified studies:** Our search identified 2,478 publications with possible relevance. From their structured abstracts, we reviewed 118 for full study analysis. Of these, 14 studies met the inclusion criteria.

**Study characteristics:** The doses of n-3 PUFA ranged from 0.85 to 4.8 g/day for the studies with EPA and DHA and from 1.0 to 6.3 g/day for the studies with ALA. The Jadad quality scores (Jadad quality rating 0 to 5, with 5 indicating highest quality study) ranged from 1 to 4.<sup>6</sup> The included studies had sample sizes ranging from 59 to >13,000 subjects studied.

**Characteristics of dietary intervention:** The core group of 14 studies included 6 studies with fish oil, 2 studies with fish, 5 studies with ALA supplements, and 2 studies with an ALA-enriched diet. Of the ALA supplement trials, several included supplementation with flaxseed oil, mustard seed oil, soybean oil, or ALA-enhanced margarine.

**Characteristics of study participants:** The studies had recruited participants from northern Europe, Southern Europe, and India. Participants were recruited from vegan populations and meat-consuming populations. In addition, studies were conducted in low-fish consumption and moderate-to-high fish consumption populations. Table 1 lists the estimated background fish or n-3 PUFA consumption.

**Characteristics of individual fish oil studies:** Of the 6 fish oil studies, only 3 were designed and powered to analyze hard cardiac end points. The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI) trial, which was the largest, had a 2 × 2 factorial design and included fish oil capsules and vitamin E capsules.<sup>7</sup> In that study, 10,000 patients were randomized to fish oil (850 mg EPA plus DHA, EPA/DHA ratio 1:2), with or without vitamin E (300 mg), and followed for 3.5 years. The primary combined end point was death, nonfatal myocardial infarction, and stroke. Fish oil reduced the primary end point by 15% (4-way analysis), and vitamin E had no effect on any end point. When analyzing secondary end points, a relative risk reduction of 20% was seen for total mortality. This effect was seen early and was driven by a 45% reduc-

tion in sudden death, suggesting an antiarrhythmic effect.<sup>7</sup> These positive results occurred in a group of patients already on a prototypical heart healthy Mediterranean diet (88% ≥1 fish serving/wk, 88% ≥1 fruit serving/day, 55% ≥1 vegetable serving/day). In addition, patients were receiving standard pharmacologic therapy for secondary prevention of CHD (46% statin, 83% aspirin, and 39% β blockers by study end). This trial was limited by its open-label design and lack of a control group.

The Indian Study on Infarct Survival was a randomized, placebo-controlled study of 360 Indian patients <1 day after myocardial infarction.<sup>8</sup> Participants were enrolled into 1 of 3 groups: a group receiving fish oil (1.08 g/day EPA and 0.72 g/day DHA), a group receiving mustard seed oil 20 g/day (ALA content 2.9 g/day), and a placebo group receiving aluminum hydroxide 100 mg/day. The combined primary end point was total cardiac events (sudden cardiac death plus total cardiac deaths plus nonfatal reinfarction). The fish oil group had a 30% reduction in total cardiac events. The study population in this trial had unique features. First, the patients entered the study within 24 hours of their myocardial infarction symptoms, and second, although the investigators did not provide any baseline dietary data, it is known that a high percentage of patients living in that part of India are vegetarians. This baseline diet might have resulted in underestimating the effect of plant-based omega-3 fatty acids. Study limitations included the unique characteristics of the study population (vegetarian south Asians), and that the patients were 1 day after myocardial infarction and not treated aggressively with modern post-myocardial infarction therapies. Only 30% of patients were receiving β blockers and 20% angiotensin-converting enzyme inhibitors; the use of lipid-lowering drugs was not reported.

Nilsen et al<sup>9</sup> studied the effect of omega-3 fatty acids on subsequent cardiac complications in patients recently hospitalized with myocardial infarction. In Norway, 300 patients were enrolled within 1 week of myocardial infarction and followed for 1.5 years. Patients randomized to the treatment group received 4 capsules of 1-g fish oil daily (EPA 2.24 g/day, DHA 1.12 g/day). The placebo control group received 4 g of corn oil (59% linoleic acid, 24% oleic acid, 17% stearic acid, 0% ALA). The primary end point was defined as cardiac death, cardiac resuscitation, recurrent myocardial infarction, or unstable angina. The results of this study did not demonstrate any clinical benefit from fish oil; however, certain important limitations were present. The patients enrolled in this study lived in a coastal area, and the baseline diet was rich in fish containing omega-3 fatty acids. Another potential confounder with this study was the corn oil placebo. Some studies have suggested that corn oil may be antiarrhythmic and thus could potentially reduce sudden death. Also, observational cohort studies seem to suggest a threshold effect with fish-based omega-3 fatty acids; thus, consuming more fish than the threshold might have no added benefit.

von Schacky and others<sup>10</sup> evaluated 223 patients with

Table 1  
Randomized controlled clinical trials of omega-3 fatty acids and cardiovascular outcomes

Trial	n-3 (Type/Dose)	Control (Type/Dose)	n	Mean Follow-up (mo)	Previous MI (%)	Baseline Fish or n-3 Intake	All-Cause Mortality (RR, 95% CI)
<b>Fish Oil</b>							
GISSI Italy, 1999 <sup>7</sup>	EPA + DHA (1:2) 0.85 g/d	Control or vitamin E	11,234	42	100	73% >1 serving fish/wk	0.79 (0.66–0.93)
Singh, India 1997 <sup>8</sup>	EPA + DHA (1:1) 1.8 g/d	100 mg Aluminum hydroxide	360	12	100	ND	ND
Nilsen, Norway 2001 <sup>9</sup>	EPA + DHA (1:2) 3.4 g/d	Corn oil 4 g/d	300	18	100	3 servings fish/wk	1.0 (0.45–2.2)
Von Schacky 1999 Germany <sup>10</sup>	EPA + DHA (3:2) 1.85 g/d	Vegetable oil blend 1.85 g/d	223	24	57	ND	0.5 (0–5.5)
Leng, UK, 1998 <sup>11</sup>	EPA 0.27 g/d	Sunflower seed oil 3 g/d	120	24	29	ND	1.0 (0.21–4.8)
Sacks USA, 1995 <sup>12</sup>	EPA + DHA (3:2) 4.8 g/d	Olive oil 12 g/d	59	28	56	ND	0.3 (0.01–7.1)
<b>Fish</b>							
Burr, UK, 2003 <sup>14</sup>	EPA 2.65 g/wk	“Sensible eating” EPA 0.12 g/wk	3,114	108	50	0.54–0.67 g/wk	1.15 (0.86–1.36)
Burr, UK 1989 <sup>13</sup>	2.4 g/wk	No fish advice	2,033	24	100	0.7 g/wk	0.73 (0.56–0.93)
<b>ALA supplements</b>							
Natvig, Norway, 1966 <sup>15</sup>	ALA 5.25 g/d Linseed oil 10 ml/d	ALA 0.13 g/d Sunflower oil 10 ml/d	13,578	12	8	ND	1.07
Leren, Norway 1966 <sup>16</sup>	ALA 1.0–1.9 g/d (soybean oil)	Usual diet	412	60	100	ND	0.75 (0.52–1.06)
MRC Soya-Bean UK, 1968 <sup>17</sup>	ALA 5.9 g/d soybean oil	Usual diet	393 men	54	100	ND	0.86 (0.49–1.50)
Bemelmans Netherlands 2002 <sup>18</sup>	ALA 6.3 g/d (margarine 15% ALA)	Margarine (0.3% ALA) 1 g/d	282	24	ND	2.1 servings fish/wk	4.3 (0.46–41)
Singh India 1997 <sup>8</sup>	ALA 2.9 g/d	Aluminum hydroxide	360	12	90	ND	ND
<b>ALA-enriched diet</b>							
Singh India 2002 <sup>19</sup>	ALA 1.8 g/d (SD 0.4)	ALA 0.8 g/d (SD 0.2)	1,000	24	50	1.1 g/d (10 g/day MSO)	0.63 (0.38–1.04)
De Lorgeril, France 1999 <sup>20</sup>	ALA-fortified margarine (1.0–1.9 g/d)	Usual care	605	27	100	3 servings fish/wk	0.44 (0.21–0.94)

CVD = cardiovascular disease; MI = myocardial infarction; MSO = mustard seed oil; ND = not determined.

Table 1 Con't

CVD Death (RR, 95% CI)	Cardiac Death (RR, 95% CI)	Sudden Death (RR, 95% CI)	Fatal MI (RR, 95% CI)	Nonfatal MI (RR, 95% CI)	All Strokes (95% CI)	All CVD Events (95% CI)	Quality Score
0.70 (0.56–0.86)	0.65 (0.51–0.82)	0.55 (0.51–0.82)	0.68 (0.53–0.88)	0.91 (0.68–0.94)	1.2 (0.81–1.9)	0.80 (0.68–0.94)	3
ND	0.52 (0.29–0.95)	0.24 (0.05–1.1)	ND	0.52 (0.3–0.9)	ND	0.71 (0.48–1.1)	13
ND	1.0 (0.39–2.6)	ND	ND	1.4 (0.75–2.6)	ND	1.1 (0.84–1.3)	4
ND	ND	ND	0.5 (0–14.7)	0.4 (0.1–2.9)	ND	ND	3
1.0 (0.15–0.69)	ND	ND	ND	0.75 (0.18–3.2)	3.0 (0.32–28)	0.86 (0.43–1.7)	5
0.3 (0.01–7.1)	0.3 (0.01–7.1)	ND	0.3 (0.01–7.7)	0.45 (0.04–4.7)	2.7 (0.12–64)	ND	3
ND	1.26 (1.00–1.58)	1.54 (1.06–2.23)	ND	ND	ND	ND	1
ND	0.67 (0.51–0.89)	ND	0.7 (0.5–0.9)	1.5 (0.97–2.3)	ND	ND	2
ND	1.0	ND	ND	ND	1.43	ND	2
0.73 (0.50–1.06)	ND	1.00 (0.61–1.64)	0.43 (0.21–0.89)	0.77 (0.47–1.27)	ND	ND	2
1.06 (0.59–1.9)	0.97 (0.54–1.76)	ND	1.05 (0.49–2.23)	0.97 (0.54–1.76)	ND	0.99 (0.61–1.64)	2
1.44 (0.09–23)	ND	ND	ND	0.16 (0.01–2.9)	0.29 (0.01–5.9)	0.16 (0.02–1.3)	3
ND	0.61 (0.34–1.1)	0.25 (0.05–1.1)	ND	0.59 (0.35–1.0)	ND	0.82 (0.56–1.2)	3
ND	ND	0.38 (0.15–0.95)	0.71 (0.34–1.5)	0.49 (0.30–0.81)	0.54 (0.22–1.3)	ND	3
ND	0.35 (0.15–0.83)	0.06 (0.003–1.02)	ND	0.32 (0.15–0.70)	0.11 (0.01–2.1)	0.53 (0.38–0.74)	4

angiographically proven CHD and followed them for 2 years. Patients in the treatment group received 6 g of fish oil daily (3.3 g/day EPA plus DHA, EPA/DHA ratio 3:2) for 3 months and then 3 g/day for 21 months. The placebo controls were treated with capsules containing a blend of oils comparable to that of the typical European diet (placebo capsules 0% ALA, 0% EPA, 0% DHA). Although the primary end point was angiographic (luminal diameter), clinical events were recorded. The loss of luminal diameter was not statistically significant. Seven cardiovascular events occurred in the control group and 2 in the fish oil group ( $p = 0.10$ ). This difference, however, was not statistically significant.

Two small fish oil trials are also listed in Table 1. A study by Leng et al<sup>11</sup> included 120 patients with known peripheral vascular disease; cardiac events were a secondary end point. Sacks et al<sup>12</sup> conducted a trial with 59 participants designed to look at angiographic end points and recorded cardiac events. These 2 studies failed to show a reduction in cardiac death, myocardial infarction, or revascularization rates.<sup>12</sup>

**Characteristics of individual fish diet studies:** The previously mentioned trials increased omega-3 fatty acid consumption by providing a supplement; however, other investigators have studied the effect of n-3 PUFAs by instructing patients to eat more fish.

The first of these trials was the Diet And Reinfarction Trial (DART). In this randomized controlled factorial study, 2,033 men 4 to 6 weeks after myocardial infarction were followed for 2 years.<sup>13</sup> Participants were randomized to receive advice on each of the following 3 dietary factors: (1) fat intake (<30% of total calories); (2) fiber intake ( $\geq 18$  g/day); and (3) fatty fish intake (2 servings of oily fish weekly). The primary end point was total mortality; secondary end points included cardiac death and nonfatal myocardial infarction.

Fish advice resulted in a 29% ( $p < 0.05$ ) reduction in mortality; other forms of advice had no effect on mortality. The 2-year incidence of nonfatal myocardial infarction was not reduced by any of the 3 dietary interventions; however, the incidence of cardiac death in the fish group was reduced by 33% ( $p < 0.05$ ). The investigators proposed that the mortality benefit was driven by a reduction in sudden death. More importantly, the results of their study suggest that diets used to prevent mortality from coronary heart disease need to focus on more than just their effects on lipoprotein levels. This concept was underscored by the following facts. First, the 29% reduction in mortality occurred independent of the serum cholesterol levels. Second, the serum cholesterol increased in the fish advice group. Finally, the amount of fish consumed was only 300 g of fish per week or 2.5 g of EPA per week, an amount too small to effect triglyceride levels. The limitations of this study included a lack of blinding.

In another randomized controlled factorial trial by the same investigators, 3,114 men with angina were followed

for 9 years. Participants were randomized to 1 of 4 groups and given varying advice: group 1, eat more fish; group 2, eat more fruit; group 3, eat more fish and fruit; and group 4, no advice.<sup>14</sup> The participants in group 1 were told to eat 2 servings per week of oily fish from the ocean. Those that could not eat fish were given fish oil capsules 3 g/day. Group 2 was told to eat 4 portions of fruit daily and 8 g of fiber. Group 3 received the same advice as groups 1 and 2. Group 4 only received advice on “sensible eating.” The end points in this study were total mortality and cardiac mortality. All-cause mortality was not altered by any type of advice, and the risk of cardiac death was higher among those given the fish advice (1.26; 95% confidence interval [CI] 1.00 to 1.58;  $p = 0.047$ ). The risk of sudden cardiac death was also higher for the fish advice group (1.54; 95% CI 1.06 to 2.23;  $p = 0.025$ ). The results of this study were unexpected, and its several limitations are discussed.

Participants in this study were only required to have a history consistent with angina; however, only 50% of participants had documented CHD, raising uncertainty about the trial being a true secondary prevention study. Also, the study was discontinued for 12 months because of interrupted funding. The effect this interruption had on dietary patterns and n-3 PUFA intake is difficult to determine. When the study was resumed, only 10% of the study participants received dietary questionnaires, making assessment of dietary compliance less reliable. The background fish consumption of group 1 before the trial seemed to be high compared with that in other studies. If a threshold effect exists with fish and omega-3 fatty acids, a benefit from consumption of additional fish would not be expected.

**Characteristics of patient ALA dietary supplementation trials:** In the Norwegian Vegetable Oil experiment, the largest ALA supplement trial, 13,000 men, mostly without known CHD, aged 50 to 59 years, were followed for 1 year.<sup>15</sup> In this double-blind trial, patients were randomized to receive 10 ml of flaxseed oil daily; 10 ml of this rich source of ALA would provide 5.25 g of ALA daily. The control group received sunflower oil, which contains no ALA (0% ALA, 65% linoleic acid, 23% oleic acid, and 12% stearic acid). The end points in this trial included all-cause death, sudden death, and myocardial infarction. The mortality from all causes, as well as from CHD, was the same in the 2 groups. More patients had previous angina pectoris or myocardial infarction in the flaxseed oil group ( $p < 0.02$ ). This trial was limited by several major confounders. Thirty percent of the patients stopped taking the flaxseed oil in the first year because the negative results from another earlier linseed oil trial in Norway were widely reported in the lay press. The omega-6-rich sunflower oil used as a control may have had a cardioprotective effect. Also, the event rate in the study participants was significantly lower than the event rate of the background population. Other limita-

tions, in addition to the short duration of the trial, included a lack of information on the percentage of study participants taking aspirin or other cardioprotective medications.

ALA was also studied in the Oslo Diet Heart Study. This randomized controlled trial included 412 men with a history of myocardial infarction. Those randomized to the treatment group were given soybean oil (7% ALA, 50% linoleic acid, 26% oleic acid) 15 to 30 g/day (1 to 1.9 g ALA/day).<sup>16</sup> They were also given advice to eat more fish and less fat and were provided with free fish rich in omega-3. The control group received no soybean oil or fish. The end points included fatal myocardial infarction, sudden death, nonfatal myocardial infarction, and total mortality. No significant change was noted in total mortality; however, a risk reduction of 43% in fatal myocardial infarction was demonstrated (95% CI 0.21 to 0.89,  $p = 0.004$ ) and a 23% reduction in nonfatal myocardial infarction, which did not reach statistical significance. The results of this trial were limited by the multiple changes in the treatment group, including advice on a low-fat diet and fish supplementation. This trial had a sample size of 412 and thus was not adequately powered to study clinical end points. The choice of soybean oil for a trial designed to study the effect of ALA was also problematic, because soybean oil is only 7% ALA but is a rich source of omega-6 fatty acids, such as linoleic acid (50%).

The Medical Research Council Soya-Bean Trial also studied the effect high doses of soybean oil on hard cardiac end points in 393 patients.<sup>17</sup> The participants were followed for  $\leq 6$  years. No significant reduction was found in cardiac events (relative risk [RR] 0.99, 95% CI 0.61 to 1.64). A trend was noted toward a reduction in all-cause mortality; however, the 95% CIs were wide (RR 0.86, 95% CI 0.49 to 1.50). This study was statistically powered to detect a 50% reduction in cardiac events, so smaller reductions may have been missed. The trial was confounded in that patients unable to tolerate soybean oil ( $n = 20$ ) were switched to corn oil, which contains no n-3 PUFAs.

The Mediterranean Alpha-linolenic Enriched Groningen Dietary Intervention Study (MARGARIN) study was a double-blinded, randomized, controlled,  $2 \times 2$  factorial study. A total of 282 patients were followed for 2 years.<sup>18</sup> Participants were randomized to receive a margarine rich in ALA (ALA 15%) or margarine with minimal ALA (ALA 0.3%). These participants were also randomized to receive advice on how to eat a Mediterranean style diet or a leaflet on standard Dutch dietary guidelines. During the 2-year period, 1 patient in each group died, and 3 myocardial infarctions occurred in the control group and only 1 in the treatment group. These differences were not statistically significant, and the trial was not designed to study cardiac events.

Singh et al<sup>8</sup> studied 360 patients from India. These patients were enrolled within 24 hours of myocardial infarction. As discussed previously, this study had a fish oil arm; however, in another arm of the study, patients received 20 g of mustard seed oil, a rich source of ALA (14.5% ALA).<sup>8</sup> A

placebo group received aluminum hydroxide capsules. At the end of 1 year, a trend toward reduced cardiac events, but no statistically significant reductions in cardiac death (RR 0.61, 95% CI 0.34 to 1.1), sudden death, or nonfatal myocardial infarction (RR 0.59, 95% CI 0.35 to 1.0) was observed. This study was limited by its small size, because mustard seed oil is a widely consumed oil in India, and the investigators did not provide information on background consumption rates.

**Characteristics of patient trials with ALA-enriched diet:** In the Indo-Mediterranean Diet Heart Study, investigators attempted to increase the intake of ALA by teaching patients a diet that was rich in ALA rather than increasing ALA in the form of a capsule or dietary supplement.<sup>19</sup> In this randomized, single-blind, placebo-controlled trial, 1,000 Indian patients with CHD or multiple CHD risk factors were followed for 2 years. The treatment group was instructed to eat 500 g of fruit, vegetables, and nuts daily. In addition, they were encouraged to eat 500 g of whole grains and 3 to 4 servings of mustard seed oil, a rich source of ALA, which provided, on average, 1.8 g of ALA daily (14.5% ALA). The primary combined end point was nonfatal myocardial infarction, fatal myocardial infarction, and sudden cardiac death. A 49% reduction occurred in the primary combined end point (95% CI 0.34 to 0.73). In addition to the mustard seed oil, many dietary changes were implemented, making it difficult to attribute all the cardiovascular benefit to the ALA-rich mustard seed oil.

The Lyon Diet Heart Study was a single-blind, randomized, control study involving 605 French patients within 6 months of myocardial infarction. The mean follow-up for the participants was 27 months.<sup>20</sup> Patients in the experimental group were given 1 hour of dietary instruction on eating a Mediterranean style diet by a research dietitian. Patients were also provided with a free supply of an ALA-enriched spread (5% ALA) to replace the use of any butter or margarine. The control group received instruction in a diet similar to the American Heart Association Step 1 diet. The primary end point was a combined end point of cardiac death and nonfatal myocardial infarction. At approximately 2 years the group receiving the ALA-enriched spread had a 73% RR reduction (risk ratio 0.27, 95% CI 0.12 to 0.69,  $p = 0.001$ ) for the combined end point of cardiac death and nonfatal myocardial infarction. This risk reduction persisted when patients were followed up at 4 years. Patients in the treatment arm consumed an average of 1.8 g of ALA per day and the previously mentioned reduction in cardiac death occurred without a change in cholesterol levels. The increase in plasma ALA correlated with a reduction in CHD when tested by multivariate analysis. Although the results of this trial were promising, 1 important limitation should be discussed. A differential intake of other nutrients, in addition to ALA, was present, making it difficult to evaluate the effect of ALA alone. The treatment group consumed significantly fewer total calories and saturated fat and con-

sumed significantly more monounsaturated fat and ascorbic acid. In addition, differences were present in nut and fish consumption.

## Discussion

Despite the heterogeneous nature of the clinical trials reviewed, including significant differences in study quality, a few general conclusions can be made. A clear trend seems to emerge (Table 1) that suggests important differences in cardiovascular outcomes (total mortality, CHD deaths, sudden deaths, and nonfatal myocardial infarction) between omega-3 fatty acid supplementation with fish oil (EPA, DHA) or fish versus supplementation with plant based ALA supplementation.

The 6 fish oil trials included in our review varied significantly in the EPA and DHA dosage (0.27 to 4.8 g/day), as well as the trial duration (12 to 42 months). Three of the trials were conducted exclusively with patients with CHD, with most having had myocardial infarction. The other 3 trials included a mix of patients with CHD or multiple cardiovascular risk factors. The study quality for the fish oil trials was generally very good.

Only 3 fish oil trials were prospectively designed to evaluate specific clinical end points (e.g., total mortality, CHD death, fatal myocardial infarction, and nonfatal myocardial infarction) of which the GISSI Prevenzione trial was the largest ( $n = 11,324$ ). A few general trends emerged with the fish oil trials (Table 1), in particular the reduction in total mortality, cardiovascular deaths, and fatal myocardial infarction, including sudden death. The results are particularly dominated by the robust results of the largest trial, the GISSI trial. In that study, the CIs were very narrow for cardiovascular deaths, fatal myocardial infarction, and total mortality, with only a small reduction seen in nonfatal myocardial infarction. The GISSI trial reported a 21% reduction (95% CI 0.66 to 0.93) in total mortality. It appears that most of the reduction in total mortality and cardiac death seen in this trial was derived from a 45% reduction in sudden death (RR 0.55, 95% CI 0.51 to 0.82), and the reduction in nonfatal myocardial infarction was minimal (RR 0.91, 95% CI 0.68 to 0.94).<sup>7</sup> Thus, in aggregate, the results of the bulk of the fish oil trials suggest a significant reduction in total mortality and fatal CHD deaths and a possible strong antiarrhythmic effect.

Of the 2 dietary fish trials, in which patients were instructed to eat fish known to be rich in n-3 PUFAs (EPA, DHA), the results appear to be mixed. In these 2 trials, the type of fish consumed and the methods of preparation were not well reported nor were the other changes in the diet induced by the higher fish intake. Of these 2 trials, 1 was so seriously limited (Burr et al<sup>14</sup>) from a methodologic standpoint that no useful conclusions could be drawn from this study. In the other dietary fish trial (DART, Burr et al<sup>13</sup>) with higher methodologic quality (Table 1), a 27% decrease

in total mortality (RR 0.73, 95% CI 0.56 to 0.93) was demonstrated without a statistically significant reduction in nonfatal myocardial infarction (RR 1.5, 95% CI 0.97 to 2.3). This would seem to support the theory that fish-based n-3 PUFAs (EPA, DHA) may impart their cardioprotective effect by acting as an antiarrhythmic agent. Also, the long-term 10-year follow-up of this cohort after the trial was terminated, showing no long-term benefit from the dietary fish advice. This finding might be expected if the cardioprotective mechanism is largely antiarrhythmic.<sup>21</sup>

The 6 trials with ALA supplements and an ALA-enriched diet were more difficult to draw conclusions from than the fish oil studies. Similar to the fish and fish oil trials, the studies varied significantly in background diets, study settings (France, India, United Kingdom, The Netherlands), and baseline CHD risk. ALA supplements varied in composition from capsules to customized margarines to prescribed doses of ingested oils (soybean oil, flaxseed oil).

In aggregate, the ALA-enriched studies, although of poorer design and limited power, suggested possible benefits in reducing sudden death and nonfatal myocardial infarction (Table 1). However, the CIs were much wider than those in the fish oil studies. These results suggest that the plant-based n-3 PUFA, ALA, may impart its cardioprotective effects by way of an antiarrhythmic mechanism and through another cardioprotective mechanism that reduces nonfatal myocardial infarction.

These differences in clinical outcomes among EPA, DHA, and ALA suggest possible differences in their mechanisms. A more comprehensive overview of the possible mechanisms of omega-3 fatty acids has been highlighted elsewhere.<sup>22</sup>

The reduction in sudden death demonstrated in clinical trials, along with studies demonstrating that 1 serving of fish per week increases heart rate variability, has resulted in many mechanistic studies attempting to explain how n-3 PUFAs impart their antiarrhythmic effect.<sup>23</sup> It has been hypothesized that n-3 PUFAs stabilize the electrical activity of cardiac myocytes by inhibiting sarcolemmal ion channels.<sup>24</sup> Some investigators have suggested that n-3 PUFAs inhibit voltage-gated sodium channels, resulting in an increased relative refractory period and an increase in the threshold voltage for depolarization.<sup>24</sup> Others have proposed that the n-3 PUFAs maintain the integrity of L-type calcium channels and prevent cytosolic calcium overload during periods of ischemic stress.<sup>25</sup> A recent meta-analysis of trials with fish oil suggest that fish oils reduce arrhythmias by decreasing heart rate.<sup>26</sup> However, recent trial's with fish oil in patients using defibrillators have shown mixed results.<sup>27,28</sup>

The existing clinical trials have also suggested that the n-3 PUFAs, particularly ALA, may impart cardiac benefits by preventing nonfatal myocardial infarction. Although the evidence for this is not as robust as the data for an antiarrhythmic effect, several studies have demonstrated that plant-based and marine n-3 PUFAs have effects that affect

endothelial function, inflammation, and thrombosis, thus providing a possible explanation for this reduction in non-fatal myocardial infarction.

High-dose EPA and DHA (3 to 4 g/day) has been shown to increase systemic arterial compliance, indicating that marine omega-3 PUFAs improve endothelial function.<sup>29</sup> Studies with ALA have been conflicting, with some positive and some negative studies.<sup>30</sup> Additionally, the omega-3 PUFAs exhibit an anti-inflammatory effect. EPA and DHA reduced tumor necrosis factor, interleukin-6, vascular cellular adhesion molecule-1, and E-selectin at relatively low doses ranging from 0.3 to 1 g/day.<sup>31</sup> Although fewer studies have been performed, the results have been mixed with respect to the effect of ALA on inflammatory markers such as C-reactive protein, vascular cellular adhesion molecule-1, E-selectin, and interleukin-6.<sup>32</sup>

Overall, the mechanistic studies with EPA and DHA have pointed to an antiarrhythmic effect, and data with ALA are less conclusive. Studies attempting to attribute other antiatherogenic properties to EPA, DHA, and ALA have not been consistent, and many of these studies have demonstrated effects at doses much higher than those used in clinical end point trials.

As a result of the previously mentioned omega-3 PUFA trials and recent epidemiologic evidence, the American Heart Association has published guidelines for the consumption of fish and fish oil, indicating that patients with CHD should try to consume a combination of EPA and DHA totaling 1 g/day. Many patients, however, do not enjoy eating fish or have concerns about pollutants. In contrast, rich sources of ALA, including canola and flax seed meal, can be easily incorporated into the United States diet. If clinical trials demonstrate that ALA is as effective as EPA and DHA in reducing cardiovascular events, the public health implications could be significant.

In conclusion, the evidence supports a role for fish oil (EPA, DHA) or fish in secondary prevention, because the clinical trials have demonstrated a reduction in total mortality, CHD death, and sudden death. The evidence from these trials has indicated that EPA plus DHA supplementation in the range of 0.5 to 1.8 g/day provides significant benefit. More research is needed to determine whether the benefits of fish oil or fish extend to the United States population in secondary and primary prevention.

The data on the plant-based n-3 PUFA, ALA, is very promising. However, the existing studies were small, and a large randomized controlled trial is needed before recommendations can be definitely made for CHD prevention. The data for ALA show possible reductions in sudden death and nonfatal myocardial infarction, suggesting other potential cardioprotective mechanisms other than a predominantly antiarrhythmic role. An urgent need exists to perform more clinical trials with ALA because the results of such trials could have significant public health implications.

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