Omega-3 polyunsaturated fatty acids for cardiovascular diseases: present, past and future

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Omega-3 polyunsaturated fatty acids for cardiovascular diseases: present, past and future

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Abstract

Introduction: Large-scale epidemiological studies on Greenlandic, Canadian and Alaskan Eskimos have examined the health benefits of omega-3 fatty acids consumed as part of the diet, and found statistically significant relative reduction in cardiovascular risk in people consuming omega-3 fatty acids.

Areas covered: This article reviews studies on omega-3 fatty acids during the last 50 years, and identifies issues relevant to future studies on cardiovascular (CV) risk.

Expert Commentary: Although a meta-analysis of large-scale prospective cohort studies and randomized studies reported that fish and fish oil consumption reduced coronary heart disease-related mortality and sudden cardiac death, omega-3 fatty acids have not yet been shown to
be effective in secondary prevention trials on patients with multiple cardiovascular disease (CVD) risk factors. The ongoing long-term CV interventional outcome studies investigate high-dose, prescription-strength omega-3 fatty acids. The results are expected to clarify the potential role of omega-3 fatty acids in reducing CV risk. The anti-inflammatory properties of omega-3 fatty acids are also important. Future clinical trials should also focus on the role of these anti-inflammatory mediators in human arteriosclerotic diseases as well as inflammatory diseases.

**KEY WORDS:** eicosapentaenoic acid, docosahexaenoic acid, cardiovascular disease, omega-3 fatty acid, pro-resolving mediators
1. Introduction
Mortality rate from atherosclerotic diseases [particularly myocardial infarction (MI)] remains high in industrialized countries, and was reported to be about 20% in United States in 1995 [1]. Epidemiological studies have thus focused on differences in lifestyle, in particular dietary habits, between countries that differ in the incidence of atherosclerosis-associated MI. A study conducted in seven countries [2] reported that the mortality from ischemic heart disease was lower in Japan and Mediterranean countries than in the United States and Northern European countries, and highlighted the role of unsaturated fatty acids which are abundant in the Japanese and Mediterranean diets. In this context, an epidemiological study of Greenlandic, Canadian and Alaskan Eskimos suggested that omega-3 fatty acids were important in preventing atherosclerotic diseases [3-6]. After these studies, the health benefits of omega-3 fatty acids consumed as part of the diet have been extensively researched in large-scale epidemiological studies, clinical outcomes trials and meta-analyses, the results of which showed a statistically significant reduction in the relative risk of cardiovascular disease (CVD) in persons consuming omega-3 fatty acids [7,8]. In 1983, a highly purified eicosapentaenoic acid preparation for human use was first reported in Japan [9]. Omega-3 fatty acids are now widely recognized as having an important role in preventing atherosclerotic diseases as well as a wide range of other diseases and conditions including diseases of the central nervous system (such as dementia) and cardiovascular (CV) system (such as arrhythmia, and chronic heart failure (CHF)), autoimmune diseases (including rheumatoid arthritis and psoriasis) and carcinogenesis, as well as in defense against infection.

Since great advances have been made in recent research on omega-3 fatty acids, it is a good time to review current studies with a background of past research. This article reviews high-impact studies on omega-3 fatty acids during the last 50 years, and presents an overview of their pharmacological features and actions, mechanisms of disease control and clinical effects in relation to CVD, and discusses the findings of studies of omega-3 fatty acid preparations currently available as highly purified eicosapentaenoic acid-ethyl ester (EPA-E; Epadel) and eicosapentaenoic acid-ethyl ester/docosahexaenoic acid-ethyl ester (Lotriga; containing the same active ingredients as Omacor/Lovaza) [10,11].

2. Pharmacology and Physiological Effects of Omega-3 Fatty Acids on CV Risk
Omega-3 fatty acids in the body are primarily available as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and less abundantly available as docosapentaenoic acid (DPA) [12]. Omega-3 fatty acids are incorporated into chylomicron triglycerides (TG) in the gastrointestinal tract and transported to the liver, where EPA and DHA are incorporated into TG as very-low-density
lipoproteins (VLDL) and released into the blood stream. Only a small proportion of omega-3 fatty acids are available as free fatty acids, most of which are bound to albumin [13].

Although hypercholesterolemia is widely recognized as an important CV risk factor, some studies have indicated hypertriglyceridemia as an additional CV risk factor [14,15]. Omega-3 fatty acids have been reported to reduce serum TG in patients with hypertriglyceridemia [16], increase high-density lipoprotein cholesterol and low-density lipoprotein cholesterol, and reduce small dense low-density lipoprotein cholesterol in a dose-dependent manner. However, these beneficial effects are difficult to achieve even with cardioprotective diets rich in omega-3 fatty acids or with small amounts of omega-3 fatty acids, and therefore require consumption of large doses of omega-3 fatty acids.

There is strong evidence that reduction in TG concentration is caused by mechanisms such as reduced hepatic very-low-density lipoprotein-triglyceride synthesis and secretion, and increased TG clearance from chylomicrons and VLDL particles [17]. Elevated TG concentrations are reported to be associated with, and may contribute to, the presence of highly atherogenic, small, dense LDL particles and decreased concentrations of high-density lipoprotein cholesterol, both being factors associated with increased risk of CVD [18]. Recent evidence from genetic studies of apolipoprotein (Apo) CIII, an inhibitor of lipoprotein lipase that affects triglyceride metabolism, suggests that triglycerides are causally involved in atherosclerosis and coronary heart disease (CHD) [19]. EPA has been shown to significantly reduce triglycerides and Apo C-III without raising LDL-C in patients with very high triglycerides and in statin-treated patients with high triglycerides [20,21]. In addition, a Japanese study has shown that Lotoriga (EPHA/DHA) increases mean LDL particle size and LDL-cholesterol/Apo B ratio, and reduces Apo CIII [22].

A meta-analysis of randomized studies [23] reported that fish oil supplementation lowers blood pressure modestly after fish oil consumption, possibly caused by reduced systemic vascular resistance but not lowered cardiac output. Increased production of nitric oxide by consumption of omega-3 fatty acids may increase expression of endothelial nitric oxide synthase. Indeed, several randomized studies found that intake of omega-3 fatty acids improved serum markers of endothelial dysfunction, such as E-selectin, VCAM-1, and ICAM-1 [24,25]. A meta-analysis revealed that intake of omega-3 fatty acids improved flow-mediated vasodilation, among other parameters of endothelial function [26]. Tousoulis et al. [27] reported that omega-3 fatty acid improved endothelial function evaluated by flow-mediated dilation (FMD) and arterial stiffness by carotid-femoral pulse wave velocity (PWV), with a parallel anti-inflammatory effect in adults with metabolic syndrome. Merino et al. [28] also reported that omega-3 fatty acid consumption improved small peripheral artery
function in patients with intermediate-high cardiovascular risk, evaluated by small artery reactive hyperemia index (saRHI). Moreover, Chan et al. [29] reported that omega-3 fatty acid supplementation improved arterial elasticity measured by pulse contour analysis of the radial artery, in patients on statin therapy for familial hypercholesterolemia. Tagetti et al. [30] found no overall association of omega-6 and omega-3 fatty acid intake or their ratio with blood pressure decrease, but they observed an interaction between CYP4F2 V433M genotype and total omega-3, alpha-linolenic acid and linoleic/alpha-linolenic ratio. Higher omega-3 polyunsaturated fatty acid (PUFA) intake was significantly associated with a more pronounced blood pressure decrease over time in subjects with the 433VV genotype.

A meta-analysis of randomized studies [31] revealed modest reduction in heart rate after fish oil consumption. Compared to blood pressure that shows clear response even for low doses of omega-3 fatty acids, the dose–response relationship for heart rate is apparently not as linear as that for blood pressure. Dietary fish oil and omega-3 fatty acids lower heart rate by direct effects on cardiomyocytes [32,33] and indirect effects on circulatory dynamics involving ventricular diastolic filling and vagal tone. In Japanese general population, omega-3 fatty acid intake attenuates the effect of high resting heart rate on cardiovascular mortality risk [34]. Heart rate is associated with CV events, which suggests that CV event reduction attributable to omega-3 fatty acids may be due in part to the effects of omega-3 fatty acids on heart rate.

Fish intake decreases the risk of fatal MI and sudden cardiac death associated with CHD [35], and their anti-arrhythmic properties are of particular interest. Omega-3 fatty acids affect the electrophysiology of ventricular and atrial cardiomyocytes; particularly, EPH/DHA are speculated to improve cardiomyocyte excitability and intracellular Ca\(^2+\) variability by blocking the Na\(^+\) and Ca\(^2+\) channels in cardiomyocytes [33]. However, it remains unclear whether these effects are specific to omega-3 fatty acids, because similar effects have been reported for omega-6 fatty acids.

Omega-3 fatty acids affect the fibrinolytic and coagulation systems. A dose of 0.27 to 4.8 g/day of EPA or EPA + DHA prolongs bleeding time, but this prolongation has no consistent association with clinical bleeding [36]. Indeed, there is no clear increase in bleeding risk associated with intake of omega-3 polyunsaturated fatty acids even at a dose as high as 4 g.

Omega-3 fatty acids also have anti-inflammatory properties. An epidemiological study in Greenland [37] found that autoimmune diseases such as bronchial asthma and psoriasis were extremely rare among Eskimos subsisting primarily on fish. Several subsequent animal and human studies provided evidence that omega-3 fatty acids, particularly EPA, have anti-inflammatory and immunomodulatory
properties [38,39].

The omega-6 fatty acid arachidonic acid (AA) is stored within cell membranes. It is released in response to cell stimulation and is metabolized by pro-inflammatory lipid mediators such as prostaglandin and leukotriene in the AA cascade, thereby aggravating pre-existing inflammation. Omega-3 fatty acids are also stored within cell membranes, where they replace and thus reduce the storage of AA. Furthermore, while omega-3 fatty acids are also metabolized by proinflammatory lipid mediators in the AA cascade, their active metabolites are assumed to be less potent than those of AA, thus tipping the balance toward inhibition of inflammation [40].

It is important to note that atherosclerosis is suppressed in leukotriene receptor B-knockout mice [41] and by administration of EPA [42]. DHA has not received as much attention as EPA, but recent report indicates that DHA-rich fish oil is more potent than EPA-rich fish oil in suppressing inflammation [43]. In addition, DHA-rich fish oil prolonged survival in a mouse model of systemic lupus erythematosus, a typical autoimmune disease [44]. The factors involved have been identified to be resolvins and neuroprotectins produced from omega-3 fatty acids, particularly DHA, at the end of an inflammatory process [45]. These metabolites are potent anti-inflammatory lipid mediators (Figure 1) [46]. Progression of atherosclerosis is suppressed in mice overexpressing 12/15-lipoxygenase, which overproduce these anti-inflammatory lipid mediators [47]. However, the role of these anti-inflammatory mediators in human atherosclerosis remains to be determined.

In patients with end-stage renal disease (ESRD), CVD is the main cause of mortality. Mortality of CVD in these patients is 10–20 times higher than in the general population [48,49]. Accelerated atherosclerosis is the most important cause of mortality and morbidity in patients on dialysis. Kajbaf et al. [50] performed a clinical trial to assess the effect of omega-3 supplementation (3 g/day) on atherosclerosis progression by measuring carotid intima-media thickness (cIMT) in hemodialysis (HD) patients, and reported that omega-3 supplementation decreased cIMT significantly.

3. Omega-3 Fatty Acids and CVD

The amount of fish oil required for manifestation of clinical effects on CVD and the time required for the onset of action vary depending on the disease being treated. In addition, the clinical outcomes of fish oil supplementation vary greatly in relation to the endpoints used to evaluate its effectiveness. Risk reductions in CHD-related mortality and sudden cardiac death are the most important CVD risk–lowering benefits of omega-3 fatty acids. A meta-analysis of large-scale prospective cohort studies and randomized studies [35] reported that fish and fish oil consumption reduced CHD-related mortality and sudden cardiac death, although these beneficial effects did not exhibit a linear dose–
response relationship. A subsequent meta-analysis of 13 randomized controlled trials [51] found a significant reduction in cardiac death after fish oil supplementation, but this effect was nonsignificant after adjustment for multiple covariates. In the Japanese general population, omega-3 fatty acid intake was inversely and independently associated with long-term risk of total CVD mortality [52]. De Oliveira Otto et al. [53] reported that both dietary and circulating eicosapentaenoic acid and docosahexaenoic acid, but not alpha-linolenic acid or n-6 PUFAs, were inversely associated with CVD incidence. These findings indicate that fish oil may reduce fatal MI or sudden cardiac death.

However, secondary prevention trials did not show a clear benefit for omega-3 fatty acids [54,55], perhaps in part because many of the study participants were concomitantly treated with aspirin, angiotensin-converting enzyme inhibitors, beta-antagonists, and statins during the studies. The large-scale Risk and Prevention Study [56] showed that omega-3 fatty acids did not clearly reduce CHD-related mortality in patients with multiple CVD risk factors. A possible reason for the failure of these secondary prevention studies to show significant benefits for fish oil is that the study participants had received aggressive pharmacotherapy, which may have reduced the effectiveness of omega-3 fatty acids against cardiac death. The authors of the studies indicated that larger sample sizes would be needed to yield statistically significant results. Regarding primary prevention, intake of tuna and dark fish, alpha-linolenic acid, or marine omega-3 fatty acids was not associated with risk of major CVD in a cohort of women without a history of cardiovascular disease [57]. From pooling 19 cohort’s studies, omega-3 biomarkers ALA, DPA, and DHA were associated with a lower risk of fatal CHD [58].

In contrast, several observational studies [59-62] found that fish oil and omega-3 fatty acids contributed to prevention of non-fatal MI and acute coronary syndrome, although subsequent large-scale randomized studies reported mixed outcomes. Some reported benefits of omega-3 fatty acids, most importantly protection against CV death [63-65]; while other studies failed to show such benefits [54,55,66]. Indeed, a meta-analysis of randomized trials [51] found that the risk of non-fatal CVD was lower in persons receiving fish oil, but the decrease was not significant. Thus, the benefit of fish oil for non-fatal CVD remains unclear.

In an Italian cohort study (AGE-IM), levels (as percentage of whole blood fatty acids) of total PUFAs, total omega-3 PUFAs and total omega-6 PUFAs were lower in MI patients than in matched control subjects [67]. These data suggest an association of not only total omega-3, but also total omega-6 blood levels, with cardiovascular risk. Another study revealed that higher consumptions of marine (EPA/DHA) and plant (alpha-linolenic acid) omega-3 fatty acids are both associated with
reduced risk of cardiovascular mortality in a Chinese population [68].

A recent study has suggested that serum EPA to AA ratio (EPA/AA ratio) is a predictive marker of major coronary events in a Japanese population [69]. Microalbuminuria is also recognized as an independent risk factor for cardiovascular morbidity and mortality in the general population [70,71]. A higher urinary albumin concentration increased the risk of both CV and non-CV death, with the increase being significantly higher for CV mortality than for non-CV mortality. Fukami et al. [72] reported a strong association between EPA/AA ratio and microalbuminuria. Albuminuria has been associated with vascular abnormalities including reduced vascular dilatation, arterial stiffness and venous thromboembolism [73,74], and albuminuria is now recognized as an indicator of endothelial dysfunction. Endothelial dysfunction and subclinical inflammation may link albuminuria to cardiovascular disease [75]. An inverse association of serum EPA/AA ratio with prevalence of microalbuminuria suggests the protective effect of high EPA/AA ratio on endothelial dysfunction. Although the pathophysiological significance of the serum EPA/AA ratio as a predictor of CV risk is unclear, EPA/AA ratio has been shown to correlate with the composition of omega 3 fatty acids in organic membranes such as red cell membrane, which may affect cell functions [76].

A prospective cohort study of 2,735 adults without CHF [77] reported an inverse correlation between blood concentration of omega-3 polyunsaturated fatty acids and incidence of CHF in elderly subjects. Other cohort studies [31,78] reported that increased intake of boiled or grilled, but not fried fish, contributed to prevent CHF onset. However, very few studies have investigated the protective effects of omega-3 polyunsaturated fatty acids against new-onset CHF. Additional data from primary prevention settings are needed. With respect to secondary prevention, a large-scale randomized, double-blind, placebo-controlled trial of 7,046 patients with existing CHF [8] found a significant survival benefit in those given omega-3 fatty acids (Lotriga), with improvement in left ventricular ejection rate after a mean treatment duration of 3.9 years [79]. Based on these findings, omega-3 fatty acids are described as effective against CHF in the American College of Cardiology/American Heart Association (ACC/AHA) guidelines [80].

A few small-scale randomized studies on the effect of fish oil in patients with defibrillators implanted for ventricular tachycardia [81,82] yielded mixed results. Meta-analyses [83] also showed no significant benefit. These studies varied in design. Therefore, new and better designed studies are required to establish definitive conclusions. A study of fish oil in patients with atrial fibrillation (AF) [84] reported reduced risk of developing AF. However, a subsequent large-scale randomized study [85] showed no reduction in incidence of postoperative AF, and meta-analyses of published studies [85,86] concluded that fish oil and omega-3 fatty acids had no benefit against AF. Thus, the effects
of fish oil intake in preventing postoperative AF and in secondary prevention of AF in patients with existing AF remain unclear. Large-scale, prospective intervention studies are required to determine whether fish oil protects against new-onset AF in non-AF patients.

Meta-analyses of relatively large, prospective cohort studies [87,88] showed that fish oil intake did not correlate with the incidence of hemorrhagic stroke, but correlated inversely with the incidence of ischemic stroke in subjects receiving a moderate dose of fish oil. However, prospective intervention studies yielded inconsistent results. A sub-analysis of the JELIS trial on Epadel (highly purified EPA) [89] showed no benefit in primary prevention but some benefit in secondary prevention of stroke. Other studies showed that omega-3 fatty acids had no protective effect against stroke onset [54,66].

A recent study (OMEGA-REMODEL, Omega-3 Acid Ethyl Esters on Left Ventricular Remodeling After Acute Myocardial Infarction trial) reported that in patients with acute myocardial infarction, treatment with 4 g omega-3 fatty acids for 6 months in addition to standard treatment decreased the left ventricular end-systolic volume index (LVESVI) and non-infarct myocardial fibrosis [90]. In this prospective, multicenter, double-blind, placebo-controlled study comparing omega-3 fatty acids at 4 g per day with placebo containing corn oil, mean LVESVI decreased by 5.4% from baseline in the omega-3 fatty acid group, but increased by 1.2% in the placebo group. Non-infarct myocardial fibrosis regressed by an average of 2.1% in the omega-3 fatty acid group, but progressed by an average of 3.4% in the placebo group. Improvements in infarct size and left ventricular ejection fraction did not differ significantly between the two groups. Myeloperoxidase (a biomarker of inflammation) and ST2 (a biomarker of myocardial fibrosis) decreased in the omega-3 fatty acid group compared to the placebo group. This study thus demonstrated that treatment with omega-3 fatty acids in the recovery phase following acute myocardial infarction improved left ventricular remodeling and non-infarct myocardial fibrosis, presumably by suppressing inflammation both at systemic and myocardial levels.

The effects of fish oil on CVD vary widely depending on the endpoint used, and may be attributable to differences in omega-3 fatty acid dosage and duration of use as well as patient characteristics (particularly, disease severity and use of concomitant medications) among studies. Omega-3 fatty acids may not offer sufficiently potent protection against CVD risk, and any benefit might be masked in simple meta-analyses. According to a review by Mozaffarian and Rimm [35], the amounts of EPA and DHA required to improve pathological conditions such as arrhythmia and hypertriglyceridemia vary depending on the condition, and the appropriate ratio of EPA to DHA has not been elucidated. These possibilities should be considered when conducting studies or
interpreting study results.

4. Molecular mechanism of action of omega-3 fatty acids on heart disease

Omega-3 fatty acids such as EPA and DHA are converted from alpha-linolenic acid, and are not produced endogenously by humans and other mammals. Although epidemiological studies have proved that ingestion of omega-3 fatty acids from food prevents heart failure, the molecular mechanism of action has remained unknown. Recent development of liquid chromatography-mass spectrometry (LC-MS)-based lipidomic analysis has led to discoveries of pro-resolving mediators derived from omega-3 fatty acids, such as resolvins, protectins and maresins. These molecules have attracted attention in recent years. They possess distinct chemical structures and exert anti-inflammatory effects in a stereospecific manner. These mediators are commonly called specialized pro-resolving mediators (SPMs) (Figure 1).

The resolvin E (RvE) series are synthesized from EPA through conversion of 18-hydroxyeicosapentaenoic acid (18-HEPE) by aspirin-acetylated COX2 or CYP450 monoxygenase. RvE1 actively switches off leukocyte trafficking to the inflamed site, promotes the clearance of inflammatory cells and debris, and suppresses cytokine production, thereby leading to resolution of acute inflammation [91]. DHA-derived mediators such as protectins, resolvin D series, and maresins, are generated by 15-lipoxygenase (15-LOX) in humans or by 12/15-LOX in mice.

Evidence accumulated in recent years has shown that SPMs have direct cardioprotective action in vivo. Keyes et al. [92] reported that administration of RvE1 attenuated the infarct size in rats subjected to ischemia/reperfusion injury. The results of their study suggest that RvE1 directly affects cardiomyocytes and protects against cardiac injury. Another study found that during acute inflammation following myocardial infarction in mice, RvD1 promoted the production of SPMs in the spleen and induced a switch to anti-inflammatory M2 macrophages in the left ventricle to prevent myocardial fibrosis and maintain cardiac function [93].

Histopathological changes (remodeling) such as myocardial hypertrophy, inflammatory cell infiltration, and interstitial fibrosis occur when the heart is subjected to pressure, eventually leading to heart failure. Endo et al. [94] used fat-1 transgenic mice expressing Caenorhabditis elegans n-3 fatty acid desaturase, an enzyme that converts n-6 PUFAs to n-3 PUFAs. They induced aortic valve stenosis in the mice by surgery, resulting in pressure overload that caused cardiac hypertrophy. In pressure overload-induced transgenic mice, cardiomyocyte hypertrophy was not different from that in wild type mice, but the contractile ability of the heart was maintained with no decrease even at 4 weeks after pressure loading (heart failure period). Furthermore, interstitial fibrosis and macrophage
infiltration were markedly suppressed. Their experiment of transplanting bone marrow cells of fat-1 transgenic mice into wild type mice revealed that the cardioprotective action of omega-3 fatty acids was mediated by CD68-positive macrophages recruited from the bone marrow. Co-culture experiments of macrophages with cardiac fibroblasts showed marked increases of metabolites derived from EPA, in particular 18-HEPE, in macrophages isolated from fat-1 transgenic mice. Furthermore, addition of 18-HEPE to cardiac fibroblasts resulted in dose-dependent suppression of IL-6 production.

5. Large-scale Clinical Studies of Omega-3 Fatty Acids and Issues to be Resolved

The effects of fish oil on CVD vary widely depending on the endpoint evaluated, and may be attributable to the differences in omega-3 fatty acid dosage and duration of use as well as patient characteristics (especially lifestyle, disease severity, and use of concomitant drugs) among studies. Omega-3 fatty acids have been commercially available for 20 years in many countries, and several large-scale studies have examined their effects [7,8,56,64,66] (Table 1). Early studies showed that they were effective for secondary prevention of CV events [7,64] and reduction of all-cause mortality in patients with CHF [8]. While Omacor was found to be ineffective in several recent studies [56,66], these studies had several major limitations including low dose of omega-3 fatty acids used, insufficient statistical power, and enrollment of patients with normal or nearly normal baseline triglyceride levels [95].

Two ongoing long-term CV interventional outcome studies investigate high-dose, prescription-strength omega-3 fatty acids. The REDUCE-IT (NCT01492361) trial investigates Vascepa containing high-purity icosapent ethyl, the ethyl ester of EPA. The STRENGTH (NCT02104817) trial investigates Epanova that contains EPA as the free fatty acid, and evaluates the reduction of CV events in patients at high risk for CV events with persistently high triglyceride levels and are receiving statin therapy. The results of these trails are expected to clarify the potential role of omega-3 fatty acids in reducing CV risk.

6. Relationship between statins and ω3 fatty acids

As mentioned above, the health benefits of omega-3 fatty acids have been extensively researched. Large-scale epidemiological studies, clinical outcomes trials, and meta-analyses have demonstrated significant reduction of relative cardiovascular risk. The balance between EPA or DHA and AA in the human body is likely to be important for regulating the production of mediators and subsequently vascular function. Indeed, serum EPA to AA ratio (EPA/AA) has been found to be a good biomarker for the risk of cardiovascular disease not only in the general population [96], but also in a post-hoc analysis of the results of a clinical trial [69].
The efficacy of statin for both primary and secondary prevention of cardiovascular disease has been established [97], and low-density-lipoprotein cholesterol (LDL-C)-lowering therapy with statin has been used as the first-line treatment. Despite significant LDL-C lowering with statin, substantial residual cardiovascular risk remains [98], and several risk factors such as low level of high-density lipoprotein cholesterol and high level of triglycerides have attracted attention. A particularly interesting finding is that increase in plasma AA concentration and decrease in plasma omega-3 fatty acid concentration and/or plasma omega-3/AA ratio have been observed in patients treated with statins [99], and these may be associated with the residual risk after initiation of statin treatment. The above-mentioned findings suggest that statin regulates the endogenous metabolism of long-chain polyunsaturated fatty acids (LCPUFAs). LCPUFAs are endogenously metabolized from omega-6 and omega-3 PUFA precursors by position-specific desaturation and carbon-chain elongation reactions [100]. The AA-dominant endogenous synthesis of LCPUFAs resulting in decreased plasma omega-3 concentration and/or omega-3/AA ratio during statin treatment may be clinically very important, because serum EPA/AA ratio has been reported to be a good biomarker for the risk of cardiovascular disease not only in the general population [96], but also in clinical trial subjects [69]. Therefore, it seems rational to recommend omega-3 LCPUFA supplementation for patients on statin treatment, in order to maintain the plasma omega-3 concentration and omega-3/AA ratio.

7. Conclusion
Since a series of epidemiological studies of Greenlandic, Canadian and Alaskan Eskimos were published in the late 1970s, numerous epidemiological/observational and large-scale randomized studies have investigated the effectiveness of omega-3 fatty acids in the prevention of atherosclerotic diseases, particularly CHD-related fatal MI and sudden cardiac death. However, the effectiveness of omega-3 fatty acids for secondary prevention of non-fatal MI and CHD has not been established, presumably because the effects are prone to be diminished or masked in aggressively treated patients. Nevertheless, omega-3 fatty acids have a wide range of therapeutic properties; they improve lipid metabolism, lower blood pressure and heart rate, counteract arrhythmia, improve vascular endothelial function, and counteract clotting and inflammation.

8. Expert commentary & five-year view
Epidemiological studies at Greenlandic, Canadian and Alaskan Eskimos suggested that fish oil plays an important role in the prevention of atherosclerosis [3]. Following this innovative study, the health benefits of diets containing omega-3 fatty acids have been demonstrated in large-scale epidemiological studies and the statistically significant reduction in relative CV risk was also demonstrated with large-scale epidemiological studies, clinical outcomes trials, and meta-analyses.
Although it has not yet been clearly shown that omega-3 fatty acids are effective in secondary prevention trials of patients with multiple CVD risk factors [54-56], one of the reasons is that subjects were already receiving medications, and this may have reduced the effectiveness of omega-3 fatty acids on cardiac death. One of the important points to assess the clinical effect of fish oil on CVD is that the amount of omega-3 fatty acids required to develop such effects and the time required for the onset of action are greatly different depending on the endpoint used for evaluation. From these points of view, two ongoing long-term CV interventional outcome studies, the REDUCE-IT (NCT01492361) trial and the STRENGTH (NCT02104817) trial, investigate high-dose, prescription-strength omega-3 fatty acids. The results are expected to clarify the potential role of omega-3 fatty acids in reducing CV risk.

The anti-inflammatory properties of omega-3 fatty acids are also important. Omega-3 fatty acids are metabolized to pro-inflammatory lipid mediators in the arachidonic acid cascade and their active metabolites are thought to be less efficacious than those derived from arachidonic acid, but they sedate inflammation [40]. Recent studies have discovered that at the end of the inflammatory process, potent anti-inflammatory lipid mediators such as resolvins and neuroprotectins are produced from omega-3 fatty acids, especially from DHA [45,46]. Animal study has also shown that progression of atherosclerosis is inhibited in 12/15-lipoxygenase-overexpressing mice that overproduce these anti-inflammatory lipid mediators [47]. Future clinical trials should also focus on the roles of these anti-inflammatory mediators in human inflammatory diseases as well as arteriosclerotic disease.

10. Key Issues

- The role of omega-3 fatty acids in the prevention of atherosclerosis has been established by large-scale epidemiological studies, clinical outcome trials, and meta-analyses.

- Omega-3 fatty acids have not been clearly shown to be effective in recent secondary prevention trials on patients with multiple CVD risk factors. One of the reasons is that the subjects were treated aggressively with medications, thereby reducing the effectiveness of omega-3 fatty acids on cardiac death.

- Potent anti-inflammatory lipid mediators such as resolvins and neuroprotectins have been found to be produced from omega-3 fatty acids, especially from DHA, at the end of the inflammatory process.
• In patients treated with statins, the increase in plasma AA and decrease in plasma omega-3 fatty acid concentration and/or plasma omega-3/AA ratio may be associated with the residual cardiovascular risk. In order to maintain plasma omega-3 concentration and omega-3/AA ratio, omega-3 fatty acid supplementation may be recommended.

• Research on the roles of anti-inflammatory mediators is necessary not only for arteriosclerotic diseases but also for inflammatory diseases.

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Declaration of Interest
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References

Papers of special note have been highlighted as:

* of interest
** of considerable interest


This is a landmark study focusing on plasma lipids and lipoprotein pattern to investigate the very low incidence of ischemic heart disease in Greenlandic Eskimos.


11. Tatsuno I, Saito Y, Kudou K, Ootake J. Long-term safety and efficacy of TAK-085 in


23. Geleijnse JM, Giltay EJ, Grobbee DE, Donders AR, Kok FJ. Blood pressure response to fish oil supplementation: metaregression analysis of randomized trials. *J.*


**35.** Mozaffarian D, Rimm EB. Fish intake, contaminants, and human health: evaluating the risks and the benefits. *JAMA : the journal of the American Medical Association,*
The health benefits and potential contamination of fish (finfish or shellfish) result in confusion over the role of fish consumption in a healthy diet. This review article finds that the benefits of fish intake exceed the potential risks for major health outcomes.


This interesting article reports a lower frequency of autoimmune diseases in Greenlanders.

**38. Prickett JD, Robinson DR, Steinberg AD. Dietary enrichment with the polyunsaturated fatty acid eicosapentaenoic acid prevents proteinuria and prolongs survival in NZB x NZW F1 mice. The Journal of clinical investigation, 68(2), 556-559 (1981).

This is an early report demonstrating that fish oil prevents proteinuria and prolongs survival in an animal model of systemic lupus erythematosus using NZB x NZW F1 mice.


55. Kromhout D, Giltay EJ, Geleijnse JM. n-3 fatty acids and cardiovascular events


This large-scale interventional study demonstrates that omega-3 fatty acids protect against sudden death after myocardial infarction.


This large-scale interventional study shows that highly concentrated EPA prevents major coronary events in Japanese hypercholesterolaemic patients treated with statin.


**91. Serhan CN. Pro-resolving lipid mediators are leads for resolution physiology. *Nature*, 510(7503), 92-101 (2014).**

This article reviews the discovery of pro-resolving lipid mediators and their physiological functions.


100. Abedi E, Sahari MA. Long-chain polyunsaturated fatty acid sources and evaluation of their nutritional and functional properties. *Food Science & Nutrition*, 2(5),
Figure 1. Anti-inflammatory lipid mediators derived from omega-3 fatty acids.

Table 1. Large-scale clinical studies of omega-3 fatty acids conducted to date.
Table 1

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<td>Hypercholesterolemia (&gt;250 mg/dl)</td>
<td>CHF</td>
<td>IGT/IFG/DM</td>
<td>Multiple CV risks</td>
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<td>Baseli</td>
<td>16 2</td>
<td>154.2</td>
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<td>-3 : 150</td>
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<td>preparation</td>
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<td>Dosage</td>
<td>1 1.8</td>
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<td>No. of</td>
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<td>18,64</td>
<td>7,046</td>
<td>12,6</td>
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<td>Follow-up</td>
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<td>74.4</td>
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<td>CV event</td>
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<td>Yes</td>
<td>No</td>
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<td>29%</td>
<td>100</td>
<td>23%</td>
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<tr>
<td>Use of</td>
<td>41%</td>
<td>?</td>
<td>94%</td>
<td>71%</td>
<td>75%</td>
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<tr>
<td>Use</td>
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<td>Reference number</td>
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