Clinical Trial Evidence for the Cardioprotective Effects of Omega-3 Fatty Acids

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The notion that marine omega (ω)-3 fatty acids might have beneficial cardiovascular effects was first suggested by epidemiologic studies in Greenland Inuits published in the late 1970s. These simple observations spawned hundreds of other studies, the confluence of which strongly suggests a true cardioprotective effect of ω-3 fatty acids. The strongest confirmation has come from the publication of three randomized clinical trials, all of which reported benefits to patients with preexisting coronary artery disease. The most convincing of these was the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI)-Prevezione study, in which 5654 patients with coronary artery disease were randomized to either ω-3 fatty acids (850 mg/d) or usual care. After 3.5 years, those taking the ω-3 fatty acids had experienced a 20% reduction in overall mortality and a 45% decrease in risk for sudden cardiac death. These findings support the view that relatively small intakes of ω-3 fatty acids are indeed cardioprotective, and suggest that they may operate by stabilizing the myocardium itself.

Introduction

Since the late 1970s, interest in the possible cardioprotective effects of fish oils rich in omega (ω)-3 fatty acids (FAs) has grown markedly [1]. The two marine-derived ω-3 FAs, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), now appear to exert beneficial effects on both circulating risk factors and on the heart itself. This review focuses on the three randomized, controlled, prospective trials of ω-3 FAs (or oily fish) that evaluated clinically important endpoints in patients with coronary heart disease (CHD). This review then addresses possible mechanisms to explain the observed outcomes, and ends with a discussion of the implications for clinical implementation.

GISSI-Prevenzione Study

The largest study to probe the cardiovascular benefits of ω-3 FAs was the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI) Prevenzione Study [2••]. The objective of the study was to determine whether ω-3 FA supplementation could reduce morbidity and mortality in patients with CHD. The investigators identified 11,324 patients who had survived a myocardial infarction (MI) within the last 3 months. Qualifying patients were randomized to one of four study groups: 1) the ω-3 FA group received one capsule per day of a highly concentrated product containing about 850 mg of EPA and DHA, 2) the vitamin-E group received 300 mg/d of synthetic α-tocopherol, 3) the combined treatment group received both, and 4) the control group received neither. Because the study was conducted in Italy, all patients were presumably consuming some variation of the "Mediterranean diet." In addition, the patients were generally receiving up-to-date medical therapy: 92% were taking antiplatelet drugs, 47% were taking angiotensin-converting enzyme (ACE) inhibitors, and 44% were taking β-blockers. Cholesterol-lowering drugs (primarily statins) were being taken by less than 5% of the patients at the outset of the study (in 1993); however, this had increased to 45% by the end, due largely to the publication of the Scandinavian Simvastatin Survival Study (4S) [3] in 1994. Therefore, the effects observed reflected the added benefits of ω-3 FA and vitamin-E therapy over and above good dietary and medical therapy.

Because there was minimal benefit noted in the vitamin-E group, we focus specifically on the effects in the ω-3 FA-only (n=2836) and control groups (n=2828). After a mean follow-up of 3.5 years, the group receiving ω-3 FAs alone had a relative risk for the primary endpoint (death, nonfatal MI, or nonfatal stroke) of 0.85 (0.74 to 0.98) compared with the control group. Relative risk for all fatal events from any cause was 0.80 (95% CI, 0.67 to 0.94). The survival curves for these two groups reveal that the protective effect of the ω-3 FAs was detectable within

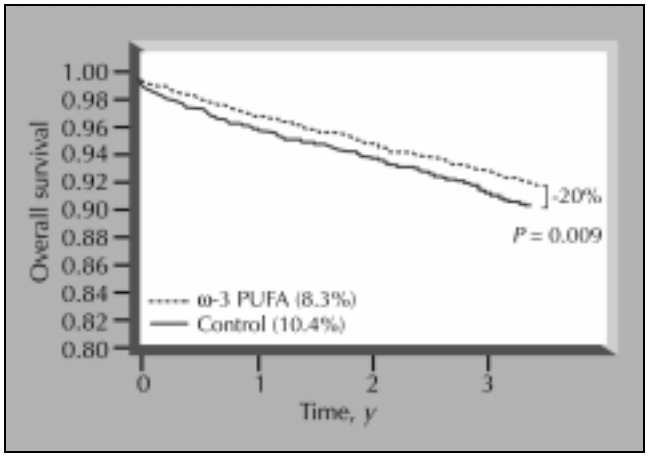

Figure 1. Comparison of survival curves for the control and ω-3 polyunsaturated fatty acid (PUFA) groups in GISSI Prevenzione [2••]. Percent of patients having died by the end of the study is given in parentheses.

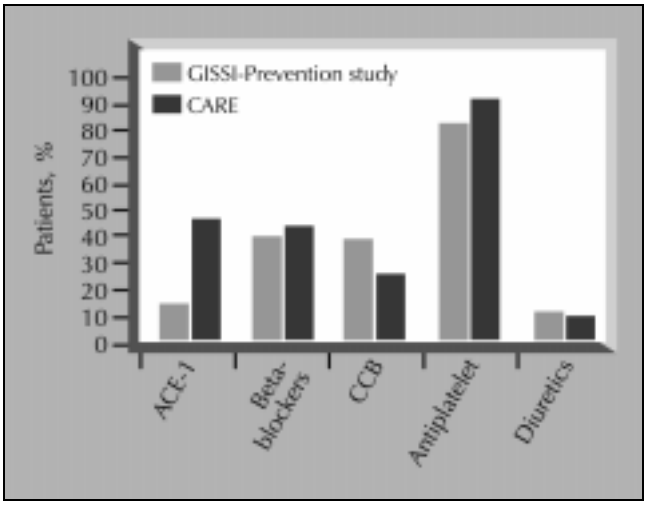

Figure 2. Comparison of the percent of patients in CARE [8] and the GISSI-Prevention study [2••] who were being treated with cardioprotective drugs at the beginning of each study. In addition to these drugs, statin treatment was allowed in GISSI, with 45% of patients also taking statins at the study's end. (ACE—angiotensin-converting enzyme; CCB—calcium channel blocker.)

approximately 1 month of initiating therapy (Fig. 1). The rapidity of onset suggests that the mechanism may involve either direct action of ω-3 FAs on the myocardium itself, or some acute metabolic alteration (perhaps changes in platelet or endothelial function [4,5] or adhesion molecule metabolism [6]), rather than changes in arterial plaque architecture. Another unexpected finding was a 45% (95% CI, 0.40 to 0.76) reduction in relative risk for sudden cardiac death. There was no benefit of concomitant vitamin E. Side effects for the ω-3 FA group were minimal, with 3.8% of patients dropping out due to gastrointestinal disturbances, compared with 2.1% in the vitamin-E group. Interestingly, the overall drop-out rate by the end of the study was 29% in the ω-3 FA group. The GISSI results were based (appropriately) on an intention-to-treat analysis. In other words, the clinical events experienced by patients dropping out of the ω-3 FA group were included with those experienced by the compliant patients. This has the effect of underestimating the true effect of therapy.

Fish oils rich in ω-3 FAs are best known as triglyceride-lowering agents [7]. An important mechanistic question of this study is, "Did 850 mg/d of ω-3 FAs alter serum lipid levels?" After 6 months of therapy, there was, in fact, a statistically significant decrease in serum triglyceride levels; however, compared with control patients, it was less than 5%. No other lipid parameter was altered, and there were no significant changes in fibrinogen or glucose among the four treatment groups. Thus, ω-3 FAs did not materially change known CHD risk factors.

The GISSI authors summarized their findings as follows: "In this population of patients who had myocardial infarction and Mediterranean diet habits, and who were well-treated with up-to-date preventive pharmacological interventions, long-term n-3 polyunsatured fatty acids (PUFA) 1-g daily, but not vitamin E 300-mg daily, was beneficial for [reducing] death, and for combined death, nonfatal myocardial infarction, and stroke."

It is instructive to compare the GISSI results with those from other major secondary prevention studies in CHD (Table 1). Of all the studies, the patients in the Cholesterol and Recurrent Events (CARE) trial [8] were the most comparable with the GISSI Prevenzione population. Similar numbers and types of patients with similar low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol levels were included in these two trials. Despite the GISSI study being shorter in duration (3.5 years versus 5 years), and the patients in the GISSI study receiving more modern pharmacotherapy (including 45% of patients taking statins by the end of the trial; [Fig. 2]), clinical outcomes were better in the GISSI study than in the CARE study. Only 1.6 lives/1000/y were saved with pravastatin in the CARE study, compared with five in GISSI. In the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) trial [9], whose patients had a higher baseline risk, pravastatin saved the lives of approximately five CHD patients/1000/y, and in the even higher-risk 4S population, simvastatin saved no more lives than ω-3 FAs did in the GISSI study. To the extent that the beneficial effects noted in the Diet and Reinfarction Trial (DART) study were due to ω-3 FAs, they were even more effective here, saving nearly three times as many lives as statins did in any trial. The implications of this finding are that ω-3 FAs may be as important as statins for the prevention of death in post-MI patients.

Despite these encouraging findings, it must be borne in mind that GISSI Prevenzione was not a blinded, placebo-controlled trial; therefore, more studies will be needed to confirm its findings. On the other hand, GISSI was prospective, randomized, controlled, and it included a very large number of well-treated, at-risk patients. What's more, it was carried out in a relatively "real world" setting,

Table 1. Comparison of effects on total mortality in major coronary heart disease secondary prevention trials

Study	No. of patients	Duration, y	Intervention	Baseline lipids, mg/dL		Relative risk reduction, %	Absolute risk reduction, %	Lives saved/1000 patients/y	P value
				LDL-C	HDL-C				
CARE [8]	4159	5	Pravastatin	139	39	9	78	1.6	0.37
VA-HIT [29]	2531	5.1	Gemfibrozil	112	32	11	1.7	3.3	0.23
GISSI-Prevenzione [2••]	5664	3.5	Omega-3 fatty acids	138	42	2	2.1	6	0.008
DART [10]	2033	2	Oily fish	250*	37	27	3.5	17.5	<0.05
LIPID [9]	9014	6.1	Pravastatin	150	36	22	3.1	5.1	0.001
Lyon Heart Study [30]	605	3.8	Mediterranean Diet	175	45	56	3.0	7.9	0.03
4 S [3]	4444	5.4	Simvastatin	188	46	29	3.3	6.1	0.0003

*Total cholesterol ; LDL-C not given.
HDL-C—high-density lipoprotein cholesterol; LDL-C—low-density lipoprotein cholesterol.

and evaluated an essentially nutritional product that is without known side effects or drug interactions. On balance, the GISSI Prevenzione was a landmark study, illustrating more clearly than any previous trial the potential role that ω-3 FAs may play in the prevention of CHD.

The Diet and Reinfarction Trial

The stimulus for the GISSI Prevenzione trial was the Diet and Reinfarction Trial (DART) [10]. This trial was a multicenter, secondary prevention trial conducted in Wales and published in 1989. It compared the effects of three different dietary interventions in 2033 post-MI patients. A factorial design was used, which allowed for three, essentially independent, interventions to be tested in one study. The interventions involved giving dietary advice to 1) reduce total fat intake to less than 30% of energy, 2) increase cereal fiber intake to 18 g/d, or 3) consume 200 to 400 g of oily fish per week. Patients assigned to the fish group who were unable or unwilling to consume fish were given the option of taking three fish oil capsules per day, providing a total of 900 mg EPA and DHA. The patients were then followed for cardiac events and total mortality for the next 2 years.

As in the GISSI trial, the other interventions tested (in this case, fat or fiber advice) had no clinically important impact, thus the study focused primarily on the effects of advising patients to consume oily fish. After 2 years of follow-up, total mortality was 12.8% in the control group and 9.3% in the fish-advice group (Table 1). This translated into a 27% reduction ($P<0.05$). As noted earlier, the DART study may be the most effective secondary prevention trial reported to date, with nearly 18 patient lives saved/1000/year. Of course, this was not a placebo-controlled, double-blind trial; nevertheless, its findings were sufficiently provocative to stimulate the initiation of the GISSI Prevenzione study.

There is naturally some question whether the DART effect was due to the oil or the fish. Might there not be some unknown component of fish that was beneficial, or perhaps the fish was substituted for some other noxious dietary component? In a post hoc attempt to address this question, Burr *et al*. [11] examined the clinical outcomes in the subgroup of patients assigned to the fish-advice group who, because they did not want to eat fish, were given capsules. This group (27% of patients) was matched with patients in the "no fish-advice" group, who had their index MIs at about the same time. The ischemic heart disease (IHD) and total death rates in these two matched groups (227 patients each) were then compared. The group given capsules experienced a 4.4% death rate with 3.5% ischemic heart disease (IHD) deaths, compared with 10.1% and 9.3%, respectively, in the control group. These differences were statistically significant. The GISSI trial has now confirmed the results of Burr *et al.'s* post hoc analysis in isolating the effect to EPA and DHA, not fish as such.

The fact that ω-3 FAs may operate via a novel mechanism to reduce cardiac death, which was observed by the DART study, was confirmed by GISSI. In the DART study, although total IHD events (fatal and nonfatal) tended to be reduced by oily fish consumption (-14%, P=ns), the greatest impact of fish advice was on fatal events (-32%, $P<0.01$), not on nonfatal events (+50%, P=ns). This suggested that ω-3 FAs may be protecting the myocardium from the ravages of ischemia, and thus preventing the development of fatal arrhythmias. The 45% reduction in sudden cardiac death reported in GISSI is consistent with this possibility.

There had been experimental support for this mechanism of action as far back as the late 1970s, when Black *et al.* [12] and Culp *et al*. [13] demonstrated that ω-3 FAs protected cats and dogs during experimental ischemia. This line of research was latter expanded by McLennan *et al*. [14,15] to rats and monkeys, and by Kang and Leaf [16] and Billman *et al.* [17] to arrhythmia-prone dogs and cultured myocardial cells. Together, these investigators have confirmed that in experimental settings, ω-3 FAs do have antiarrhythmic effects. Confirmation of this hypothesis in humans began to accumulate with the 1995 publication of a nested case-control trial from Seattle. Siscovick *et al.* [18] reported a highly significant, dose-dependent, inverse relationship between erythrocyte ω-3 FA levels (a biomarker for ω-3 FA intake) and risk for sudden cardiac death.

The Indian Experiment of Infarct Survival

The third randomized, controlled trial to test the effects of ω-3 FAs in CHD patients was published by Singh *et al.* [19] in 1997. About 360 patients admitted to the hospital with a suspected MI were randomized to fish oil (6 capsules per day, providing approximately 2 g of ω-3 FAs), mustard seed oil (a source of α-linolenic acid, the plant-derived parent ω-3 FA; 2.9 g/d provided in 20 mL of oil), or placebo (aluminum hydroxide, 100 mg). After 1 year, a variety of clinical outcomes were tabulated (Fig. 3), and revealed that both forms of ω-3 FAs appeared to markedly diminish risk for adverse clinical events. Although it was a small study and relatively short in duration, the study lends further support to the use of ω-3 FAs in the preventive regimen for the cardiac patient.

Safety

As the evidence for beneficial effects of ω-3 FAs has continued to mature, the question of safety has also been addressed. In 1997, the US Food and Drug Administration concluded that dietary intakes of up to 3 g/d of EPA and DHA are "generally recognized as safe" [20]. That is to say that ω-3 FAs may be incorporated into the general food supply (up to 3 g/d) with no health concerns. Because all three trials discussed above utilized less than this intake, these FAs now appear to be both efficacious (for secondary prevention of CHD) and safe.

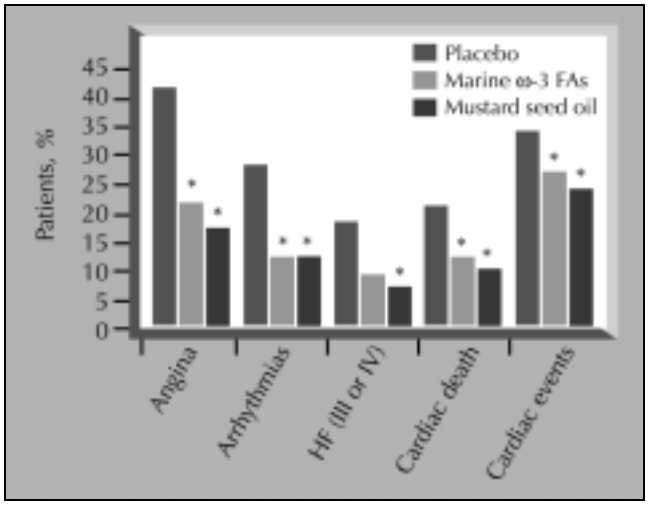

Figure 3. Indian Experiment of Infarct Survival–IV [19]. Effects of 1 year of therapy with either placebo, marine ω-3 fatty acids (FAs), or mustard seed oil in patients admitted for suspected myocardial infarction. Groups included 118, 120, and 122 patients, respectively. (HF—heart failure.) (*Asterisk* indicates that $P<0.05$ vs placebo group.)

Conclusions

Our understanding of the role of ω-3 FAs in secondary prevention of CHD is becoming clearer. Intakes of about 1 g/d have been shown to confer clinically meaningful benefits to patients with preexisting CHD. Whether they have a role in primary prevention has not yet been rigorously addressed; it would seem likely that they would. Indeed, the pathophysiology responsible for second heart attacks is similar to that producing first heart attacks. Statins, which were first shown to be effective in secondary prevention, are now known to confer benefit in the primary prevention setting as well [21,22]. In addition, the epidemiologic support for a primary protective role of ω-3 FAs is substantial [23–28]. Thus, it seems appropriate to consider recommending increased ω-3 FA intakes both for patients with, and for patients at high risk for, CHD. Whether this is accomplished by dietary changes or by supplementation appears to be immaterial; benefits have been documented in both settings. Patients should obtain these FAs from whichever source they prefer. In conclusion, after 25 years of ω-3 FA research, there is sufficient evidence to support a recommendation that cardiac patients increase their EPA and DHA intake.

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- •• Of major importance

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