



Role of Polyunsaturated Fatty Acids in Cardiovascular Diseases

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ABSTRACT

Polyunsaturated fatty acids (PUFAs) particularly ω -3 PUFAs showed great assure in prevention of cardiovascular diseases (CVD). The evidence for CV benefits of PUFA comes from eicosapentaenoic acid (EPA) with or without docosahexaenoic acid (DHA) in primary prevention, after myocardial infarction (MI), with heart failure (HF). The epidemiologic studies and trials showing the benefits of PUFA, specifically EPA and DHA, in CV prevention and provide potential mechanisms. The target EPA and DHA consumption should be at least 500 mg/day for individuals without basic evident CV disease and at least 800 to 1,000 mg/day for individuals with known coronary heart disease (CHD) and heart failure (HF) and optimal dosing and relative ratio of DHA and EPA ω -3 PUFA that provides maximum cardio-protection at risk of CVD as well in treatment of atherosclerotic, arrhythmic, and primary myocardial disorders.

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Introduction

The dietary components other than fats and oils, including proteins, carbohydrates, fiber and trace minerals, may also affect blood lipid levels and the development of atherosclerosis. The possible relationship between diet (particularly fats) and Coronary Heart Disease (CHD) remains uncertain, and the appropriateness of specific dietary recommendations for the general population is not agreed upon. The nutritionists emphasize moderation in the consumption of fat as well as other nutrients. While atherosclerosis is the slow, progressive narrowing of an artery that gradually reduces blood flow, the actual precipitating event of a heart attack is frequently thrombosis, the formation of a blood clot that can lodge in an artery blocking blood flow. If the blockage of the artery is complete, a heart attack or stroke may result. The atherosclerosis (including elevated serum cholesterol levels) is related to thrombotic risk. The specific dietary

Fatty Acids (FAs) might affect thrombotic tendency, ω -3 PUFAs (e.g., from fish oils) have antithrombotic effects (1-6). The mechanisms of these effects appear to involve the metabolism of compounds related to eicosanoids. In contrast to the effects of ω -3 PUFAs, dietary long-chain Saturated FAs (SFAs), such as stearic acid, is thrombogenic to humans. Although SFAs may play a role in thrombotic events, there is a relationship to thrombotic risk and to elucidate the possible mechanism of action. Lipoprotein (a), or Lp(a), particle similar to LDL, is a risk factor for CHD due to its high serum levels in many heart attack victims. Lp (a) levels are thought to be largely controlled by genetic factors, however, the diet also may influence Lp (a) levels (7, 8). The LDL particle size may influence vulnerability to CHD. An abundance of smaller size LDL particles has been associated with increased CHD risk. The larger LDL is characterized as phenotype A and the smaller LDL as phenotype B. Phenotype B has been shown to be atherogenic and is associated with lower HDL levels, higher triglycerides, higher levels of intermediate density lipoproteins, and an increased risk of CHD. Although LDL phenotypes A and B are thought to be determined by genetics only, substantial reductions

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in energy from fat could be detrimental to certain individuals. The dietary factors influence the risk of CHD. The three most important dietary risk factors for atherogenesis are saturated fat Cholesterol (Chl), and obesity. Two-step dietary guidance program designed to reduce total fat, saturated fat and Chl, which it believes could reduce average blood Chl levels. The high amount of carbohydrate intake is increased to replace those calories lost through reductions in fat intake. In particular, the mortality from CHD decreased. Specific reasons for decreasing mortality due to CVD are not known. However, recognition and increased public awareness of major risk factors (cigarette smoking, hypertension, and elevated serum Chl) and more effective treatment of CHD have probably played roles. The ω -3 PUFAs, contained in marine fish oil, such as EPA and DHA, lead to cardioprotection and reduce sudden cardiac death (SCD) (9). The molecular mechanisms by which ω -3 PUFAs exert their cardioprotective effects are not fully understood. The ω -3 PUFAs putatively affect membrane ion channels (10, 11). They exert antihypertensive, antiproliferative, anti-inflammatory, and anticoagulative properties (12). In hypertensive rats, ω -3 PUFA treatment lowered blood pressure (BP) (13). The reduced vasoconstriction was mediated by inhibition of angiotensin II (Ang II)-induced intracellular Ca^{2+} mobilization and protein kinase C phosphorylation (14). The ω -3 PUFA treatment lowered BP and improved renal and cardiac damage (15). Dietary ω -3 PUFAs and direct renin inhibition improve electrical remodeling of high human rennin hypertension. Fish oil is obtained in the human diet by eating oily fish, such as herring, mackerel, salmon, albacore tuna, and sardines, or by consuming fish oil supplements or cod liver oil. However, fish do not naturally produce these oils, but obtain them through the ocean food chain from the marine microorganisms that are the original source of the omega-3 PUFA found in fish oils. Numerous prospective and retrospective trials from many countries have shown that moderate fish oil consumption decreases the risk of major CV events, such as Myocardial Infarction (MI), SCD, CHD, Atrial Fibrillation (AF), and recently, death in patients with Heart Failure (HF) (16-18). Considerable attention has been directed at the various classes of FAs and their impact on the prevention and treatment of CVDs. Most of the evidence for benefits of the ω -3 PUFA has been obtained for EPA and DHA, the long-chain FAs in this family. The alpha-linolenic acid (ALA) is the plant-based precursor of EPA. The ω -3 PUFA at a dose of approximately 1 g/day used to prevent the patients with CHD (19). The health benefits of these long chain FAs are numerous and remain an active area of research. Effects of the long chain ω -3 PUFA in the prevention of various CVDs has been evaluated in this review.

Diet and Cardiovascular Disease

Cardiovascular diseases (CVD), which include heart attack and stroke, are the leading causes of death in the world wide. The principal form of CVD is coronary heart disease (CHD) or heart attack. Atherosclerosis, the gradual blocking of arteries with deposits of lipids, smooth muscle cells, and connective tissue, contributes to most deaths from CVD. The CVDs are chronic degenerative diseases (CDD). A number of risk factors for CVD have been identified. These include positive family history of CVD, cigarette smoking, hypertension (high BP), elevated serum cholesterol (Chl), obesity, diabetes, physical inactivity, male sex, age, and excessive stress. Although these risk factors have been associated statistically with the incidence and mortality of CVD. A considerable interest began to develop a possible relationship between dietary fat and the incidence of CHD. Since diet can affect serum Chl and heart attack risk increases with increased serum Chl levels. The diet modification is to achieve lower serum Chl levels. These diet modifications include reducing consumption of total fat, saturated fat, and Chl. The total serum Chl is distributed largely between two general classes of lipoprotein carriers, low-density lipoprotein (LDL) and high-density lipoprotein (HDL). The largest portion of total Chl is in the LDL fraction, and elevated levels of LDL Chl are associated with increased CHD risk. High levels of HDL Chl have been associated with protection against CHD. One factor that has been related to increased levels of HDL Chl is regular exercise. However, diet or exercise related modifications of LDL or HDL levels will affect development of CHD. Uses of high PUFAs containing diet will be reduce serum Chl levels of the population. Chl management established that LDL Chl should continue to be the main target of Chl lowering efforts. Age (>45 years in men and >55 years in women) considered as a high risk factor for CHD. The levels of total Chl and the LDL and HDL fractions in the blood are influenced by a combination of factors, including age, sex, genetics, diet, and physical activity. Diet and exercise are factors which individuals can modify and recommended for reduction of risk factors for chronic diseases such as CHD. The three major categories of dietary FAs (SFAs, MUFAs, and PUFAs) appear to influence total, LDL, and HDL Chl in different ways. Diets high in SFAs increase total as well as LDL and HDL Chl levels compared to diets low in SFAs. The specific SFAs palmitic (main SFAs in the diet), myristic and lauric acids are considered to be Chl rising. MUFAs (e.g., olive, canola) and PUFAs (e.g., sunflower, corn, soybean) are Chl lowering when they replace significant levels of SFAs in the diet. The PUFAs lower LDL and total Chl. The diets high in MUFAs compared with PUFAs decrease LDL Chl while maintaining HDL Chl levels (20). The effect of consuming PUFA and MUFA are effective to decrease in the amount of both LDL and HDL Chl level in blood. Numerous epidemiologic and

observational studies have been published on the CV benefits of ω -3 PUFA (16, 17, 21). These observations raised speculation on the potential benefits of ω -3 PUFA (particularly EPA and DHA). Evidence has raised the concern that intrusion of dietary habits, including massive amounts of shortening and other saturated fats may partly overwhelm the cardioprotective effects of ω -3 PUFA (21). The ω -3 PUFA showed reduction in major CV events (22). The effects of ω -3 PUFA are used to prevent the CHDs. In MI patient, ω -3 PUFA, either in the form of oily fish or fish oil capsules, reduced mortality with the benefit almost attributable to a reduction in CHD mortality (23). The reduction in CV events was particularly impressive in who consumed fish oil capsules as opposed to simply increasing dietary fish consumption, likely indicating a threshold effect of ω -3 PUFA. Further analyses showed that this endpoint reduction was driven by a highly significant 45% reduction in SCD (23, 24).

Major Classes of Fatty Acids

I. ω -9 Oleic acid: Most vegetable oils (canola, olive); animal fats.

II. ω -6 Linoleic acid: Many vegetable oils (corn, safflower, soybean).

III. ω -3 α -linolenic acid: Selected vegetable oil (flaxseed, canola).

EPA: Marine oils and fish and DHA: Marine oils and fish

Potential EPA and DHA Effects

Antiarrhythmic effects, improvements in autonomic function, decreased platelet aggregation, vasodilation, decreased BP, anti-inflammatory effects, improvements in endothelial function, plaque stabilization, reduced atherosclerosis, reduced FFAs and triglycerides and up-regulated adiponectin synthesis (25-27).

Reduced Collagen Deposition

In hypercholesterolemia patients (70% women) were used statin alone or statin and highly purified EPA 1,800 mg/day. At the end of the 5-year study, EPA had a 19% reduction in major CVD events. Unlike the GISSI-Prevenzione study, however, which included lower doses of EPA but also DHA, the moderate dose of EPA alone in the JELIS trial was not associated with a reduction in SCD (18). Some study showed that the ω -3 PUFAs lower CV risk in both primary and secondary prevention. Some exception indicated, patients with angina treated with fish oil capsules seem to have a higher risk of SCD than untreated control subjects (28, 29). It did not show a benefit of ω -3 PUFA supplementation in post-MI patients (30, 31).

Eicosapentaenoic acid in Primary Prevention

Benefit of ω -3 PUFA therapy on total mortality,

sudden death, CHD mortality, and CV mortality (24). Eicosapentaenoic acid (EPA) (1.8 g/day) reduced the incidence of major adverse coronary events (18). This prevent secondary CHD, these results certainly raise the possibility that ω -3 PUFA may not provide additional short-term protection to low-risk patients receiving extensive modern post-MI therapies. As the only dietary source of ω -3 PUFA, ALA is considered to be inadequate because humans convert typically 5% of ALA to EPA and even less to DHA (32). In some epidemiologic studies, ALA has been inversely associated with CV events (33). ALA intake and its blood levels predicted a prognosis, independent of EPA/DHA levels, in a post-MI population (34). Nevertheless, the overall evidence is much weaker for ALA than for EPA and DHA.

Evidence of Benefit in Atherosclerosis

Several epidemiologic and necropsy studies have indicated that Japanese men have significantly lower levels of atherosclerosis than Caucasian men residing in the USA. Assessed intima-media thickness (IMT) and coronary artery calcification (CAC), both independent predictors of CV events, Japanese men have lower grades of atherosclerosis than do the Caucasians (35). The results suggested that Japanese men had the lowest level of atherosclerosis. The ω -3 PUFA serum levels correlated inversely with IMT in the Japanese men, but CAC burden was not related to ω -3 PUFA status in any cohort. Nevertheless, the differences between carotid IMT and CAC levels in the 3 groups, which persisted after adjustment for the traditional CHD risk factors, disappeared after adjustments for serum ω -3 PUFA content, suggesting that very high intake of marine-derived ω -3 PUFA has antiatherosclerotic effects (36). Despite these results, other evidence suggests that a very high intake of shortening and other saturated fats in the diet may overwhelm the beneficial effects of high ω -3 PUFA intake in Alaskan Natives and the Japanese (21).

Evidence in Arrhythmias

Chronic imbalance of the autonomous nervous system (ANS), with increases in symptomatic and/or decreases in parasympathetic tone, increases the risk of major CV events and dysrhythmias (3, 37). Several trials showed that ω -3 PUFA improve sympathovagal balance. The post-MI patients and with impaired systolic function had improvements in heart rate variability after 4.3 g/day of EPA and DHA for 12 weeks (38). Using lower doses of ω -3 PUFA showed significant reductions in resting heart rate and improvement in heart rate variability after 4 months of modest-dose ω -3 PUFA (810 mg/day EPA and DHA) (39). Fourteen weeks of moderate-dose ω -3 PUFA (1, 260 mg/day EPA and DHA) reduced the average heart rate in patients with complex ventricular arrhythmias (40). High dietary fish intake was associated with lower

heart rate, slower atrial ventricular conduction, and a substantially lower likelihood of having a prolonged QT interval (41). These studies suggest that ω -3 PUFA have benefits in improving autonomic function.

The ω -3 PUFA may prevent fatal arrhythmias via their ability to inhibit fast, voltage-dependent sodium channels and L-type calcium channels (3). Furthermore, DHA has been shown to directly inhibit the delayed rectifier potassium channel, which is responsible for the depolarization phase of ventricular and atrial cardiac potentials. Although the relative effects of DHA and EPA remain uncertain, DHA's effect on atrial and ventricular repolarization raises the possibility that DHA could provide greater protection against dysrhythmias. The beneficial effects of combined EPA and DHA against SCD but not noted with higher doses of EPA alone (18). Although ω -3 PUFA is effective in reducing SCD in post-MI and in CHD patients with LV dysfunction (22, 23), the most significant antiarrhythmic effects (3, 42) showed a 30% lower risk of Atrial Fibrillation (AF) over a 12-year follow-up in patients who consumed high quantities of non-fried fish (43, 44).

Evidence of Benefit in Heart Failure

The potential benefits of ω -3 PUFA have been extended to the prevention and treatment of HF (45, 46). A study showed an inverse association between fish and ω -3 PUFA consumption and CV mortality, especially for HF (47). These results are particularly striking in a society with a comparatively high intake of fish and background ω -3 PUFA intake. The benefit of the prescription ω -3 PUFA are including reduction in total mortality (9%) and total mortality or hospitalizations for CVDs (8%). Importantly, this therapy was safe and well tolerated, and the improvements in clinical outcomes were additive to that of other well-established HF therapies, including beta-blockers, angiotensin-converting enzyme inhibitor/angiotensin receptor blockers, and aldosterone receptor blockers.

Fish Intake and Congestive Heart Failure (CHF)

Survival free of CHF according to consumption of fish those are high in EPA and DHA (46). The effects of fish oil therapy, both EPA and DHA are potent activators of peroxisome proliferator-activator receptor (PPAR)-alpha (found in the heart) and PPAR-gamma (48). Although FAs are classically viewed as an energy substrate in the heart, they are also endogenous ligands for PPARs and regulate the expression of genes encoding key proteins controlling myocardial FA uptake and metabolism (49).

High-fat diet increases plasma FFA concentration, activating PPAR-alpha in the heart and stimulating expression of key mitochondrial proteins involving FAs oxidation (50). Dietary ω -3 PUFA from fish oil significantly increases serum levels of the cardio-protective adipokine

adiponectin in rats (51). The increase in adiponectin corresponded to significant attenuation of LV hypertrophy and correlated with decreased LV end-systolic volume. Recent evidence suggests that ligand activation of PPAR-gamma by EPA and/or DHA up-regulates adiponectin and suppression of inflammatory cytokines (52, 53), which could improve cardiac structure and function in HF (54, 55). Thus, important cardiac remodeling effects may underlie the observed clinical benefits of fish oils in HF. In a study, 5.1 g/day of EPA and DHA, showed marked improvements in inflammatory cytokines (e.g., tumor necrosis factor alpha and interleukin-1), and percent body fat in advanced HF, suggesting that fish oil may be beneficial in decreasing inflammation and cachexia in advanced HF (47, 56). Therefore, further studies are needed determining not only the optimal dose of ω -3 PUFA protection in different stages of HF but also the underlying mechanisms accountable for their benefits. The ω -3 PUFA supplementation "should join the short list of evidence-based life prolonging therapy for HF" (27).

Evidence for Benefit in Hyperlipidemia

The ω -3 PUFA ethyl ester (Lovaza), at a dosage of 4 g/day is used for the treatment of very high triglyceride levels (500 mg/dl) (57, 58). It is established that ω -3 PUFA lower plasma triglyceride concentrations (19). The mechanism for these lipid-lowering effects seems to involve activation of PPARs. Although FAs are classically observed as an energy substrate, they are also endogenous ligands for PPARs and regulate the expression of genes encoding key proteins controlling FAs uptake and metabolism and the formation of very-low-density lipoproteins carrying triglycerides in the liver (59, 60). Although the exact transcriptional mechanism by which fish oils improve lipid levels is not completely understood, ω -3 PUFA do reduce hepatic synthesis of triglycerides and increase hepatic FAs beta-oxidation. The triglyceride-lowering doses of DHA and EPA is 3 to 4 g/day. This dose typically reduces triglyceride levels by 30% to 40% (61) and has been shown to reduce severely elevated triglyceride levels (62). When added to baseline statin therapy in patients with triglyceride levels between 200 and 499 mg/dl, this dosage of ω -3 PUFA lowers triglyceride levels by close to 30% (63). Generally, there are no significant improvements in levels of LDL Chl with fish oil therapy, especially in patients with elevated triglyceride levels (61, 63). Interestingly, moderate doses of EPA resulted in 10% reductions in LDL Chl beyond that produced by low-dose statins. Nevertheless, even when LDL Chl increases with ω -3 PUFA, as it can with fibrates and occasionally with niacin, ω -3 PUFA-enriched LDL has been reported to be larger and fluffier, which is potentially less atherogenic than the smaller, denser LDL particles (64).

Additional Mechanisms and Optimal DHA/EPA Ratios

The potential mechanisms of ω -3 PUFA and CV diseases, it appears that ω -3 PUFA confer CV benefits largely through DHA and EPA enrichment of membrane phospholipids (65). In addition to mechanisms, ω -3 PUFA produces vasodilation, reduces blood pressure (66), improves arterial and endothelial function (12), and reduces platelet aggregation (67). The antiplatelet, anti-inflammatory, and triglyceride-lowering effects of ω -3 PUFA (68) require relatively higher doses of DHA and EPA (3 to 4 g/day), whereas some of the antiarrhythmic effects, reduction of SCD, and improvement in HF can be achieved at lower doses (500 to 1,000 mg/day). Nevertheless, higher doses may be even more effective in HF (69). These agents have been shown to suppress production of pro-inflammatory cytokines such as interleukin-1B, interleukin-6, and tumor necrosis factor- α (70). When administered to obese patients, 1.8 g of EPA increased the levels of adiponectin, which can reduce inflammation and improve insulin sensitivity (53), in addition to the potential beneficial HF effects. Although benefits on the autonomic nervous system are well established, studies in patients undergoing heart transplantation suggest that ω -3 PUFA can reduce heart rate independently of vagal activation (65).

Both DHA and EPA are present in most fish, generally in a 2:1 ratio, whereas fish oils typically have a ratio of 2:3 or lower (16). Although feeding pure DHA can raise EPA levels to a small extent (71), the reverse is not true (72). Additionally, DHA is far more abundant than EPA in the myocardium (67). The DHA alone or in combination with EPA may be more important for protection against dysrhythmias and SCD than EPA alone. Although the beneficial effects on dysrhythmias seem to occur at lower doses, the relative risk of SCD has been shown to be related with baseline blood levels of ω -3 PUFA (73) and, protection against CHD was also inversely related with tissue levels of EPA and, more so, with DHA levels. In addition, other substitute CV markers (arterial pressure, endothelial relaxation and attenuated vascular relaxation, and lipoproteins) may be more improved with high doses of DHA than with similar doses of EPA (74).

Safety and Adverse Effects

The most commonly observed adverse effects of ω -3 PUFA supplementation are nausea, gastrointestinal upset, and "fishy" burp (16). The higher intakes will increase hemorrhagic complications. However (22), there was no increased risk of clinically significant bleeding noted with ω -3 PUFA doses of up to 7 g of combined DHA and EPA per day, even when combined with antiplatelet therapy or warfarin. The major concerns, not about EPA and DHA per se, but about diets high in oily fish, is the consumption of contaminants, namely methyl mercury. For this

reason, the FDA has advised children and pregnant or nursing women to specifically avoid those fish with a potentially high content of mercury, such as swordfish, tile fish, king mackerel, and shark. Nevertheless, a study on women during their pregnancy and beyond found that women who exceeded the recommendation for fish intake actually had offspring with better cognitive and behavioral development than offspring of women who consumed less fish during pregnancy (75). The most commonly consumed dietary sources of ω -3 PUFA, such as salmon, sardines, trout, oysters, and herring, are quite low in mercury. Because mercury is water soluble and protein bound, it is present in the muscle of the fish but not in the oil. Therefore, fish oil supplements should contain negligible amounts of mercury (76).

Discussion

The ω -3 PUFA-based intervention reduced mortality. ω -3 PUFA supplementation reduced electrophysiological alterations, despite a 70-mm Hg difference in B.P and the development of cardiac hypertrophy. The levels of BP and cardiac hypertrophy are not the sole determinants for increased arrhythmias. Both treatments prevented inflammation, fibrosis. In humans, ω - PUFAs decreased the risk of SCD from ventricular arrhythmias in coronary artery-diseased patients (29). The study showed a 45% reduction in SCD in patients with MI (24). In patients after coronary artery bypass graft surgery, ω - PUFAs reduced atrial fibrillation (AF) by almost 55% (44). This antiarrhythmic effect also applies to Ang II-induced SCD. ω - PUFA was as effective in reducing mortality and arrhythmia induction. Slight reduction in BP showed by ω - PUFA(77). Studies in mice with restricted cardiac high Ang II levels and heart-specific mineralocorticoid receptor overexpression showed SCD, arrhythmias, and electrical remodeling despite normal blood pressure (78-80). In humans, ω - PUFA supplementation reduced the QT interval (81). A similar amelioration of repolarization parameters was demonstrated in our study. However, the distinct molecular pathways by which ω - PUFAs exert their antiarrhythmic effects and reduce the risk of SCD are unknown. ω - PUFAs may directly interact with certain cellular targets or change the microenvironment of membrane bound signaling components after being incorporated into phospholipids. Moreover, ω - PUFAs are substrates for cytochrome P450, cyclooxygenase, and lipoxygenase enzymes (82). Thus, depending on the diet, ω - PUFAs are a potential source of biologically active metabolites produced in competition with AA-derived eicosanoids. Among these metabolites, cytochrome P450-dependent epoxy derivatives may be of particular interest because they act as potent activators of cardiac ATP-sensitive potassium (KATP) channels. KATP channels play a central role in cardiac protection and are essential for the beneficial effect (83). The principal

capacity of KATP channel activation occurs already with some AA-derived metabolites (epoxyeicosatrienoic acids) but is largely exceeded by their EPA- and DHA-derived counterparts (84). Enhanced epoxyeicosatrienoic acid generation was shown to exert cardioprotective effects via KATP channel activation. (85-87). Taken together, we speculate that the effects of ω -PUFAs are in part mediated by cytochrome P450-dependent formation of alternative highly potent KATP channel activators. The ω -PUFAs may be future potent therapeutic agents providing cardioprotection and reduction in the risk of arrhythmias in particular. The therapy might be useful in patients with hypertension induced heart disease. The ω -PUFA signaling pathway may present new candidates for antiarrhythmic drugs (26).

Conclusions

Combined EPA and DHA in a dose of approximately 1,000 mg/day have been used for the patients with CHD. For those individuals without CHD, this has been shown to be equivalent to about 500 mg/day of combined EPA and DHA, the intake associated with the lowest risk for CHD death in several studies. Several organizations have provided guidelines that address increasing consumption of fish. These recommendations, similar to CHD, should also be extended to patients with HF (800 to 1,000 mg of combined EPA/DHA daily). In patients with hypertriglyceridemia, moderate to high doses of ω -3 PUFA (4 g/day) is used (88-90), and can also be used safely combined with any other lipid therapies (statins, fibrates, niacin, and so on). The optimal dosing in various populations, especially those with HF, as well as the effects of various doses on the primary and secondary reduction of AF and more detailed mechanisms responsible for the benefits noted. The potential benefits of assessing blood levels of ω -3 PUFA are effective in CVD protection. Finally, studies are needed to determine the optimal mixture of DHA relative to EPA in various populations (91-93), to determine the role of ω -3 PUFA in maximally treated contemporary post-MI patients or other patients with relatively low-risk CHD. The potential beneficial effects of ω -3 PUFA including prevention of CHD, MI, SCD, HF, atherosclerosis, and AF.

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