

Efficacy of Omega-3 Fatty Acid Supplementation in Primary and Secondary Prevention of Coronary Heart Disease

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Cardiovascular disease is the leading cause of death in the western world. For many years scientists have questioned the clinical advantage of lowering triglyceride levels for primary as well as secondary prevention of coronary artery disease. Although in recent years increased levels of serum triglycerides have been acknowledged as a risk factor for CAD [1], currently only one official recommendation exists [2]. An increase of 1 mmol/L has been associated with a 32% and 76% overall increased risk of cardiovascular disease in men and women respectively [3]. After adjustments for high density lipoprotein-cholesterol and other risk factors, the risk for CVD was attenuated but still remained statistically significant at 14% for men and 37% for women [3].

Other studies have shown that hypertriglyceridemia is associated with increased mortality in patients with known CHD [4], reduced event-free survival following coronary artery bypass graft surgery [5], and ischemic stroke [6]. A recent report from the National Health and Nutrition Examination Survey [7] emphasizes the lack of secondary preventive strategies despite frequent medical evaluation, and urges medical staff to increase patient awareness of CHD risk factor modification.

Omega-3 fatty acids of fish and fish oil are non-pharmacologic agents that effect blood lipids. Although both animal and human studies have shown that omega-3 polyunsaturated fatty acids lower triglyceride levels [8], no single mechanism of action has been identified [1] despite the fact that a wide range of biological effects has been recognized.

The multifaceted effects of eicosapentaenoic (EPA, 20:5n-3) and docosahexaenoic (DHA, 22:6n-3) acids are antithrombotic, anti-hypertensive and anti-inflammatory [9], and also include the prevention of arrhythmias [10], retardation of the atherosclerotic plaque [8], improvement in endothelial and vascular function [11], and stability of atherosclerotic plaque [12]. Two recent reports have emphasized the benefit of high n-3 PUFA intake and the prevention of sudden cardiac death both in primary [13] and secondary [14] prevention of CAD. The Nutrition Committee of the American Heart Association established recommendations for n-3 PUFA this year.

"A dietary (i.e., food-based) approach to increasing omega-3 fatty acid intake is preferable. Still, for patients with CHD, the dose of omega-3 (~1 g/d) may be greater than what can readily be achieved through diet alone. These individuals, in consultation with their physician, could consider supplements for CHD risk reduction. Supplements could also be a component of the medical management of hypertriglyceridemia, a setting in which even larger doses (2-4 g/d) are required" [15].

In this review we delineate the clinical manifestations for which the use of omega-3 PUFA should be considered in order to optimize patient treatment.

Omega-3 PUFA: observational studies

Numerous epidemiologic studies have established an association between n-3 PUFA and reduced risk of CHD [16-18]. Albert et al. [19] investigated prospectively the association between fish consumption and the risk of sudden cardiac death in 20,551 American male physicians aged 40-84 who were free of myocardial infarction, CVD and cancer at baseline for 11 years. They found that the multivariate relative risk of sudden death was 0.48 for men who consumed fish at least once a week compared to those who consumed fish less than once a month. The researchers concluded that consuming at least one meal of fish per week might substantially reduce the risk of sudden cardiac death in men. Siscovick et al. [20] further support the potential cardiac benefits of modest dietary n-3 PUFA intake from seafood, demonstrating a reduced risk of cardiac arrest in humans. Measuring both directly with a questionnaire and indirectly with a biomarker, they found that the intake of one fatty-fish meal/week was associated with a reduction in the risk of cardiac arrest, while higher consumption was not associated with any further reduction in such a risk. More recently, in the Seven Countries Study, the association between total, lean and fatty-fish consumption and the risk of CHD mortality was examined in 1,088 Finnish, 1,097 Italian and 553 Dutch men aged 50-69 years and free of CHD [16]. After a 20 year follow-up no association was found between total and lean-fish consumption regarding CHD mortality. However, fatty compared with non-fatty fish intake was associated with a 34% reduction in CHD mortality in all three countries. This finding suggests that the high n-3 PUFA concentration in fatty fish (15 g of fatty fish, such as mackerel or herring, provides about 400 mg of n-3 fatty acids, whereas 15 g of less fatty fish, such as cod or plaice, provides about 50 mg of n-3 fatty acids) is responsible for the lower incidence of CAD. Furthermore, the Kuopio Ischemic Heart Disease Risk Factor Study

CAD = coronary artery disease

CVD = cardiovascular disease

n-3 = omega-3

PUFA = polyunsaturated fatty acids

supports the hypothesis that n-3 PUFA plays a cardioprotective role in CHD. Rissanen et al. [17] also found that a high proportion of the fish-derived fatty acids DHA and DPA (docosapentaenoic acid) in the serum of 1,871 men from eastern Finland aged 42–60 years without known CHD at baseline is associated with a decreased risk of acute coronary events. Men receiving the highest proportion of serum DHA and DPA had a 44% reduced risk of acute coronary events compared with those receiving the lowest. In an attempt to explain the inconsistency of results in numerous studies associating fish intake or circulating levels of fish-derived fatty acids and CHD, the authors suggest that mercury may play a role. Fish and fish products are a dominant source of mercury in food. Despite high fish consumption in Finland, cardiovascular diseases are

common. The authors suggest that the high mercury content in Finnish lakes may attenuate the protective effect of n-3 PUFA by promoting the preoxidation of unsaturated fatty acids, such as DHA and DPA, thereby inhibiting an important antioxidant mechanism in humans.

Omega-3 PUFA in primary prevention of CHD

[Table 1]

Many studies have consistently demonstrated the efficacy of n-3 PUFA in reducing triglyceride levels in humans and have recommended their use for reducing the risk of CVD [2,8]. The hypolipidemic effect of DHA and EPA in humans is believed to be

DHA = docosahexaenoic acid

DPA = docosapentaenoic acid

EPA = eicosapentaenoic acid

Table 1. Summary of clinical trials of the effect of n-3 PUFA in primary prevention

Authors	Subjects	Study design	Length weeks (months)	Diet restriction	Treatment	Results
Stalenhoef et al. [24]	28 primary hypertriglyceridemic patients	PC, DB, R	12 (3)	NCEP step 1 diet	Omacor 4 g/day vs. gemfibrozil 1,200 mg/day	O ↓ TG by 37%, G ↓ TG by 40%, O ↑ HDL by 11%, G ↑ HDL by 17%, O ↓ VLDL by 33%, G ↓ VLDL by 39.7%, O ↑ LDL by 29%, G ↑ LDL by 33.6%. The LDL-C increase represents mainly an increase in more buoyant LDL-C subfraction profile
Calabresi et al. [23]	14 familial combined hyperlipidemic, without overweight	DB, PC, R	24 (4)	Standard low fat diet for at least 6 months prior to trial initiation	Omacor 4 g/day	O ↓ TG by 27% compared to baseline and 21% compared to placebo, O ↓ VLDL-C by 18% and 29% compared to baseline and placebo respectively, O ↑ LDL-C by 25% and 21% compared to baseline and placebo respectively. O did not change the small dense LDL subfraction. O causes redistribution of LDL-C subclasses towards less dense lipoprotein particles.
Nordoy et al. [21]	41 healthy patients with defined hyperlipidemia without lipid-lowering medication	DB, PC, R	10–15	Typical Norwegian diet	Simvastatin 20 mg/day + Omacor 4 g/day or simvastatin 20 mg/day + placebo	Addition of n-3 PUFA to simvastatin further decreases the TG levels. HDL-C was not affected.
Stark et al. [25]	36 postmenopausal women (19 on HRT and 16 not on HRT)	DB, PC, R	4 (1)	Not mentioned. Study performed in Canada.	4 g EPA + DHA per day or placebo	Treatment with w-3 PUFA was associated with highly significant decrease (26%) in TG level. TG:HDL ratio ↓ 28% with n-3 PUFA supplementation. No significant change in T.chol:HDL-C, LDL-C:HDL-C, T.chol concentration, heart rate, SBP, DBP or arterial pressure.
Kurabayashi et al. [26]	23 premenopausal and 118 postmenopausal hyperlipidemic women aged 46 to 62 (T.chol 220–280 mg/dl and TG 150–400 mg/dl)	Prospective observational DB, PC, R	48 (12)	Not mentioned. Study performed in Japan.	Estriol 2 mg/day (control) or EPA 1,800 mg + estriol 2 mg/day	TG ↓ 27% in the EPA supplement group and ↑ 7.5% in control, LDL-C ↓ 8.3% and 8.1% in control and EPA group respectively but without significant difference. HDL-C remain almost unchanged.
Nordoy et al. [22]	42 (12 women, 29 men) aged 25–60 with combined hyperlipidemia	DB, PC, R	10–15 weeks	Habitual Norway diet without lipid-lowering drugs, antioxidants or fish concentrate intake.	Simvastatin 20 mg/day for 5–10 weeks ↓. Randomization ↓ Simvastatin 20 mg/day alone or simvastatin 20 mg/day + Omacor 4 g/day	Both treatments reduced postprandial hypertriglyceridemia. The degree of postprandial hypertriglyceridemia was reduced significantly more when n-3 PUFA were added. Combination therapy reduced the thrombotic potential associated with intake of fat-rich meals.

TG = triglycerides, DB = double-blind, PC = placebo-control, R = randomized, NCEP = National Cholesterol Education Program step I diet = <30% of total calories a day from fat (maximum 10% saturated fat) and cholesterol <300 mg/day, O = Omacor (each capsule contains 850–882 mg EPA and DHA as ethylesters in the average ratio of EPA to DHA of 1:2), DM = diabetes mellitus.

primarily due to a reduction in hepatic triglyceride-rich synthesis, thereby diminishing secretion of triglyceride-rich lipoprotein from the liver into the circulation, rather than an increased clearance of very low density lipoprotein [2].

In recent years the efficacy of n-3 PUFA (EPA and DHA) to favorably alter lipid levels was investigated in primary prevention trials by comparing the supplemented group either to the controls or to the administration of fibrate or estriol. Nordoy and co-workers [21] studied the additional efficacy and safety of EPA and DHA to simvastatin in patients with defined hyperlipidemia. When n-3 PUFA was added to the simvastatin treatment, a significant reduction in serum triglyceride was observed ($P < 0.001$), whereas HDL-C was not affected. Furthermore, neither the levels of total cholesterol, triglyceride, apolipoproteins B and E in the low density and intermediate density lipoprotein fractions, nor the levels of lipid peroxides, were significantly affected by the addition of n-3 PUFA as compared to the addition of placebo. The potential positive effect of supplemented n-3 PUFA to simvastatin was further evaluated by Nordoy et al. [22] in patients with combined hyperlipidemia. A highly significant reduction in postprandial hyperlipemia was observed after combined treatment with simvastatin and n-3 PUFA compared with simvastatin alone. The study also showed that when patients with combined hyperlipemia are treated with diet and simvastatin with or without supplementation of n-3 PUFA, only minor changes occurred in the concentration of coagulation factors and fibrinolytic variables usually associated with increased thrombotic tendency. However, during postprandial hyperlipemia, a significant reduction in factor VII – the first enzyme involved in the extrinsic pathway of blood coagulation – was noted, suggesting that such treatment may reduce the thrombotic potential associated with intake of fat-rich meals. The authors claim, therefore, that n-3 PUFA in the diet reduces both the degree and the extent of postprandial hypertriglyceridemia, which may represent an independent predictor for CHD.

The ability of EPA and DHA to favorably correct plasma lipid/lipoprotein levels and LDL particle distribution was further supported by Calabresi et al. [23]. Familial combined hyperlipidemia patients not taking lipid-lowering medication were randomly assigned to 4 g/day of EPA and DHA or placebo for 4 months. Both triglyceride and VLDL-C decreased significantly compared with placebo. LDL-C increased in the treatment group compared to baseline and placebo, however no change in the small, dense LDL subfraction was observed. The addition of n-3 PUFA caused a redistribution of LDL subclasses toward less dense lipoprotein particles and effectively lowered triglyceride and VLDL-C levels. Stalenhoef and colleagues [24] compared the effect of 4 g/day of EPA and DHA versus gemfibrozil 1,200 mg/day on lipid and lipoprotein levels, LDL subfraction profile and LDL oxidizability. The results indicated a relatively similar effect on lipoproteins and triglycerides. LDL-C elevation represented mainly an increase in more buoyant LDL-C subfraction profile. The authors agreed that

both gemfibrozil and n-3 PUFA have anti-atherogenic properties. Despite the *in vitro* increased susceptibility of LDL to oxidation by supplemented n-3 PUFA, the role of n-3 PUFA in the course of cardiovascular disease is being downplayed by the lack of similar findings *in vivo* and the wide biological effects that may be related to protection against atherogenesis (i.e., reduced platelet aggregation and vasoconstriction and anti-arrhythmic effect). Two recent studies examined the effect of n-3 PUFA on postmenopausal women. Stark et al. [25] randomly assigned postmenopausal women on and off hormonal replacement therapy to receive either placebo oil (control) or 4 g EPA and DHA per day. Supplementation with n-3 PUFA significantly decreased triglyceride levels ($P < 0.0001$) and triglyceride:HDL ratio. No significant change in LDL-C, HDL-C, total cholesterol, heart rate, systolic blood pressure, diastolic blood pressure or arterial pressure was observed. The effect of supplemented n-3 PUFA in postmenopausal women through the decrease in triglycerides was estimated to decrease the risk of CHD by 27%. Kurabayashi and associates [26] assessed the efficacy and safety of EPA supplementation to estriol for the treatment of hyperlipidemia in Japanese women. Results showed better triglyceride reduction in the treatment group, but no change in LDL-C or HDL-C. No adverse effect to treatment was observed. The most important finding of this study, as noted by the authors, was that combination therapy with EPA and estriol significantly decreased the serum triglyceride level compared with estriol alone, and therefore might prevent hypertriglyceridemia caused by hormonal replacement therapy.

Omega-3 PUFA in secondary prevention of CHD

[Table 2]

The effect of w-3 PUFA on cardiovascular endpoints in patients with established CHD was initially evaluated using dietary fatty-fish intake, as this represented the most concentrated food source of n-3 PUFA. The Diet and Reinfarction Trial (DART) was the first randomized clinical trial to examine the effects of n-3 PUFA on survival [27]. In this study, post-myocardial infarction patients were randomly assigned to receive three dietary recommendations. After 2 years, a 29% decrease in all-cause mortality was noted among those advised to consume fatty fish ($P < 0.05$). Reduction in mortality was largely due to a decrease in CHD mortality. However, the total number of coronary events (recurrent non-fatal MI) did not change.

A decade later, the GISSI-prevention Trial [28] added some important data. In this methodologically sound study, a 30% reduction in cardiovascular death and 20% decrease in all-fatal events (cardiovascular death and stroke) were attributed to the n-3 PUFA supplementation for post-MI survivors. However, no clinical benefit was attributed to vitamin E. Bigger and El-Sherif [29] give an interesting interpretation to the clinical results of the above studies. They suggest that myocardial infarction is not substantially less likely in patients taking n-3 PUFA, but that it is less likely to be fatal because lethal arrhythmias are suppressed during acute MI.

Von Schacky et al. [30] further evaluated the effect of dietary intake of n-3 PUFA on the course of coronary artery atherosclerosis.

HDL-C = high density lipoprotein-cholesterol
LDL = low density lipoprotein
VLDL-C = very low density lipoprotein

MI = myocardial infarction

Table 2. Summary of clinical trials on the effect of w-3 PUFA in secondary prevention

Authors	Subjects	Study design	Length weeks (months)	Diet restriction	Treatment	Results
Durrington et al. [32]	59	DB, PC, R	1	NCEP step 1	Omacor 2 g b.i.d on top of simvastatin 10–40 mg/day	↓ TG by 20–30%, ↓ VLDL-C by 30–40%. No effect on LDL-C and HDL-C. No adverse effect on glycemic control in patients with DM.
Nilsen et al. [31]	300	DB, PC, R	1/2–1	Dietary habits of population, coastal area diet rich in fish products	Omacor 2 g b.i.d or corn oil	↓ TG by 18%, ↑ HDL-C by 19%. No clinical benefit between groups (subsequent cardiac events)
GISSI Trial [28]	11,324	PC, R, Open label	3.5	Mediterranean dietary habits	850–882 mg EPA and DHA or 300 mg vitamin E or both or placebo	No clinical benefit to vitamin E; ↓ in cardiovascular death by 30%; ↓ in all fatal events by 20% (not clear)
DART Study [27]	2033 men after MI	PC, R	2	Three dietary interventions: – low fat intake – increase fatty fish intake to at least 2 fish meals per week – increase fiber intake (>18 g of cereal fiber/day)	No supplement	29% ↓ in all-cause mortality for those advised to consume fish. Total number of coronary events did not change.
Von Schacky et al. [30]	223	PC, DB, R	2	Not mentioned	1.5 g EPA and DHA	Less progression and more regression of CAD on coronary angiography for supplemented group compared with control ↑ LDL-C level ↓ TG level

After 2 years of n-3 PUFA supplementation, angiographically proven CHD patients showed less progression and more regression of coronary artery disease compared with controls. In addition, triglyceride levels were significantly lower in the fish-oil group at months 1, 6, 12 and 18, but not at month 24; LDL-C levels were higher in the fish-oil group at months 6, 18 and 24. No cholesterol subfraction analysis was done.

No effect of n-3 PUFA administration early after an acute MI on subsequent cardiac events and serum lipids was recently observed by Nilsen et al. [31]. Acute MI survivors randomly assigned to n-3 PUFA or corn oil supplementation showed no clinical benefits in terms of cardiac event and revascularization, despite a favorable effect of w-3 PUFA supplementation on lipid profile. It is important to keep in mind that the dietary habits of the population in this study are typical to a Norwegian coastal area, which is very rich in fish products and, therefore, in dietary n-3 PUFA intake. This factor may help in part to explain the results.

Recently, Durrington et al. [32] examined the triglyceride-lowering effectiveness, safety and tolerability of n-3 PUFA supplementation in patients with established CHD and persisting hypertriglyceridemia added to simvastatin at doses of 10–40 mg/day. The results indicated a reduction in triglyceride and VLDL-C levels ($P < 0.0005$). No effect on LDL-C and HDL-C, or on glycemic control in patients with diabetes mellitus, was observed. Reflecting clinical practice, especially in secondary prevention, statins are the first drug of choice to correct hyperlipidemia. This study design allowed the authors to conclude that the triglyceride responses to n-3 PUFA supplementation are not influenced by the dose of simvastatin.

The possible negative effects of w-3 PUFA

The two main negative effects attributed in the literature to n-3 PUFA supplementation were an increase in LDL-C and a possible

increase in LDL-C oxidation susceptibility. Most studies evaluating the effect of omega-3 PUFA on lipid profiles did indeed show elevated levels of LDL-cholesterol, but subfraction analyses found the increase to be generally less dense (buoyant) and not atherogenic LDL particles. The importance of LDL-C particle size analyses with relation to CHD risk was emphasized recently by Benoit et al. [33]. In a prospective phase of the Quebec Cardiovascular Study, they evaluated the extent to which the risk attributed to small LDL-C (small = peak particle diameter ≤ 25.64 nm, intermediate = $25.64 < \text{LDL-PPD} < 26.05$, large = $\text{LDL-PPD} > 26.05$) may be independent of a concomitant variation in plasma lipoprotein-lipid concentration in 103 subjects who developed ischemic heart disease and 103 matched controls during a 5 year follow-up period. The results indicated that a significant proportion of the risk associated with the presence of small, dense LDL-C particles may be independent of the concomitant variation in plasma lipid concentration. Patients with the dense LDL-phenotype at baseline were at greater risk for the subsequent development of ischemic heart disease than those with larger particles (3.6 and 5.1-fold increase in odds ratios respectively). The authors concluded that the combination of small LDL particles and elevated apo-B levels represent the metabolic state most predictive of ischemic heart disease. However, the importance of other lipids, such as triglyceride, and HDL-C in relation to CHD risk, is further supported by the relatively strong association of those lipids to LDL-PPD. Mori and team [34] conducted a double-blind placebo-controlled trial with 56 overweight men aged 48.8 ± 1.1 years with mild hyperlipidemia, in order to examine the differential effects on serum lipids and lipoprotein, glucose and insulin of purified EPA versus DHA. Their study further supports the cardioprotective effect,

PPD = peak particle diameter
apo= apolipoprotein

especially of DHA. The increase in LDL-C after DHA supplementation in their study represented a shift to less atherogenic particles as measured by LDL-particle size, in addition to a significant reduction in triglyceride levels and an increase in HDL-C.

With respect to the possible harmful effect of n-3 PUFA supplementation on LDL-C susceptibility to oxidation, a recent study [35] examined the effect of three different oil supplements (sunflower, oleate and fish) on indexes of *in vivo* lipid peroxidation. A three-period, three-treatment, blinded crossover design was used. Each treatment period lasted 5 weeks and was followed by a 7 week washout interval to minimize any carryover effect from previous treatment. The 16 participants were postmenopausal women taking hormone replacement therapy. Results of the assays of *in vivo* lipid peroxidation did not uniformly support the idea that the increased number of double bonds in dietary PUFA results in increased susceptibility to lipid peroxidation. The most specific indexes of lipid peroxidation according to the authors (F₂-isoprostanes and malondialdehyde) were not higher after supplementation with fish oil than after sunflower oil and safflower oil supplementation. They provide an explanation to the inconsistent results with regard to the effect of n-3 PUFA on *in vivo* lipid peroxidation. They state that studies showing an increased potential for oxidative stress are based primarily on the results of the thiobarbituric acid assay without more specific techniques for checking lipid peroxidation. Therefore, they concluded that the potentially beneficial effects of diets rich in n-3 PUFA in preventing or ameliorating chronic conditions such as cardiovascular disease might not be offset by an increased risk of lipid peroxidation *in vivo*. The possible contribution of n-3 PUFA to oxidative stress has been further examined by Mabile et al. [36]. These researchers evaluated the effect of fish-oil consumption (3 g/day of EPA and DHA) over an 8 week period on w-3 fatty acid incorporation into erythrocyte membranes and subsequent *ex vivo* oxidative stress-induced hemolysis in 16 normolipidemic and 12 hypertriglyceridemic subjects. Results indicated that n-3 PUFA afforded the red blood cells of healthy normolipidemic subjects some protection against hemolysis. The triglyceride-lowering n-3 PUFA did not aggravate the hemolytic process in the red blood cells of subjects with hypertriglyceridemia. Although n-3 PUFA are highly susceptible to oxidation, when taken in moderate amounts and incorporated into membranes these fatty acids do not necessarily impair membrane function and therefore may represent an added benefit in the treatment of patients with hypertriglyceridemia.

The preliminary suggestion that a high level of dietary n-3 PUFA may be a risk factor for hemorrhagic strokes was introduced by Pedersen and colleagues [37]. They found a significant association between fatal hemorrhagic stroke and high levels of n-3 PUFA in perirenal adipose tissue (representative of long-term diet) in Greenlanders. To further support this theory, they cite the marked decrease in mortality rate due to hemorrhagic strokes that occurred after the traditional Japanese diet (high in n-3 PUFA) became increasingly westernized from 1950 to 1980. However, a more accurate examination of the association between dietary fish and n-3 PUFA intake and risk of stroke subtypes in women [38] indicates that higher consumption of fish and n-3 PUFA is associated with a

reduced risk of thrombotic infarction, but is not related to risk of hemorrhagic stroke. When interpreting the results, it is important to bear in mind the difference in the general dietary patterns of the two populations being analyzed, and in n-3 PUFA intake in particular.

Conclusions

There is a wealth of evidence to support the use of n-3 PUFA in optimizing therapy for patients with CHD risk factors. Treatment with n-3 PUFA in patients with established CHD and mild to moderate hypertriglyceridemia (up to 500 mg/dl) appears advantageous over the use of fibric acid for the following reasons:

- n-3 PUFA in addition to 3-hydroxy-3-methylglutaryl coenzyme-A inhibitor (statin) therapy does not increase patients' risk for rhabdomyolysis and myositis, contrary to the statin/fibrate combination.
- n-3 PUFA may confer additional benefits with regard to cardiovascular disease, such as anti-arrhythmic, antihypertensive, antithrombotic and anti-inflammatory properties as well as plaque stability.
- An effective dose (1–3 g/day) can be naturally obtained by diet without the need for supplementation.
- Low cost [29].
- Absence of reported adverse events: n-3 PUFA supplementation (EPA and DHA) up to 3 g per day was recently recognized as safe by the U.S. Food and Drug Administration [39].

This review supports other investigators [29,37] who believe that n-3 PUFA (EPA and DHA) either in the form of dietary intake (when feasible) or as a supplement should be used to optimize the health of CHD patients.

Despite 150 years of research and approximately 30 years of medical interest in the relationship between n-3 fatty acids and cardiovascular disease, the guidelines of most national and international cardiology societies do not embrace the use of n-3 fatty acids for secondary prevention of coronary atherosclerosis [40]. Only recently has the American Heart Association published its recommendations [15]. The cause is multifactorial, as reviewed coherently and precisely by Von Schacky [30] and Dyerberg et al. [40]. However, the main reason is probably the scarcity of studies investigating the pharmacologic n-3 fatty acid intervention and examining the cardiovascular hard endpoints such as mortality and morbidity. Therefore, "To be fully accepted as a preventive modality, at least one step, a convincing and methodologically impeccable trial with clinical endpoints conforming to present standards, needs to be taken" [40].

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