**MARINE OMEGA-3 FATTY ACIDS IN THE PREVENTION
OF CARDIOVASCULAR DISEASE**

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ABSTRACT

Omega-6 ($\omega 6$) and omega-3 ($\omega 3$) fatty acids are two classes of dietary polyunsaturated fatty acids derived from linoleic acid ($18:2\omega 6$) and α -linolenic acid ($18:3\omega 3$), respectively. Enzymatic metabolism of linoleic and α -linolenic acids generates arachidonic acid ($20:4\omega 6$) and eicosapentaenoic acid ($20:5\omega 3$; EPA), respectively, both of which are substrates for enzymes that yield eicosanoids with multiple and varying physiological functions. Further elongation and desaturation of EPA yields the 22-carbon fatty acid docosahexaenoic acid ($22:6\omega 3$; DHA). The main dietary source of EPA and DHA for human consumption is fish, especially oily fish.

There is considerable evidence that EPA and DHA are protective against cardiovascular disease (heart disease and stroke), particularly in individuals with pre-existing disease. $\omega 3$ Fatty acids benefit multiple risk factors including blood pressure, blood vessel function, heart function and blood lipids, and they have antithrombotic, anti-inflammatory and anti-oxidative actions. $\omega 3$ Fatty acids do not adversely interact with medications. Supplementation with $\omega 3$ fatty acids is recommended in individuals with elevated blood triglyceride levels and patients with coronary heart disease. A practical recommendation for the general population is to increase $\omega 3$ fatty acid intake by incorporating fish as part of a healthy diet that includes increased fruits and vegetables, and moderation of salt intake. Health authorities recommend the general population should consume at least two oily fish meals per week.

1. Introduction

Observational studies from more than forty years ago showed the Greenland Inuit population had a low incidence of coronary artery disease and a reduced prevalence of arthritis, psoriasis, asthma and diabetes, that most likely related to their lifestyle and in particular to their distinctive diet [1-3]. The Greenland Inuit diet derived mainly from cold water fish and arctic mammals such as seal and whale. It contained higher protein and fat, lower carbohydrates and significantly greater amounts of omega-3 (ω 3) polyunsaturated fats, particularly eicosapentaenoic acid (EPA, 20:5 ω 3) and docosahexaenoic acid (DHA, 22:6 ω 3), rather than omega-6 polyunsaturated fats such as linoleic acid (18:2 ω 6) and arachidonic acid (20:4 ω 6) that are characteristic of the Western diet [2]. The plasma fatty acid profile of the Inuit population was consistent with these differences in dietary fats. They had a more favourable lipid profile, typically lower in triglycerides, cholesterol, low density lipoprotein cholesterol (LDL-C) and very low density lipoprotein cholesterol (VLDL-C), and higher in high density lipoprotein cholesterol (HDL-C). They also had reduced blood clotting and thrombosis [1-3].

2. Sources, Biochemistry and Metabolism Of ω 3 and ω 6 Fatty Acids

ω 6 and ω 3 Fatty acids represent two classes of polyunsaturated fatty acids that derive from linoleic acid (18:2 ω 6) and α -linolenic acid (18:3 ω 3), respectively (Figure 1). The nomenclature for the ω 6 and ω 3 fatty acids relates to the presence of a double bond at the sixth or third carbon, respectively, from the methyl terminus of the fatty acid chain. Metabolism of linoleic and α -linolenic acids by desaturase and elongase enzymes generates arachidonic acid and EPA, respectively. Both arachidonic acid and EPA are substrates for cyclooxygenase, lipoxygenase and cytochrome P450 enzymes, yielding eicosanoids and mediators of inflammation resolution with multiple and varying physiological functions. Further metabolism of EPA yields the 22-carbon fatty acid DHA. There are numerous reports

that the eicosanoids derived from EPA are generally less biologically active than those from arachidonic acid [4], or they antagonise the action of those metabolites derived from arachidonic acid [5].

FIGURE 1: Metabolism of linoleic acid and α -linolenic acid to arachidonic acid and eicosapentaenoic acid, respectively. Both arachidonic acid and eicosapentaenoic acid are substrates for cyclooxygenase, lipoxygenase and cytochrome P450 enzymes, yielding eicosanoids and lipid mediators of inflammation resolution. Eicosapentaenoic acid is further elaborated to docosahexaenoic acid.

Western diets are generally more abundant in ω 6 fatty acids that are found mainly in vegetable oils rich in linoleic acid. The dietary intake of α -linolenic acid, found in plant oils

such as linseed oil (~53%), canola oil (~10%), soybean oil (~7%) and walnut oil (~10%), is relatively low. Humans are unable to pre-form linoleic acid and α -linolenic acid, and thus these fatty acids are termed “essential” dietary fatty acids. Humans are also unable to convert ω 6 fatty acids to ω 3 fatty acids and have a very limited capacity to convert α -linolenic acid to EPA and DHA [6]. Thus, the main dietary sources of EPA and DHA are fish especially oily fish such as mackerel, salmon, cod, mullet, herring and flounder.

3. Evidence from Population Studies

A number of population studies and meta-analyses have examined the relationship between ω 3 fatty acids and cardiovascular disease [7-15]. In a meta-analysis comprising 15,806 patients, Bucher et al [7] showed that ω 3 fatty acids associated with a 30% reduction in fatal myocardial infarction and sudden death ($P<0.01$), and a 20% reduction in overall mortality ($P<0.001$). Whelton et al [10] in 19 studies comprising 228,864 participants, showed that fish consumption associated with a risk reduction of 17% for fatal coronary heart disease (CHD) ($P<0.005$) and 14% for total CHD ($P<0.005$). A meta-analysis by He et al [8] that included 222,364 individuals, showed the relative risk for CHD mortality was reduced by 23% in those that ate fish 2-4 times/week, compared with individuals who either never ate or consumed less than one fish meal per month.

Two recent meta-analyses by Maki et al [15] and Alexander et al [14] assessing use of EPA and/or DHA supplements provide additional support that these fatty acids confer benefits on cardiovascular health. In an analysis of 14 randomised controlled trials including 71,899 subjects, Maki et al [15] reported an 8.0% ($P=0.015$) lower risk for cardiac death with ω 3 fatty acids versus controls. A meta-analysis by Alexander et al [14] that included 8 randomised controlled trials and 16 prospective cohort studies incorporating 732,000 individuals examined EPA+DHA from foods or supplements and CHD, including myocardial

infarction, sudden cardiac death, coronary death, and angina. The data showed that among randomised controlled trials there was a non-significant 6% reduction in CHD risk with EPA+DHA. However, subgroup analyses indicated a statistically significant CHD risk reduction with EPA+DHA among higher-risk populations, including participants with elevated triglyceride levels (16% reduction) and elevated low-density lipoprotein cholesterol (14% reduction). Meta-analysis of data from prospective cohort studies showed a statistically significant 18% reduction for higher intakes of EPA+DHA and risk of any CHD event. However, not all meta-analyses have shown benefits of ω 3 fatty acids on cardiovascular outcomes [16-18]. Rizos et al. [18] reported ω 3 fatty acids did not associate with a lower risk of all-cause mortality, cardiac death, sudden death, myocardial infarction or stroke, in a meta-analysis of 20 studies and 68,680 patients. The observed effect was not associated with study specific or population-specific characteristics. It is noteworthy that the relative risks for cardiac death and sudden death were reduced by 9% ($P=0.01$) and 13% ($P=0.06$) respectively by ω 3 fatty acids, but the authors adopted a conservative statistical approach and inexplicably set the p-value for significance at 0.0063.

Population studies have shown that increased dietary ω 3 fatty acids, particularly as fatty fish, associates with a lower risk of heart failure and stroke. A meta-analysis by Djousse et al [19] comprising 176,441 subjects and 5,480 incident cases of heart failure, showed a 15% reduced relative risk ($p=0.04$) for heart failure when comparing the highest to lowest category of fish intake. Further, Mozaffarian et al [20] showed eating tuna or other broiled or baked fish, but not fried fish associated with a reduced incidence of heart failure. An analysis by Xun et al [21] that included 402,127 individuals, reported a 9% reduced risk of total stroke in those who ate 2-4 fish meals/week relative to those that ate less than one fish meal per month. The protective effect was only evident with ischaemic stroke.

4. Evidence from Randomised Controlled Trials

Several large randomised controlled trials have confirmed ω 3 fatty acids benefit patients with CHD. The Diet and Reinfarction Trial (DART) in 2,033 men with recent myocardial infarction showed ω 3 fatty acids as oily fish or fish oil capsules reduced all-cause mortality by 29% [22]. The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto (GISSI) study [23] randomised 11,323 post-myocardial infarction patients and showed that after 1 year ω 3 fatty acids reduced total and cardiovascular mortality, and sudden cardiac death, by 21%, 30% and 45%, respectively. A follow-up study in nearly 7,000 patients with class II to IV heart failure (GISSI-HF), showed that ω 3 fatty acids reduced total mortality by 9% and total mortality or hospitalisation for cardiovascular diseases by 8% [24]. The Japan EPA Lipid Intervention Study (JELIS) in 18,645 statin-treated hypercholesterolaemic patients, showed a 19% reduction in major cardiovascular events after 5 years in patients randomised to EPA [25].

It is noteworthy that several recent studies have not shown benefits of ω 3 fatty acids in at-risk patient populations. In the OPERA study that included 1,516 patients undergoing cardiac surgery, ω 3 fatty acids did not reduce the risk of post-operative atrial fibrillation relative to placebo [26]. The ORIGIN trial [27] in 12,536 patients with or at high risk for diabetes, reported that ω 3 fatty acids did not reduce the rate of cardiovascular events. In 12,513 patients with multiple cardiovascular risk factors or atherosclerotic vascular disease but not myocardial infarction, ω 3 fatty acids did not reduce cardiovascular mortality and morbidity [28]. The reasons for these negative results may relate to a number of factors. Firstly, ω 3 fatty acids likely confer greater benefit in patients that have experienced a recent myocardial infarction or heart failure due to their antiarrhythmic effects. Secondly, some of the studies have had limited power to detect a reduction in sudden deaths from cardiac causes or arrhythmic events. Other important factors include trials that have used doses of ω 3 fatty

acids lower than what has been previously shown to have an effect, the presence of multiple confounding comorbidities, effects of concomitant medications and the likelihood that patients are already receiving a high level of clinical care. Studies may also have been confounded by participants already consuming a relatively high intake of ω 3 fatty acids which would limit the likelihood of detecting additional benefits of ω 3 fatty acid supplementation. In this regard, von Schacky [29] has suggested that most studies have recruited trial participants irrespective of their baseline blood EPA+DHA status which is an important predictor of events. Blood levels of EPA+DHA show a large inter-individual variability in responding to increased intake, leading to a significant overlap of EPA+DHA levels between intervention and control groups. Thus it has been suggested future studies should recruit participants with low baseline blood EPA+DHA levels and treat with individually tailored doses of EPA+DHA to a pre-specified target range. Similarly, Visioli [30] has suggested a lipidomic approach to screen suitable patients and correlation of the blood fatty acid profile with outcomes. An additional potential confounding factor to explain the negative findings from recent studies supplementing EPA+DHA could be a reduction in bioavailability as a result of taking supplements with other foods.

5. Influence of ω 3 Fatty Acids on Cardiovascular Risk Factors

The benefits of EPA and DHA relate to their capacity to alter numerous physiological pathways [31] and cardiovascular risk factors including blood pressure [32-36], cardiac function [31, 34, 37], arterial compliance [38], vascular reactivity [39, 40] and lipids [41, 42]. EPA and DHA also have anti-platelet [43], anti-inflammatory [44], pro-resolving [45] and anti-oxidative actions [46]. EPA and DHA have differential effects on blood pressure, heart rate, lipids and vascular reactivity [47].

5.1. Blood Pressure

Meta-analyses of randomised controlled trials providing fish meals or fish oil supplements unequivocally show ω 3 fatty acids lower blood pressure [32, 33, 35, 36]. Morris et al [35] showed blood pressure was reduced $-3.0/-1.5$ mmHg (systolic/diastolic blood pressure) with an average dose of 4.8g/day ω 3 fatty acids, with the strongest effect in treated and untreated hypertensive individuals ($-3.4/-2.0$ mmHg). Appel et al [32] showed blood pressure fell $-5.5/-3.5$ mmHg in untreated hypertensive individuals and $-1.0/-0.5$ mmHg in normotensives with 3g/day of ω 3 fatty acids. Geleijnse et al [33] reported ω 3 fatty acids reduced blood pressure by $-2.1/-1.6$ mmHg, with the greatest effects in individuals older than 45 years and those that were hypertensive ($-4.0/-2.5$ mmHg). Miller et al [36] showed systolic blood pressure (-1.52 mm Hg) and diastolic blood pressure (-0.99 mm Hg) were reduced by ω 3 fatty acids, with strongest effects among untreated hypertensive subjects ($-4.51/-3.05$ mm Hg). To put these blood pressure changes into perspective, a 2 mmHg reduction in systolic blood pressure in adults is associated with a 4% fall in coronary death and 6% reduction in stroke [48].

The blood pressure-lowering effects of ω 3 fatty acids are potentiated by sodium restriction [49] and antihypertensive medication.[50]. Bao et al [51] also showed that ω 3 fatty acids were additive to the blood pressure-lowering effects of weight reduction in overweight treated hypertensives. Blood pressure monitored over a 24-hour period fell $-6.0/-3.0$ mmHg in patients consuming a daily fish meal, $-5.5/-2.2$ in those that completed a weight loss program that reduced weight by 5.6 kg over 12 weeks, and $-13.0/-9.3$ in individuals that combined the two regimens. Mori et al [52] have also shown that the blood pressure lowering effects of ω 3 fatty acids are predominantly due to DHA.

5.2. Vascular Function and Arterial Compliance

Human studies and experimental animal models provide convincing evidence that the blood pressure-lowering effects of ω 3 fatty acids are in part due to improvements in vascular

function [34, 39]. Further, Mori et al [40] provided evidence for differential effects of EPA and DHA on vascular function in humans. The blood pressure changes following supplementation with DHA but not EPA in dyslipidaemic patients [52], were associated with significant improvements in endothelial and smooth muscle function as well as reduced vasoconstrictor responses in the forearm microcirculation [40]. The effects of ω 3 fatty acids on vasoreactivity are likely due to their incorporation into endothelial membranes with a consequent increase in membrane fluidity, calcium influx, and endogenous synthesis and release of nitric oxide. These changes likely affect enzyme activity, receptor affinity and transport capacity of the cell, including synthesis and/or release of nitric oxide. Animal studies suggest the blood pressure-lowering effects of ω 3 fatty acids may also relate to alterations in catecholamines and ATP [53].

The effects of ω 3 fatty acids on blood pressure are also mediated by changes in arterial compliance, which in turn is affected by endothelial function. Pase et al [38] in a meta-analysis, showed that ω 3 fatty acids significantly improved both pulse wave velocity and arterial compliance.

5.3. Cardiac Function

Increased heart rate is a risk factor for cardiovascular death, particularly sudden death [54]. Mozaffarian et al [37] showed in a meta-analysis that ω 3 fatty acids reduce heart rate by -1.6 bpm, with a greater reduction in individuals with a baseline heart rate greater than 69 bpm (-2.5 bpm) and in those studies of longer than 12 weeks duration (-2.5 bpm). These data suggest the antihypertensive effects of ω 3 fatty acids associate with a significant cardiac component possibly mediated by effects on cardiac myocytes, autonomic nerve function or β -adrenoreceptor activity. Using continuous 24-hour measurements of heart rate, Bao et al [51] showed that a combination of weight loss and dietary ω 3 fatty acids significantly reduced heart rate in overweight treated hypertensive patients. Heart rate was reduced 4.3 bpm by a

daily fish meal, 1.8 bpm following weight loss and 6.1 bpm by a combination of the two regimens. Mori et al [52] also showed DHA had a greater effect than EPA in reducing heart rate in humans [52]. The mechanisms by which ω 3 fatty acids affect heart rate likely relate to their incorporation into myocardial cells and altering electrophysiological function [55].

Studies in humans show that ω 3 fatty acids increase heart rate variability in patients at high risk of sudden cardiac death and in healthy individuals. In this regard, Xin et al [56] in a meta-analysis showed that short term ω 3 fatty acids favourably affect the frequency domain of heart rate variability as indicated by enhancement of vagal tone. Heart rate variability is a surrogate index of autonomic nerve function and low heart rate variability independently predicts cardiovascular disease mortality in patients with coronary artery disease or chronic heart failure [57] and in healthy populations [58]. These data suggest enhanced vagal tone may be an important mechanism underlying the antiarrhythmic effect of ω 3 fatty acids.

5.4. Plasma Lipids

ω 3 Fatty acids have very little effect on total cholesterol and LDL-C [41, 42], but they increase HDL-C [59, 60]. The greatest effect of ω 3 fatty acids is on triglycerides with reductions of 20-30% reported [31]. Mori et al [60, 61] further showed the triglyceride-lowering actions of ω 3 fatty acids were attributable to both EPA and DHA. The fall in plasma triglycerides with ω 3 fatty acids is due to a reduction in hepatic VLDL-cholesterol synthesis. The mechanisms include reduced fatty acid availability for triglyceride synthesis as a result of decreased *de novo* lipogenesis, a reduction in the delivery of non-esterified fatty acids to the liver, increased fatty acid β -oxidation, altered enzymatic activity for triglyceride assembly in the liver and increased hepatic synthesis of phospholipids instead of triglycerides [41, 42, 62]. Clinical trials show ω 3 fatty acids can complement lipid lowering therapy in dyslipidaemic patients. In this regard, Chan et al [63] showed that ω 3 fatty acids in addition to statin therapy resulted in optimal changes in the lipid profile as reflected by decreased plasma triglycerides

and increased HDL-C. High-doses of ω 3 fatty acids can also be useful adjunct therapy in the treatment of hypertriglyceridaemia.

5.5. Glucose Homeostasis and Diabetes

Meta-analyses have consistently shown that ω 3 fatty acids have no significant effect on fasting glucose, insulin sensitivity or glycated haemoglobin in patients with Type 2 diabetes [64]. A systematic review of 540,184 individuals and 25,670 cases of incident diabetes mellitus showed fish and/or seafood consumption, or consumption of EPA+DHA, were not significantly associated with risk of diabetes [65].

5.6. Platelet Function and Thrombosis

The inhibitory effects of ω 3 fatty acids on thrombosis are related to their capacity to reduce the risk for sudden cardiac death and all-cause mortality [8, 22, 23]. Knapp et al [66] showed that ω 3 fatty acids decreased thromboxane A_2 (TXA₂) a vasoconstrictor and aggregator derived from arachidonic acid, and increased thromboxane A_3 (TXA₃) the analogous but substantially less biologically active EPA-derived metabolite (Figure 2). Fischer et al [67]

FIGURE 2: Structure of thromboxane A₂ (TXA₂) and prostaglandin I₂ (PGI₂) from

arachidonic acid, and thromboxane A₃ (TXA₃) and prostaglandin I₃ (PGI₃) from EPA.

showed ω3 fatty acids increased prostaglandin I₃ (PGI₃) derived from EPA, without a fall in prostaglandin I₂ (PGI₂) which derives from arachidonic acid (Figure 2). PGI₃ is equipotent in its vasodilatory and anti-aggregatory activities to PGI₂. An hypothesis suggests that an overall increase in total PGI₂ and PGI₃ formation in conjunction with reduced total thromboxane (TXA₂ and TXA₃), could favourably alter thrombotic, endothelial and vascular responses following dietary ω3 fatty acids. Other factors that could contribute to a decrease in clinical atherothrombosis include improvements in blood rheology [68] and reduced PDGF-like proteins [69] following ω3 fatty acids. Mori et al [70] have also shown that the anti-aggregatory effects of ω3 fatty acids are influenced by the background level of dietary fat and the source of ω3 fatty acids.

5.7. Inflammation

The anti-inflammatory and immunomodulatory effects of ω3 fatty acids are mediated via attenuation of inflammatory eicosanoids and leukotrienes, cytokines, oxidative stress, and by altering endothelial and cell-cell activation, and immune cell function [44]. EPA is a preferred substrate of the lipoxygenase pathway leading to the formation of the relatively inactive leukotriene B₅ (LTB₅) at the expense of leukotriene B₄ (LTB₄); the latter derived from arachidonic acid is a potent chemotactic factor for leukocytes [44].

FIGURE 3: Structure of leukotriene B₄ (LTB₄) and leukotriene B₅ (LTB₅) from arachidonic

acid and EPA, respectively.

ω 3 Fatty acids reduce *ex vivo* formation of pro-inflammatory cytokines following stimulation of monocytes/lymphocytes with lipopolysaccharide [44]. *In-vitro*. ω 3 fatty acids have been shown to decrease the expression of pro-inflammatory cytokines, cell-adhesion molecules and monocyte adhesion to endothelial cells [71]. Attenuation in adhesion molecule expression by ω 3 fatty acids was accompanied by decreased binding of human lymphocytes and monocytes to cytokine-stimulated endothelial cells [71].

5.8. Lipid mediators of inflammation resolution

Evidence shows the resolution of inflammation is an active process accompanied by the biosynthesis of potent lipid mediators that stimulate the resolution of inflammation with consequent return to tissue homeostasis. Serhan et al [45] have described chemically and functionally distinct mediators, including E-series resolvins derived from EPA via P450 metabolism or aspirin-acetylated cyclooxygenase (COX-2), and D-series resolvins, protectins and maresins derived from DHA via lipoxygenase or aspirin acetylated COX-2 (Figure 4)

FIGURE 4: Structure of resolvin E1 (RvE1) from EPA, and resolvin D1 (RvD1), protectin

D1 and 7(R)-Maresin1 from EPA.

[45]. These mediators act via G-coupled protein receptors and have potent anti-inflammatory and pro-resolving actions that increase with time during the inflammatory process [45]. Lipid mediators of inflammation resolution reduce airway inflammation, colitis, arthritis and post-operative pain [45]. Studies in humans are providing convincing evidence that dietary ω 3 fatty acids increase blood and tissue levels of lipid mediators of inflammation resolution [72]. Mori et al have shown that ω 3 fatty acid supplementation increased plasma lipid mediators of inflammation resolution in healthy adults [73, 74], in individuals with the metabolic syndrome [75], arthritis [76], chronic kidney disease [77] and in placental tissue of pregnant women [78].

5.9. Oxidative Stress

Increasing evidence shows abnormal production of free radicals leads to increased stress on cellular structures and causes changes in molecular pathways that underpins the pathogenesis of a number of human diseases, including cardiovascular and neurological diseases, and cancer. In this regard, Mori et al [46] have shown plasma and urinary F₂-isoprostanes, measured by gas chromatography-mass spectrometry, are reduced following ω 3 fatty acids. F₂-isoprostanes are lipid peroxidation products derived from the non-enzymatic free radical oxidation of arachidonic acid in membrane lipids and are considered the most reliable biomarkers of *in vivo* lipid peroxidative damage. The mechanisms by which ω 3 fatty acids attenuate oxidative stress likely involve decreased leukocyte activation and immunomodulatory actions [79].

5.10. Effects on Plaque Stabilization

There is some evidence that ω 3 fatty acids may alter plaque morphology, suggestive of increased stability. These findings could represent an important mechanism by which ω 3 fatty acids reduce ischaemic cardiovascular events. In this regard, Thies et al [80] showed that ω 3

fatty acids were readily incorporated into the atherosclerotic plaque of patients with carotid atherosclerotic disease undergoing carotid endarterectomy and that this associated with a reduced number of macrophages in the plaque.

5.11. The ω 3 Index

Harris and von Schacky [81] have proposed a measure, termed the Omega-3 Index and defined as the sum of EPA+DHA in erythrocytes, that may serve as a marker for cardiovascular health and CHD. They further suggested that an Omega-3 Index of $\geq 8\%$ associates with cardioprotective benefits whereas an index of $\leq 4\%$ gives the least cardioprotection [81], an hypothesis supported by data from studies in patients with acute coronary syndrome [82] and stable CHD [83].

6. Guidelines for ω 3 Fatty Acid Intake

The American Heart Association [84] and other global health authorities have made population-based dietary recommendations for ω 3 fatty acids. Current guidelines suggest individuals should consume approximately 500 mg/day of EPA and DHA [85], which is achievable with at least two 100g serves of fish per week, preferably oil fish species such as fresh tuna, salmon, mackerel, herring and sardines [86], and preferably broiled or baked, but not fried [20]. The most practical recommendation for increasing dietary ω 3 fatty acids is to incorporate fish as part of a healthy diet that includes increased fruits and vegetables, and moderation of salt intake. Individuals with CHD should be encouraged to increase ω 3 fatty acid to approximately 1g daily [86], based largely on data from clinical trials [23]. ω 3 Fatty acid supplements at doses 2-4g/day should be considered in combination with other lipid therapies in patients with hypertriglyceridaemia [86]. These doses of ω 3 fatty acids are achievable with high-quality encapsulated ω 3 fatty acid supplements free of contaminants.

ω 3 Fatty acid supplements do not associate with adverse effects other than occasional

gastrointestinal upset and a “fishy burp”. The latter is preventable by taking capsules with a cold beverage and a meal. Although there are some concerns that high intakes of ω 3 fatty acids could potentially increase the risk of bleeding when taken in conjunction with antiplatelet or anticoagulant medications, there was little evidence to date of adverse effects. However, Bays [87] suggested clinicians should be mindful of increased bleeding as a theoretical possibility. Further, some clinicians advise patients to discontinue fish oil supplements 4-7 days prior to invasive procedures with the highest risk for bleeding complications. Postoperatively, clinicians should consider the cardiovascular advantages of recommencing ω 3 fatty acid supplements given cardiovascular and thrombotic events are often common complications after major surgeries.

It should be noted that some fish species may contain levels of methylmercury and environmental contaminants, which is very much dependent on the location where these fish are caught. However, these substances are only present at highest levels in predatory fish such as shark, swordfish, marlin and larger species of tuna, and marine mammals. Health advisory bodies suggest women who are either pregnant or may become pregnant, lactating women and young children, to limit consumption of such fish species in order to minimize their exposure to these contaminants [86].

7. Conclusions

Current evidence strongly supports the concept that ω 3 fatty acids beneficially influence a number of cardiometabolic risk factors, with the strongest evidence from studies examining dietary fish consumption. Dietary intake of fish has consistently been associated with lower incident rates of heart failure, lower sudden cardiac death, stroke and myocardial infarction. The recent American Heart Association Science Advisory [84] concluded that treatment with ω 3 fatty acids is reasonable for (1) secondary prevention of CHD and sudden cardiac death

among patients with prevalent CHD; and (2) secondary prevention of adverse outcomes in patients with heart failure. The Australian National Heart Foundation supports these recommendations and suggests evidence continues to be positive for the role of ω 3 fatty acids in the treatment of hypertriglyceridaemia [88]. Whilst there may be some benefit in atrial fibrillation and hypertension, further trials are required to support any firm recommendations [88]. ω 3 Fatty acids do not have adverse interactions with lipid-lowering drugs or antihypertensive and antithrombotic medications. Small doses of 1g/day are achievable with consumption of 2-3 oily fish meals/week. Higher doses up to at least 4g/day have no clinically significant adverse effects and are achievable with encapsulated preparations now available. Overall there is good evidence that increased dietary ω 3 fatty acids should be encouraged. In particular, fish should be considered an important component of a healthy diet.

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Conflicts Of Interest: none

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