N-3 Polyunsaturated Fatty Acids in Coronary Heart Disease: A Meta-analysis of Randomized Controlled Trials

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PURPOSE: Observational studies have shown an inconsistent association between n-3 polyunsaturated fatty acids and the risk of coronary heart disease. We investigated the effects of dietary and nondietary (supplemental) intake of n-3 polyunsaturated fatty acids on coronary heart disease.

SUBJECTS AND METHODS: We searched the literature to identify randomized controlled trials that compared dietary or nondietary intake of n-3 polyunsaturated fatty acids with a control diet or placebo in patients with coronary heart disease. Studies had to have at least 6 months of follow-up data, and to have reported clinical endpoint data. We identified 11 trials, published between 1966 and 1999, which included 7951 patients in the intervention and 7855 patients in the control groups.

RESULTS: The risk ratio of nonfatal myocardial infarction in patients who were on n-3 polyunsaturated fatty acid-enriched diets compared with control diets or placebo was 0.8 (95% confidence interval [CI]: 0.5 to 1.2, $P = 0.16$; Breslow-Day test for heterogeneity, $P = 0.01$), and the risk ratio of fatal myocardial infarction was 0.7 (95% CI: 0.6 to 0.8, $P < 0.001$; heterogeneity $P > 0.20$). In 5 trials, sudden death was associated with a risk ratio of 0.7 (95% CI: 0.6 to 0.9, $P < 0.01$; heterogeneity $P > 0.20$), whereas the risk ratio of overall mortality was 0.8 (95% CI: 0.7 to 0.9, $P < 0.001$; heterogeneity $P > 0.20$). There was no difference in summary estimates between dietary and nondietary interventions of n-3 polyunsaturated fatty acids for all endpoints.

CONCLUSION: This meta-analysis suggests that dietary and nondietary intake of n-3 polyunsaturated fatty acids reduces overall mortality, mortality due to myocardial infarction, and sudden death in patients with coronary heart disease. **Am J Med. 2002;112:298–304.** ©2002 by Excerpta Medica, Inc.

An inverse relation between the intake of n-3 polyunsaturated fatty acids, mainly from fish, and mortality due to coronary heart disease, has been reported in several (1,2) but not all prospective studies (3,4). The protective effect of n-3 polyunsaturated fatty acids has been attributed to eicosapentaenoic acid and docosahexanoic acid, which are present in fish oil, and alpha-linolenic acid, which is present predominantly in soybean, flaxseed, and canola oils. N-3 polyunsaturated fatty acids reduce the incidence of coronary heart disease by several mechanisms. Studies have reported a dose-dependent effect on blood pressure (5); however, these findings were not confirmed in larger trials (6,7). N-3 polyunsaturated fatty acids reduce platelet adherence and enhance endothelium-dependent vasodilatation (8–10). There is evidence from clinical trials (11,12) and animal studies (13) that n-3 polyunsaturated fatty acids may also protect against ventricular arrhythmia (12). These mechanisms may be important in reducing the incidence of coronary events in people with underlying atherosclerosis.

Results from an earlier meta-analysis suggested that n-3 polyunsaturated fatty acids reduce the incidence of restenosis in patients undergoing percutaneous transluminal coronary angioplasty (14), contrary to findings from a larger trial (15). We therefore reviewed randomized controlled trials to investigate the effect of dietary or supplemental intake of n-3 polyunsaturated fatty acids on fatal and nonfatal myocardial infarction and overall mortality.

METHODS

We searched MEDLINE, EMBASE, Pascal BioMed, and Index Medicus for all randomized controlled trials, published in all languages from 1966 through August 1999, which compared n-3 polyunsaturated fatty acids, given either as supplements or via dietary intervention, with

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placebo or a control diet. We combined the terms omega 3 fatty acids, fish oils, diet, dietary therapy, and cardiovascular disease with text searches using the terms random or control. We also searched the Cochrane Library and references of relevant publications for additional trials.

Study Selection and Data Abstraction

We included studies based on the following criteria. First, trials had to be randomized and to have compared dietary or supplemental intake of n-3 polyunsaturated fatty acids with a control diet or placebo. Second, trials had to report fatal or nonfatal myocardial infarction and overall mortality. Trials with angiographic primary endpoints were eligible if they reported myocardial infarction and mortality data. Third, we only considered trials that followed patients who had either myocardial infarction or angiographically established coronary heart disease for at least 6 months. We excluded studies of restricted patients who had undergone coronary bypass surgery or heart transplantation.

Study eligibility and quality were determined via blinded assessment by two pairs of investigators. Disagreements were resolved by consensus. We assessed the quality of included trials using a modified score that comprised the following (16): randomization of participants; blinding of patients, caregivers, and those assessing outcome; and complete description of subjects who withdrew or dropped out. The scoring system gave 1 point to each item, if present. If randomization was concealed (central allocation), and if double blinding was conducted with an identical placebo, the study received another point, thus yielding a total score of 0 to 5 points. Agreement for eligibility (kappa [κ] = 0.66) and trial quality ($\kappa = 0.58$) was good.

Statistical Analysis

We assessed publication bias by inspecting funnel plots (graphs of the sample size of each trial and the pooled summary estimates for different outcomes). We pooled data from each trial using a fixed-effects model (17), and used a random-effects model if the Breslow-Day test for heterogeneity (18) yielded a P value <0.10.

To explore variability (heterogeneity) of study results, we examined the magnitude of the treatment effects in relation to the type of intervention (supplemental versus dietary intake), the duration of the intervention (mean follow-up $\geq$12 months), and whether patients, caregivers, and outcome assessors were blinded to allocation (19). We tested the differences in combined estimates of subgroups, and used the z score for each subgroup by dividing the difference in the log relative risk of the subgroup summary by the standard error of the difference. All analyses were performed using SAS software version 6.12 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Our literature search identified 406 studies, and 369 additional articles were reviewed in the Cochrane Library. We identified 177 trials, and excluded 129 that were not related to coronary heart disease, 26 that had a follow-up of less than 6 months or did not report clinical endpoint data, and 7 that were duplicate publications. Four studies included patients who had undergone heart transplantation or bypass surgery, and were therefore also excluded.

Eleven trials fulfilled our inclusion criteria: 2 of dietary intervention (20,21) and 9 of supplementation with n-3 polyunsaturated fatty acids (15,22–29). There were 7951 patients in the intervention groups and 7855 patients in the control groups (Table 1). In trials of supplementation with n-3 polyunsaturated fatty acids, the dose for eicosapentaenoic acid varied from 0.3 to 6.0 g, whereas the dose for docosahexanoic acid ranged from 0.6 to 3.7 g. Only one trial involved patients who had peripheral arterial disease or coronary heart disease (26). Between 33% and 100% of the patients had a previous myocardial infarction. The mean age was 49 to 66 years, and the average follow-up lasted 20 months (range, 6 to 46 months). At enrollment, mean total cholesterol levels in study groups were 4.8 to 6.5 mmol/L, mean low-density lipoprotein (LDL) cholesterol levels were 2.8 to 4.5 mmol/L, and mean triglyceride levels were 1.5 to 2.4 mmol/L. In the intervention groups, the changes in mean total cholesterol levels varied from -8.8% to 6.0%; changes were between -10.9% and 8.8% for LDL cholesterol levels, and between -3.6% and -40.4% for triglyceride levels. Quality scores ranged from 2 to 5. The open trial design (20,21,23,29) and the lack of documentation of blinded outcome assessment (26) were largely responsible for the low quality scores.

Ten trials documented the incidence of nonfatal and fatal myocardial infarction (Table 2). The risk ratio of nonfatal myocardial infarction in patients treated with an n-3 polyunsaturated fatty acid-enhanced diet, compared with patients assigned a control diet or placebo, was 0.8 (95% confidence interval [CI]: 0.5 to 1.2, $P = 0.16$; heterogeneity $P = 0.01$) (Figure). Among these patients, the risk ratio was 0.7 (95% CI: 0.6 to 0.8, $P < 0.001$; heterogeneity $P > 0.20$) for fatal myocardial infarction, 0.7 (95% CI: 0.6 to 0.9, $P < 0.01$; heterogeneity $P > 0.20$) for sudden death (n = 5 trials), and 0.8 (95% CI: 0.7 to 0.9, $P < 0.001$; heterogeneity $P > 0.20$) for overall death.

We found an asymmetric distribution for all endpoints, with the exception of nonfatal myocardial infarction. The smaller trials showed a larger effect size than did the one larger trial (29).

Sensitivity Analysis

None of our a priori hypotheses (the type and duration of intervention, and blinding of patients, clinicians, and

Table 1. Baseline Characteristics in Randomized Controlled Trials Comparing Dietary and Nondietary Supplementation of N-3 Polyunsaturated Fatty Acids with a Control Regimen or Placebo

Study (Reference)	Regimen	Number of Patients	Mean Follow-up (months)	Mean (± SD) Age (years)	History of Myocardial Infarction (Percentage)	Treatment with Antiplatelet Therapy (Percentage)	Total Cholesterol (mmol/L) (Mean ± SD [% Change from Baseline])	LDL Cholesterol (mmol/L) (Mean ± SD [% Change from Baseline])	Triglycerides (mmol/L) (Mean ± SD [% Change from Baseline])	Quality Score*
Burr (20)	Intervention: EPA, ~0.5 g/d; fish, 200–400 g twice weekly; or EPA/DHA, 1.5 g/d, given as 3 capsules	1015	24	56.7	19.0	4.8	6.5 ± 1.2	NA	NA	2
	Control: no advice on fish consumption	1018		56.4	22.7	4.0	6.5 [1.23]			
Reis (22)	Intervention: EPA, 6 g/d; DHA, 3.72 g/d, given as 12 capsules	137	6	60 ± 10	NA	100	NA	NA	NA	4
	Placebo: olive oil	67		57 ± 9		100				
Kaul (23)	Intervention: EPA, 5.4 g/d; DHA, 3.6 g/d, given as 10 capsules	58	6	56 ± 11	NA	100	5.6 ± 1.1 [2.6]	3.2 ± 0.7 [5.2]	2.4 ± 1.3 [−23.8]	3
	Control: no intervention	49		59 ± 9		100	5.7 ± 0.9 [−2.3]	3.3 ± 0.7 [−2.1]	2.4 ± 1.2 [2.1]	
Leaf (15)	Intervention: EPA, 4.1 g/d; DHA, 2.8 g/d, given as 10 capsules	253	6	NA	33	100	5.7 ± 1.1 [−8.8]	3.4 ± 0.9 [−5.6]	2.4 ± 1.4 [−40.4]	5
	Placebo: corn oil	250			33	100	5.7 ± 1.2 [−4.7]	3.7 ± 1.0 [5.1]	2.4 ± 1.6 [−14.6]	
de Lorgeril (21)	Intervention: alpha-linolenic acid, ~2 g/d; advice on fish consumption	302	46	53.5 ± 10	100	62.6	6.5 ± 0.1 [−4.6]	4.5 ± 0.1 [−7.7]	2.2 ± 0.1 [−9.3]	4
	Control: dietary advice by hospital dietician	303		53.5 ± 10	100	64.8	6.5 ± 0.1 [−4.5]	4.5 ± 0.1 [−6.8]	2.0 ± 0.1 [−12.5]	
Sacks (24)	Intervention: EPA, 2.9 g/d; DHA, 1.9 g/d, given as 12 capsules	31	28	62 ± 7	55.0	97	5.0 ± 0.9 [0.4]	3.2 ± 0.8 [−7.6]	1.5 ± 0.8 [−33.3]	4
	Placebo: olive oil	28		62 ± 7	57.0	93	4.8 ± 0.7 [0.4]	3.0 ± 0.7 [−4.1]	1.6 ± 0.8 [1.9]	
Singh (25)	Intervention: EPA, 1.08 g/d; DHA, 0.72 g/d, given as 6 capsules	122	12	48.5 ± 6.5	100	90.1	5.3 ± 1.1 [−4.1]	3.4 [8.8]	1.8 ± 0.2 [−9.4]	4
	Placebo: Al(OH)3, 0.1 g/d	118		49.2 ± 7.2	100	98.3	5.4 ± 1.1 [−2.8]	3.5 [0]	1.8 ± 0.2 [−6.1]	
Leng (26)	Intervention: gamma-linolenic acid, 1.68 g/d; EPA, 0.27 g/d, given as 6 capsules	60	24	65.0 ± 7.3	23.3	46.7	6.0 ± 0.9 [2.3]	2.8 ± 0.7 [−10.9]	NA	5
	Placebo: sunflower oil, 0.5 g/d	60		66.5 ± 6.9	11.9	40.0	5.9 ± 1.2 [0.5]	2.9 ± 0.9 [−4.0]		
Johansen (27)	Intervention: EPA, 2.7 g/d; DHA, 2.3 g/d, given as 6 capsules	196	6	60.3 ± 9.3	51	70.9	6.4 ± 1.3 [−1.6]	NA	2.2 ± 1.4 [−26.3]	4
	Placebo: olive oil	192		59.1 ± 9.3	50	67.2	6.5 ± 1.1 [−1.5]		2.0 ± 1.0 [−5]	
GISSI (29)	Intervention: EPA, 0.3 g/d; DHA, 0.6 g/d, given as 1 capsule	5666	42	59.2	100	92.0	5.5 [6.0]	3.6 [−8.9]	1.9 [−6.3]	3
	Control: no intervention	5658		59.4	100	91.3	5.5 [6.5]	3.6 [−7.0]	1.9 [−1.1]	
von Schacky (28)	Intervention: EPA, 1.06 g/d; DHA, 0.65 g/d, given as 3 capsules	111	24	57.8 ± 9.7	52.3	91.9	6.3 ± 1.1 [−1.6]	4.1 ± 1.1 [6.5]	2.2 ± 1.3 [−3.6]	5
	Placebo: fatty acid mixture	112		58.9 ± 8.1	50.9	91.1	6.1 ± 1.1 [−0.8]	4.0 ± 0.9 [14.3]	2.2 ± 1.1 [2.7]	

* On a scale of 0 to 5; see Methods section.

DHA = docosahexanoic acid; EPA = eicosapentaenoic acid; GISSI = Gruppo Italiano per lo Studio della Sopravivenza nell' Infarto Miocardico; NA = data not available.

Table 2. Clinical Endpoints in Randomized Controlled Trials Comparing Dietary and Nondietary Supplementation of N-3 Polyunsaturated Fatty Acids with a Control Regimen or Placebo

Study (Reference)	Regimen	Nonfatal Myocardial Infarction		Fatal Myocardial Infarction		Sudden Death		Overall Mortality	
		Number of Events and Relative Risk (95% Confidence Interval)							
Burr (20)	Intervention	49	1.5 (0.9–2.3)	78	0.7 (0.5–0.9)			94	0.7 (0.6–0.9)
	Control	33		116				130	
Reis (22)	Intervention	7	6.9 (0.4–120.6)						
	Control	0							
Kaul (23)	Intervention	4	1.5 (0.3–6.8)						
	Control	2							
Leaf (15)	Intervention			0	0.5 (0–14.6)	0	0.50 (0.0–14.6)	0	0.2 (0.0–5.4)
	Control			1		1		2	
de Lorgeril (21)	Intervention	8	0.3 (0.1–0.7)	6	0.3 (0.1–0.8)	0	0.1 (0.0–1.1)	14	0.6 (0.3–1.1)
	Control	25		19		8		24	
Sacks (24)	Intervention	1	0.5 (0.1–3.9)	0	0.4 (0–12.5)			0	0.4 (0–12.5)
	Control	2		1				1	
Singh (25)	Intervention	16	0.5 (0.3–0.9)	12	0.6 (0.3–1.3)	2	0.2 (0.1–1.1)	14	0.5 (0.3–0.9)
	Control	30		18		8		26	
Leng (26)	Intervention	3	0.8 (0.2–0.3)					3	1.0 (0.2–4.8)
	Control	4						3	
Johansen (27)	Intervention			0	0.2 (0–5.4)	1	1.0 (0.1–15.5)	1	0.3 (0–3.1)
	Control			2		1		3	
GISSI (29)	Intervention	210	0.9 (0.8–1.1)	214	0.8 (0.7–0.9)	122	0.7 (0.6–0.9)	472	0.8 (0.7–0.9)
	Control	220		265		164		545	
von Schacky (28)	Intervention	1	0.4 (0.1–2.9)	0	0.5 (0–14.7)			1	0.5 (0–5.5)
	Control	3		1				2	

GISSI = Gruppo Italiano per lo Studio della Sopravivenza nell' Infarto Miocardico.

outcome adjudicators) explained the heterogeneity observed. For all endpoints, including nonfatal myocardial infarction, in which we did find statistically significant heterogeneity, summary estimates were similar in all subgroups. For nonfatal myocardial infarction, the risk ratio in trials of dietary intervention compared with controls was 0.7 (95% CI: 0.1 to 3.2), and 0.8 (95% CI: 0.55 to 1.2) in trials of n-3 polyunsaturated fatty acid supplementation compared with controls. The risk ratio for fatal myocardial infarction was 0.5 (95% CI: 0.3 to 1.1) in dietary intervention trials and 0.8 (95% CI: 0.7 to 0.9) in supplementation trials. The one dietary trial (21) that examined sudden death generated a risk ratio of 0.1 (95% CI: 0 to 1.1), whereas the pooled estimate in the supplementation trials was 0.7 (95% CI: 0.6 to 0.9; $P = 0.09$ for the difference of summary estimates). For overall mortality, the risk ratio in trials of patients assigned n-3 polyunsaturated fatty acid-enhanced diets was 0.7 (95% CI: 0.6 to 0.9), compared with 0.8 (95% CI: 0.7 to 0.9) in supplementation trials.

DISCUSSION

Our meta-analysis suggests that a diet supplemented with n-3 polyunsaturated fatty acids may decrease mortality due to myocardial reinfarction, sudden death, and overall mortality in patients with coronary heart disease. The risk reduction for mortality was statistically significant. The mortality in control groups of trials that followed patients for an average of 1.5 years varied from 1% to 22%, suggesting that in low-risk patients (e.g., those aged <50 years and with minor uncomplicated infarctions and no comorbid conditions) with mortality of about 2% per year, approximately 250 patients would need to receive n-3 polyunsaturated fatty acid supplementation for 1.5 years to prevent a single premature death (number needed to treat). In patients with higher mortality rates of 22%, approximately 24 patients would need to be treated to prevent one event.

Our review has several limitations. First, we cannot rule out publication bias, although we performed a comprehensive literature search. The smaller trials showed a larger effect size than did the Gruppo Italiano per lo Studio della Sopravivenza nell' Infarto Miocardico (GISSI) trial (29), suggesting that small unpublished trials might have a negligible effect on outcomes, and thereby reducing estimates of treatment effect.

Second, the amount and type (pharmacological, nondietary versus dietary intervention) of n-3 polyunsaturated fatty acid varied considerably. For example, the

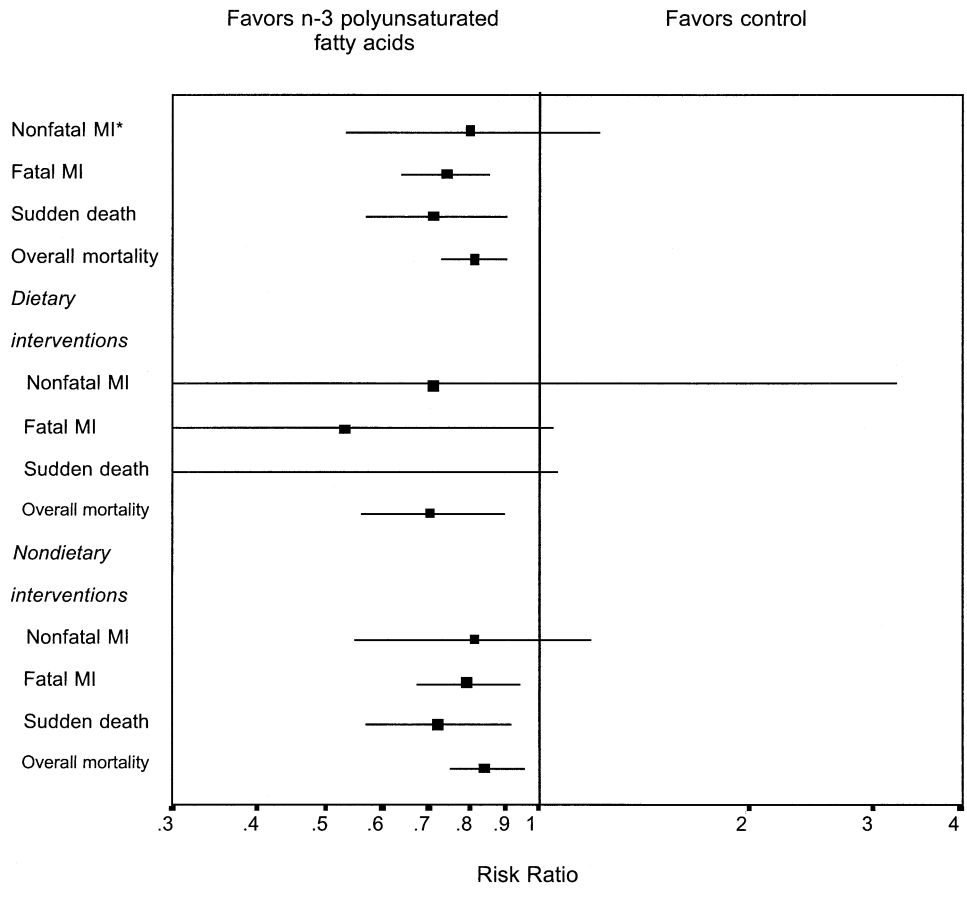

Figure. Pooled risk ratios and 95% confidence intervals for the different endpoints in randomized controlled trials of dietary and nondietary supplementation with n-3 polyunsaturated fatty acids versus control or placebo. The asterisk (*) denotes $P = 0.01$ for test of heterogeneity. MI = myocardial infarction.

GISSI trial used lower doses of eicosapentaenoic acid and docosahexanoic acid (29), whereas in another study the intake of n-3 polyunsaturated fatty acids was mainly from fatty fish (20). In the Lyon Heart Project Study (21), alpha-linolenic acid, which is a n-3 fatty acid of plant origin, and the low intake of saturated fats (8% of energy intake), was the main dietary factor that differed between the intervention and control groups. In our sensitivity analysis, we could not identify relevant differences between groups in the effects of dietary and supplement intake of n-3 polyunsaturated fatty acids on clinical endpoints. This may have been due to lack of power or our inability to identify additional relevant factors from the data.

Third, several studies had an open intervention design and used unblinded clinical endpoint assessments, which led to lower scores for trial quality, as measured with our modified Jadad score, as well as resulted in an overestimation of the treatment effects (30,31).

Finally, in most of the trials that had restenosis as the primary endpoint, no information on the diagnostic criteria or blinded outcome assessment of clinical endpoints was provided, and therefore bias may have been introduced. However, because these trials were small and contributed only few events, it is less likely that the summary estimates for fatal and nonfatal myocardial infarction were affected. In contrast, only 5 trials (15, 21, 25, 27, 29) reported the incidence of sudden death, whereas the Diet and Reinfarction Trial (DART) did not. The potential bias may not have influenced overall mortality given the consistency of the findings of a reduction in mortality in all 9 trials, including DART.

The protective effect of n-3 polyunsaturated fatty acids in coronary heart disease is mediated through various actions. N-3 polyunsaturated fatty acids reduce endothelium dysfunction by reducing sympathetic overactivity (32) and enhancing nitric oxide-mediated vasodilatation (9). They reduce the inflammatory endothelium response by inhibiting monocyte adhesion (33) and by suppressing inflammatory mediators and thromboxane Az, a prostaglandin that induces platelet aggregation and vasoconstriction (34). Platelet-derived growth factor-like proteins from vascular endothelial cells are also suppressed by n-3 polyunsaturated fatty acids, which may

attenuate endothelial cell proliferation. N-3 polyunsaturated fatty acid supplementation affects hemostatic markers of atherosclerosis, such as thrombomodulin and von Willebrand factor (35), as well as reduces insulin resistance (36).

In our analysis, the antilipidemic effect of n-3 polyunsaturated fatty acids was limited to an average 20% reduction in triglyceride levels, with little effect on LDL and HDL cholesterol levels, which is consistent with other findings (37). Of note, only a small proportion of patients received additional antilipidemic drugs (27–29). The role of triglycerides in the pathogenesis of atherosclerosis is still controversial because prospective epidemiologic studies found an inconsistent relation between triglyceride levels and coronary heart disease (38,39). Future studies should examine if the triglyceride-lowering properties of n-3 polyunsaturated fatty acids have additional effects, particular in patients with mixed hyperlipidemia and insulin resistance.

Finally, data from animal studies suggest that n-3 polyunsaturated fatty acids have antiarrhythmic effects in coronary heart disease (40,41). They may prolong the inactivated state of the sodium and calcium channels in myocytes, and inhibit the conductance of these channels (41,42). In the present analysis, all estimates from individual trials and the summary estimate showed that n-3 polyunsaturated fatty acids protected consistently against sudden death.

N-3 polyunsaturated fatty acids may lead to a considerable reduction in fatal myocardial infarction and overall mortality in the secondary prevention of coronary heart disease. Because they have different mechanisms from those of other agents that reduce coronary heart disease mortality, we suggest that adequately powered trials should study the possible added benefit of n-3 polyunsaturated fatty acid supplementation in conjunction with treatment involving statins, antiplatelets, beta-blockers, or angiotensin-converting enzyme inhibitors.

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