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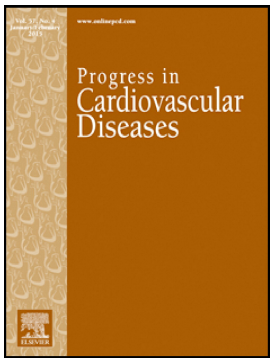

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Omega-3 Polyunsaturated Fatty Acids and Cardiovascular Health: A Comprehensive Review

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Key Words: Omega 3 Polyunsaturated Fatty Acid, Omega 3 index, Omega 6, Cardiovascular Disease, Coronary Heart Disease, Heart Failure, Heart Transplant, Sudden Cardiac Death, Myocardial Infarction

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Abstract

The potential cardiovascular (CV) disease (CVD) benefits of Omega-3 Polyunsaturated Fatty Acids (OM3) have been intensely studied and debated for decades. Initial trials were performed in patients with low use of maximal medical therapy for CVD, and reported significant mortality benefits with the use of 1 gram/day OM3 intervention following myocardial infarction (MI). More recent studies, including cohorts of patients receiving modern guideline directed medical therapy for CVD, have often not shown similar benefits with OM3 use. We conducted a literature review using PubMed, professional society guidelines, specific journal databases including *New England Journal of Medicine* and *Journal of the American College of Cardiology* from January 1, 2007 to December 31, 2017. References from selected articles were also reviewed, as well as key articles outside of the selected time-frame for their important findings or historical perspectives.

Currently, there are no Class I recommendations from the American Heart Association (AHA) for the use of OM3, however, considering the safety of this therapy and beneficial findings of some modern studies (including patients with current maximal medical therapy for CVD), the AHA has recently expanded their list of Class II recommendations, in which treatment with OM3 for CVD benefit is reasonable. This review discusses the current state of the evidence, summarizes current professional recommendations, and provides recommendations for future research.

Abbreviations

AF = Atrial Fibrillation

AHA = American Heart Association

AHRQ = Agency of Healthcare Research and Quality

ALA = Alpha-linoleic Acid

ASA = Aspirin

BP = Blood Pressure

CHD = Coronary Heart Disease

CKD = Chronic Kidney Disease

CV = Cardiovascular

CVD = Cardiovascular Disease

DHA = Docosahexaenoic Acid

DPA = Docosapentaenoic Acid

DM = Diabetes Mellitus

EPA = Eicosapentaenoic Acid

FDA = Food and Drug Administration

HF = Heart Failure

HFrEF = Heart Failure with Reduced Ejection Fraction

LDL-C = Low-density Lipoprotein Cholesterol

LVSVI = Left Ventricular Systolic Volume Index

MACE = Major Adverse Cardiovascular Events

MI = Myocardial Infarction

OM3 = Omega-3 Polyunsaturated Fatty Acid

OM6 = Omega-6 Polyunsaturated Fatty Acid

RCT = Randomized Controlled Trial

RLP = Remnant Lipoprotein

SCD = Sudden Cardiac Death

SDA = Stearidonic Acid

TG = Triglyceride

1. Introduction

The potential role of Omega-3 polyunsaturated fatty acids (OM3) in reducing cardiovascular (CV) disease (CVD) and CVD events has been studied for decades. As early as 1944, Sinclair[1] described the rarity of coronary heart disease (CHD) in Greenland Eskimos, who consumed a diet high in whale, seal and fish. While there are many well-known physiologic benefits of consuming fish or fish oil supplements, and multiple CV benefits demonstrated in several studies, there remains much controversy regarding the relationship between OM3 and CV health.

Current guidelines from the American Heart Association (AHA) recommend 2 servings of fatty fish per week for the general population,[2] and state that it may be reasonable to recommend fish or fish oil capsules (1 gram/day OM3) for CVD risk reduction as secondary prevention for patients with CHD and other atherosclerotic vascular disease.[3] More recently, the AHA concluded that OM3 treatment is reasonable for (I) secondary prevention of CHD death, (II) patients with heart failure (HF) with reduced ejection fraction (HFrEF), and (III) secondary prevention of CHD in patients with a recent CHD event, such as recent myocardial infarction (MI).[4] The purpose of this review is to evaluate the current evidence regarding OM3 and CV health, explain potential benefits and uses of OM3 and make recommendations for future research.

2. Biochemistry and Sources of OM3

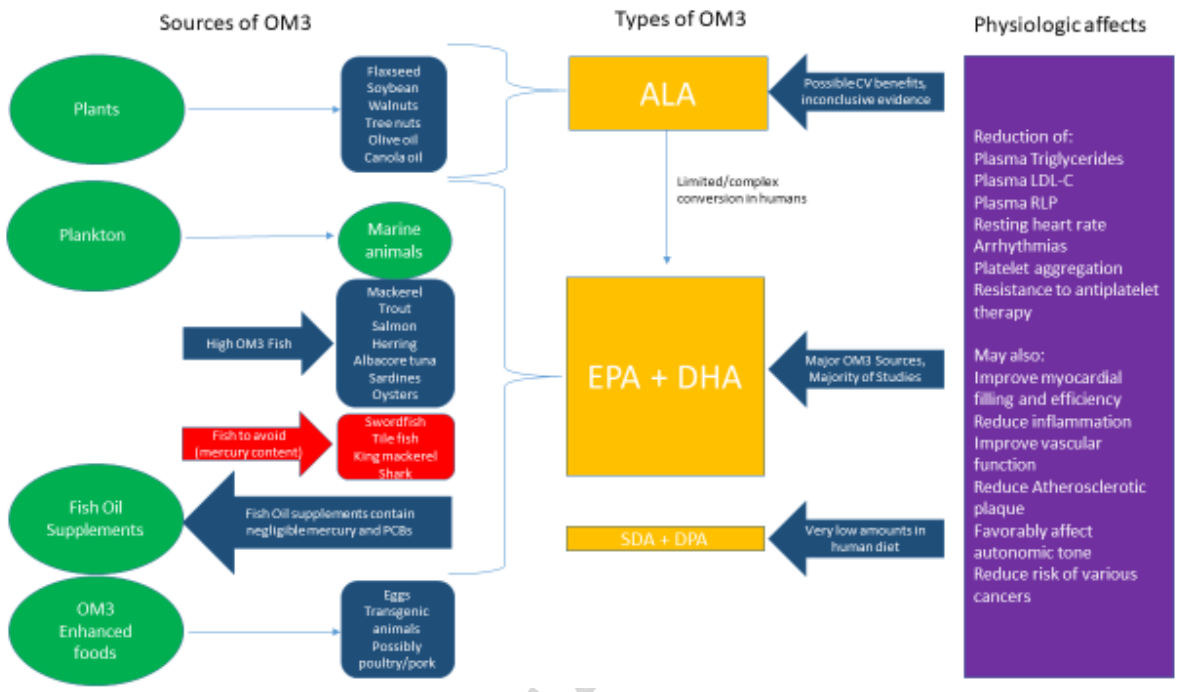
Biologically relevant families of the polyunsaturated fatty acids are the omega-6 (OM6) and OM3.[5] The major OM3 include alpha-linolenic acid (ALA, primarily in plants), eicosapentaenoic acid and docosahexaenoic acid (EPA and DHA, respectively, both primarily in marine life), and others such as stearidonic acid (SDA) and docosapentaenoic acid (DPA) are present in very low amounts in the diet.[6] ALA is found only in trace amounts in green leafy vegetables, but is found in larger quantities in plants and seeds as well as plant and seed oils such as flaxseed (also known as linseed), chia, soybean, walnuts

and other tree nuts, and olive oil and rapeseed (canola) oils.[5,7] Although ALA can be converted to EPA with subsequent conversion of EPA to DHA, this conversion is complex and limited.[5] In general, humans convert < 5% ALA to EPA and even less (0-4%) ALA to DHA.[7,8] Some studies suggest possible CV benefits of ALA, but the evidence is mixed and inconclusive overall.[8] Therefore, plant based OM3 cannot be considered a replacement for marine based OM3, specifically EPA and DHA. However, further study for the health benefits of ALA is important because of abundant global supply.[8]

EPA and DHA enter the food chain through marine phytoplankton or algae, and humans mainly obtain these OM3 from consuming fish, particularly oily fish, such as mackerel, trout, salmon, herring, albacore tuna and sardines.[5,7] Fish do not naturally produce these oils, but obtain them from consuming marine microorganisms in their natural diet.[7] Therefore, OM3 are typically found in higher levels in wild fish, as farmed fish are often grain fed, and the OM3 in fish are not synthesized de novo, but stem from unicellular organisms at the base of their natural food chain.[9]

"Stealth health" is a concept in which intrinsically enhancing OM3 content of meat from chickens and other monogastric animals such as pigs seems readily achievable, and these "stealth health" foods could be an ideal mechanism for delivering OM3 without changing dietary habits.[10] Also, transgenic animals that express the fat-1 gene from the worm *Caenorhabditis elegans* have been raised, and this gene encodes an OM3 fatty acyl desaturase that converts OM3 substrates into OM3; the supplementation with meat from these transgenic animals might permit enrichment of mammalian cells with OM3.[5] These methods may one day be used to improve the OM3 status of those whom are deficient, and without the need for dietary changes.

Figure 1: OM3 Types, Sources and Physiologic Affects



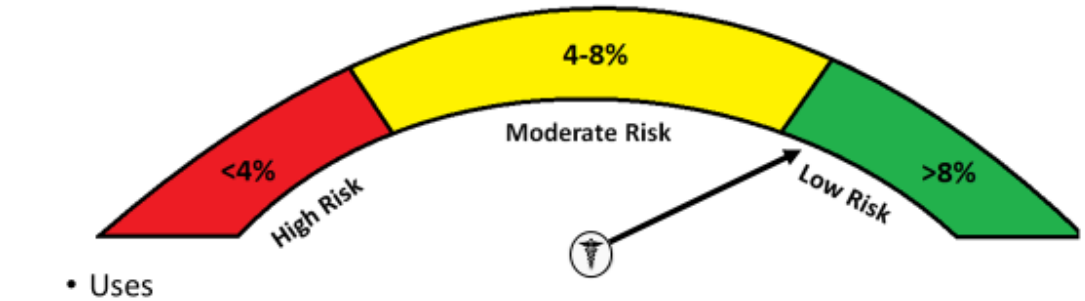
ALA = Alpha Linolenic Acid; DHA = Docosahexaenoic Acid; DPA = Docosapentaenoic Acid; EPA = Eicosapentaenoic Acid; LDL-C = Low-density Lipoprotein Cholesterol; OM3 = Omega-3 Polyunsaturated Fatty Acid; PCB = Polychlorinated Biphenyl; RLP = Remnant Lipoprotein; SDA = Stearidonic Acid

3. OM3 Index

One objective measure of an individual's OM3 status is the OM3 index, which measures the OM3 content in red blood cell membranes.[11] An OM3 index < 4% has been associated with increased CHD risk, particularly sudden cardiac death (SCD), whereas an index > 8% is considered low risk for CHD and 4-8% is intermediate risk.[11] It has been argued that a low OM3 index could serve as a novel CVD risk factor, and can also be used to reclassify individuals from intermediate CVD risk to low or high risk groups.[12] Many previous OM3 intervention trials have yielded neutral results, and it has been proposed that incorporating the OM3 index into trial designs to understand baseline OM3 levels, and treating to a target (e.g. 8-11%) will make more efficient trials and treatment possible.[12]

The OMEGA-REMODEL trial suggested that the OM3 index may serve as a useful marker of treatment efficacy,[13] and it has also been shown that the Global Registry of Acute Coronary Events score had an improved c-statistic and correctly reclassified a significant proportion of patients by the inclusion of fatty acids.[14] We have previously argued that the inadmissibility of memory recall as scientific evidence limits the use of many nutritional studies, which may explain why the relation of OM3 in the diet to clinical events is looser than the association of measured blood levels of OM3 to clinical events.[12,15,16]

Figure 2 Potential Use of the OM3 Index



- Uses
  - Objectively measure OM3 status
  - Association with CHD/SCD Risk
  - Novel CVD Risk Factor
  - Risk Stratification of patients with CVD
- Research benefits
  - Treat to Target
  - Standardization of Research Results
  - Improved c-statistic and classification for GRACE score

Note: Risk chart represents OM3 Index levels associated with risk of CHD and SCD
CHD = Coronary Heart Disease; CVD = Cardiovascular Disease; GRACE = Global Registry of Acute Coronary Events; OM3 = Omega-3 Polyunsaturated Fatty Acids; SCD = Sudden Cardiac Death

4. Physiology

OM3 have demonstrated the ability to exert beneficial physiologic effects on plasma triglyceride (TG) levels, resting heart rate, arrhythmias, atherosclerotic plaque, blood pressure (BP), platelet aggregation

and might also improve myocardial filling and efficiency, lower inflammation, improve vascular function and favorably affect autonomic tone.[5,8,17-19] With regards to BP reduction, 3 grams/day EPA + DHA has been associated with reductions of 4 mmHg and 2 mmHg of systolic and diastolic BP, respectively.[11] Antiplatelet, anti-inflammatory and TG lowering effects of OM3 require relatively higher doses of DHA and EPA (3-4 grams/day).[7] Further explanation and proposed mechanisms for some of these physiologic benefits will be described in the appropriate sections.

5. **Omega 6**

Western diets are low in OM3 but have excessive OM6, such as those in poultry, meat and most vegetable oils.[5,20] It has been stated that the human body evolved on a diet with an OM6-to-OM3 ratio of approximately 1:1, however, the modern ratio in the typical American diet is approximately 14:1 or greater.[20,21] High OM6:OM3 diet has been said to promote the pathogenesis of many diseases, including CVD, cancer and inflammatory/autoimmune diseases, whereas increased levels of OM3 (diets with a lower OM6:OM3 ratio) express suppressive pathogenic effects.[20] An expert panel for the US military unanimously agreed that a military diet with low OM6:OM3 may provide soldiers CV, immunological and surgical benefits, and that preloading with OM3 prior to combat may be beneficial and support overall resilience.[10]

Linoleic acid is the primary dietary OM6 (85-90%), and is converted to arachidonic acid, which is the substrate for a variety of pro-inflammatory molecules.[22] The inflammatory component of the CHD disease process is part of the rationale that reducing OM6 intake can reduce CHD risk. However, the AHA concluded that an OM6 intake of at least 5-10% of energy would seem to lower CHD risk, and higher amounts may even be more beneficial, and that to reduce OM6 intakes would be more likely to increase than to decrease risk for CHD.[22] However, meta-analyses of randomized trials and prospective observational studies suggest otherwise.[23,24]

6. Landmark Trial: The importance of GISSI-Prevenzione

The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardio (GISSI) – Prevenzione (GISSI-P) trial showed that 1 gram/day OM3 decreased the risk of death, nonfatal acute MI and stroke in patients surviving recent acute MI.[25] However, the study population was receiving very little current guideline directed medical treatment, for example, only 5% of patients were receiving statins at baseline.[26] Multiple later trials, including patients receiving modern optimal medical treatment for CVD, have not demonstrated as favorable results as those of GISSI-P, and it is therefore possible that OM3 has little benefit in the presence of maximal medical treatment for CVD.[4]

This landmark trial used an OM3 dose of 1 gram/day, which many subsequent intervention trials have followed. Multiple studies have demonstrated favorable CV effects using higher doses of OM3 supplementation (e.g. 4 grams/day).[13,27,28] It has been reported that the TG level is a significant independent risk factor for CHD,[11] and even though it is well established that OM3 lower TG levels, doses > 1.5 grams/day are typically needed for a clinically meaningful change.[29] Therefore, the 1 gram/day OM3 intervention in GISSI-P, and many subsequent studies, may perhaps be an insufficient dose to yield significant CVD benefits. Ongoing studies with higher dose interventions are currently underway, such as REDUCE-IT and STRENGTH.

Baseline OM3 levels are determined by diet, which is inevitably influenced by geographic location. GISSI-P and other important studies, such as JELIS, were conducted in Italy and other regions where baseline OM3 intake is significantly higher than that of North American populations. Therefore, the higher baseline levels of OM3 in these populations which demonstrated CVD benefits with an intervention of 1 gram/day OM3, may require significantly higher OM3 doses in North American populations,[30] with known OM3 deficiency, to obtain similar total OM3 levels and achieve similar benefit.

7. Recent Update from the AHA Science Advisory

In 2002, the AHA published a scientific statement recommending that patients with documented CHD consume ~1 gram/day EPA + DHA, preferably from oily fish, based on 2 large randomized controlled trials (RCTs).[4] An updated statement was released in 2017 (Table 1), and the AHA concluded that the available evidence does not support the use of OM3 supplementation in the general population who are not at high CVD risk, and there was a lack of consensus about the benefits for those at high CVD risk. The AHA continues to suggest that OM3 supplementation is reasonable for secondary prevention of CHD in patients with a recent CHD event, such as MI, and added a new recommendation for patients with HFrEF, in whom OM3 supplementation may be considered.[4]

Table 1: 2017 Updated AHA Science Advisory regarding OM3 supplementation

Cohort	**Evidence**	**Recommendation**	**Comments**
Primary prevention of CHD	No RCTs exclusively studying primary prevention of CHD	No Recommendation	
Prevention of CVD mortality in DM or prediabetes	Overall, the current evidence from RCTs suggests no benefit of OM3 among patients with or at risk for DM to prevent CVD	Class III: No benefit	
Prevention of CHD in patients with high CVD risk	2/3 trials showed no benefit from OM3 supplementation on clinical CHD	Majority: Class III: No benefit Minority:	

	JELIS showed reduced risk of the composite outcome with OM3 use, but little evidence of risk reduction in hard endpoints (non-fatal MI, CHD death)	Class IIb: Treatment is reasonable	
Secondary prevention of CHD and SCD in CHD patients	OM3 supplements may reduce CHD death, possibly through a reduction in ischemia-induced SCD, among patients with prior CHD, but the treatment does not reduce the incidence of recurrent nonfatal MI	Majority: Class IIa: Treatment is reasonable Minority: Class IIb: Treatment is reasonable	
Primary prevention of Stroke	Overall, there is no proven benefit of OM3 to reduce risk of stroke among patients without a history of stroke	Class III: No benefit	Stroke was not a primary outcome in any RCT, and there is little evidence of reduction in stroke events with OM3 supplements from

			meta-analyses
Secondary prevention of Stroke	Overall, there is no evidence of OM3 supplementation to reduce risk of stroke or other CVDs in patients with prior stroke	No recommendation	Post hoc analysis of JELIS patients with a history of stroke had 6.8% stroke recurrence who received EPA vs 10.5% in controls, for risk reduction of recurrent stroke of 20% (RR 0.80; 95% CI 0.64-0.997), number needed to treat 27 These results should be considered for hypothesis generating
Primary prevention of HF	No RCTs to date	No recommendation	
Secondary prevention of outcomes in patients with HF	Based on a single, large RCT, in which 91% pts had EF < 40%	Class IIa: Treatment is reasonable among patients with HFrEF	OM3 may reduce HF-related hospitalizations and death in patients with HFrEF

			More RCTs are needed among patients with HFpEF
Primary prevention of AF	No data from large RCTs	No recommendation	
Secondary prevention of AF in patients with prior AF	Overall, high-quality evidence from multiple RCTs does not support OM3 supplementation to prevent recurrent AF	Class III: No benefit	
AF after cardiac surgery	6 RCTs did not find OM3 reduction of postoperative AF	Class III: No benefit	
Comment: The doses of OM3 (~1000mg) used in the studies in this scientific statement (other than JELIS, 1800mg) are generally too low to meaningfully lower TG levels AF = Atrial Fibrillation; CHD = Coronary Heart Disease; CVD = Cardiovascular Disease; DM = Diabetes Mellitus; EF = Ejection Fraction; EPA = Eicosapentaenoic Acid; HF = Heart Failure; HFpEF = Heart Failure with Preserved Ejection Fraction; HFrEF = Heart Failure with Reduced Ejection Fraction; MI = Myocardial Infarction; OM3 = Omega-3 Polyunsaturated Fatty Acid; RCT = Randomized Controlled Trial; RR = Relative Risk; SCD = Sudden Cardiac Death			

8. AHRQ Evidence Update

The Agency of Healthcare Research and Quality (AHRQ) performed an evidence review of the relationship between OM3 and CVD in 2004, with an update in 2016 (Table 2).[6] Overall, the effects of OM3 on intermediate CVD outcomes remain largely unchanged. The current National Institute for Health and Care Excellence recommendations for CVD prevention concluded that the evidence does not support the use of OM3 supplements for people being treated for primary or secondary prevention, people with chronic kidney disease (CKD) or diabetes mellitus (DM).[31] It was also concluded that there is moderate strength of evidence that marine oil supplementation lowers risk of major adverse CVD events (MACE) and CVD death, and low strength of evidence that higher marine oil intake is associated with lower risk of CHD and HF.[6]

Table 2 – Updated AHRQ evidence review summary

Level of evidence	**Population**	**Outcome**
High strength	Various	Marine oils lower TG concentrations and raise HDL and LDL levels
High strength	Various	No effect of marine oils on risk of major adverse CV events, all-cause death, SCD, revascularization and BP
Moderate strength	Various	No effect of marine oils on risk of AF

Low strength	Various	No effect of marine oils on risk of CVD death, coronary disease death, total coronary disease, MI, angina pectoris, CHF, total stroke and hemorrhagic stroke
Insufficient evidence	Various	Effect of OM3 and most clinical intermediate outcomes
Observational evidence	Patients without known CVD	Evidence of no association for MACE, CVD death, total stroke death, incident coronary disease, total stroke, ischemic stroke, hemorrhagic stroke, AF and CHF
Strong RCT evidence	Patients without known CVD	No effect for BP, MAP, LDL and HDL but significantly lowers TG concentrations
Strong RCT evidence	Patients with increased risk for CVD	No effect on MACE, all-cause death, BP, LDL, HDL but significant lowering of TG concentrations
RCT evidence	Patients with known CVD	No effect for MACE, CHD death, all-cause death, MI, revascularization, total stroke, SCD, AF and CHF Strong RCT evidence of no effect on BP and LDL but protective effect for HDL and TG concentrations

AF = Atrial Fibrillation; BP = Blood Pressure; CV = Cardiovascular; CVD = Cardiovascular Disease; CHF = Congestive Heart Failure; HDL = High-density Lipoprotein; LDL = Low-density Lipoprotein; MACE = Major Adverse Cardiovascular Events; MAP = Mean Arterial Pressure; MI = Myocardial Infarction; RCT = Randomized Controlled Trial; SCD = Sudden Cardiac Death; TG = Triglyceride

9. Lipid profile and Atherosclerosis

TG elevation is an independent risk factor for CVD events,[11,32] and it is well established that OM3 reduces TG levels.[29] Generally, there is no significant improvement in low-density lipoprotein cholesterol (LDL-C) levels with fish oil therapy, especially in patients with high TG levels, who often notice increases between 5% and 50%.[7] However, this OM3-enriched LDL develops a molecular structure described as "larger and fluffier" (or pattern A LDL-C), which is potentially less atherogenic than the smaller, denser particles (pattern B LDL-C).[7]

OM3 may also reduce atherosclerosis and CVD via reduction of Remnant lipoprotein (RLP) levels.[18] RLP exerts atherogenic effects, is considered an important risk factor for CVD, has been suggested in the pathogenesis of SCD and re-stensosis following coronary angioplasty,[18] and has been reported to be a likely causal factor for CHD.[33] OM3 may consequently prevent plaque development and contribute to plaque stabilization.[18] OM3 could over many years or at higher doses alter chronic atherogenesis and/or acute plaque rupture, lowering nonfatal coronary syndromes.[8]

9.1 OM3 Formulations

EPA and DHA may be present in an ethyl ester form, TG form, as a free fatty acid or as phospholipids.[34] It has been suggested that the form consumed may affect bioavailability, but ultimately that long term daily administration resulted in similar plasma and RBC levels of EPA + DHA, irrespective of formulation.[35] Lovaza is an OM3 ethyl ester formulation approved by the US Food and Drug Administration (FDA) at a dose of 4 grams/day for the treatment of very high TG levels (≥500 mg/dl).[7]

Icosapent ethyl (Vascepa) is a high-purity EPA formulation containing >96% EPA ethyl ester, does not contain DHA, and is approved in the US to lower TG levels in adult patients with severe (≥ 500mg/dl) hypertriglyceridemia.[36] The ongoing REDUCE-IT trial has randomized patients at 470 centers worldwide, and aims to reveal if treatment for moderate TG elevation decreases CVD events, particularly among patients already receiving statin therapy.

10. Coronary Heart Disease

25 studies with 280,000 patients showed an inverse association between fish consumption and morbidity or mortality from CHD.[5] Alexander et al.[37] performed a large meta-analysis (n = 93,000 subjects in RCTs and n = 732,000 in prospective cohort studies) regarding the effects of EPA + DHA on CHD and CHD risk. EPA + DHA reduced CHD risk among subjects with TG >150 mg/dl or LDL-C > 130 mg/dl in RCTs, but not among those with normal TG levels or LDL-C < 130 mg/dl.[11] The authors concluded that EPA + DHA may be associated with reducing CHD risk, with a greater observed benefit among higher risk populations in RCTs, and higher dose (> 1gram/day EPA + DHA) had stronger impact.[37]

Information from prospective cohort studies is important, considering that greater than 50% of CVD deaths occur among individuals without diagnosed CVD, and these studies are able to evaluate populations that are healthy at baseline.[38] This is a strength not found in the AHA 2017 update regarding OM3 and CVD, as the update only considered RCTs in its analysis. Alexander et al.[37] concluded that although not significant, a 6% reduced risk of any CHD event was observed among RCTs, which was supported by a statistically significant 18% reduced risk of CHD among prospective cohort studies.

Another meta-analysis of 14 RCTs with n > 32,000 found that OM3 use in patients with CHD was not associated with a protective effect on MACE, while there seemed to be beneficial effects in reducing death from cardiac causes, SCD and all-cause mortality.[39] A 22 year study of > 20,000 patients found that OM3 supplementation was associated with a lower hazard of CHD mortality.[40] The JELIS trial in Japan

used 1800 mg/day EPA with statin therapy or statin therapy alone, finding a relative risk reduction with any major CHD event of 19% (p=0.011).[41] Patients in this study with a history of CHD in the EPA group had significantly lower incidence of major CHD events, while patients without a history of CHD did not.[41] A recent meta-analysis of >77,000 high risk individuals found that OM3 had no significant association with fatal or nonfatal CHD or any MACE.[42]

10.1 Antiplatelet therapy and OM3

The biologic response to aspirin (ASA) is not uniform,[43] and clopidogrel has a much higher incidence of low responsiveness.[44] The OMEGA-PCI study intervention of 1 gram/day OM3 showed $P2Y_{12}$ reactivity index was significantly lower by 22.2% after 1 month with OM3 compared to placebo (p=0.02).[44] The authors concluded that the addition of OM3 to dual antiplatelet therapy significantly potentiates platelet response to clopidogrel following percutaneous coronary intervention. Triple antiplatelet therapy with the addition of cilostazol has also been reported to improve the biological effects of clopidogrel.[44]

Another study by Lev et al.[43] concluded that treatment of ASA resistance by adding OM3 or increasing ASA dose (325 mg/day) seems to improve responsiveness to ASA and effectively reduces platelet activity. However, it has been shown that increasing ASA dose results in no difference in clinical efficacy for prevention of vascular events, but increased gastrointestinal side effects and bleeding.[45] Therefore, although antiplatelet agent resistance may potentially be reduced by the use of OM3, increasing ASA dosage or triple antiplatelet therapy, OM3 supplementation may be the safer option. It has previously been concluded that there was no increased risk of clinically significant bleeding with OM3 doses up to 7 grams/day DHA + EPA, even when combined with antiplatelet therapy or warfarin.[46]

10.2 Recommendations

The majority of authors from the AHA concluded that for patients at high CVD risk, treatment with OM3 is not indicated, while a minority concluded that treatment is reasonable.[4] OM3 supplements do not seem to reduce the incidence of recurrent nonfatal MI, however, the AHA concluded that even a potential reduction in CHD death of 10% would justify the use of a relatively safe therapy.[4]

11. Post Myocardial Infarction

Greene et al.[25] studied the use of 1 gram/day OM3 and found that it was independently associated with decreased risk of all-cause mortality and acute MI, in addition to a robust reduction in recurrent acute MI through 12 month follow-up. The OMEGA trial in Germany, in patients with a high baseline (85-95%) of guideline directed treatment, use of 460 mg EPA + 380 mg DHA for one year initiated 3-14 days after acute MI was associated with low arrhythmic (0.7%) and total mortality (3.7%) event rates in the placebo group, and this trial showed no benefit of EPA + DHA.[7] Although probably underpowered, these results suggest that OM3 may not provide additional short-term protection in patients receiving modern post-MI therapy.[7]

The Alpha Omega trial tested the hypothesis that low doses of EPA + DHA (400 mg/day), ALA (2 grams/day), or both reduce the risk of CVD events among patients who have had a MI.[26] This trial studied patients with a history of MI up to 10 years prior to randomization and found that OM3 compared to placebo had no effect on MACE, although post hoc analysis found reductions of approximately 50% on rates of fatal CHD and arrhythmia-related events.[26] The average daily OM3 intake in the intervention arm was <400mg/day,[25] which may also suggest that higher doses of OM3 may be needed for CVD benefits.

The OMEGA-REMODEL found that 6 months of high dose OM3 (4 grams/day) following acute MI had significant reduction of left ventricular systolic volume index (LVSVI) (-5.8%, p=0.017) and non-infarct

myocardial fibrosis (-5.6%, p=0.026) using Lovaza compared with placebo beyond current guideline-based standard of care.[13] Many studies reported that improvement of LVSVI during infarct convalescence remains the strongest favorable risk predictor, parallels reduction of post-MI mortality rates, and is part of the pathway of therapies that reduce mortality, SCD and HF.[13] Changes of LVSVI from OM3 treatment started 2-4 weeks post MI were only modest, suggesting that earlier initiation of OM3 following MI may have resulted in more significant benefit.[13]

11.1 Recommendation

According to the 2017 updated AHA scientific statement, the recommendation for patients with CHD, such as recent MI, remains unchanged from 2002: treatment with OM3 in these patients is reasonable.[4] Certainly, further study is required.

12. Risk for cardiac death

The benefits of OM3 seem most consistent for CHD mortality and SCD.[8] Higher OM3 levels may alter the risk for fatal and non-fatal CVD events through several pathways, including anti-arrhythmic effects (particularly arrhythmias related to MI), effects related to cardiac structure and function (fibrosis, myocardial oxygen demand), endothelial and autonomic function (vascular resistance and heart rate), thrombosis, BP, inflammation and lipoprotein metabolism.[8] The final common pathway for most cardiac death is arrhythmia,[8] and several different mechanisms for reduced arrhythmogenicity and SCD have been proposed.

12.1 Anti-arrhythmic properties

Animal experiments suggest that OM3 directly influence atrial and ventricular myocyte electrophysiology, potentially mediated by effects on membrane ion channels or cell-cell connexins.[8] OM3 cause steric interference with sodium, potassium and calcium channels; a blocking mechanism that

is distinct from that of other known antiarrhythmic agents.[5] OM3 may prolong the relative refractory period by modulating L-type calcium channels, preventing calcium overload during ischemic insult,[18] and in vitro and animal models show that OM3 stabilize partially depolarized ischemic myocytes, reducing susceptibility to ventricular arrhythmias.[8]

12.2 Evidence

Maki et al.[29] performed a meta-analysis (n = 71,899) reviewing OM3 supplementation and risk for CVD death, finding 8% lower risk with OM3 versus control. The authors also argued that OM3 supplementation has low risk associated with its use, and therefore even a modest benefit is clinically meaningful. 3 RCTs evaluating the effects of OM3 on recurrent ventricular tachycardia or fibrillation in patients with implantable cardioverter-defibrillator devices were evaluated, one showing 31% reduction in recurrence of these arrhythmias (p = 0.03%), whereas the other 2 trials showed no statistically significant effects.[8] Overall, these studies are limited by small sizes and brief treatment. The Singapore Chinese health study recruited 60,298 Chinese adults and found that high intake of both marine and plant OM3 are independently associated with reduced risk of CVD mortality.[19] Mozaffarian et al.[47] performed a trial in patients age 75 ±5 years without CHD, stroke or HF, and found that OM3 levels were associated with lower total mortality, fewer CVD deaths, and particularly fewer arrhythmic CHD deaths, with nearly 50% lower risk across quintiles.

12.3 Recommendations

According to the AHA, the cumulative findings from RCTs suggest that OM3 supplements may reduce CHD death, possibly through a reduction in ischemia-induced SCD, among patients with prior CHD, but the treatment does not reduce the incidence of recurrent nonfatal MI.[4] Given that the benefit of OM3 use likely outweigh any risk of treatment, the majority of co-authors concluded that treatment with OM3 is reasonable for secondary prevention of CHD death.[4]

13. Atrial Fibrillation

Considering that rhythm control strategies for Atrial Fibrillation (AF) either involve antiarrhythmic drug treatment (with modest protection against AF recurrence and non-negligible side effects) or ablation (limited by availability and high cost), safe and inexpensive alternatives certainly need to be explored.[48] The FORWARD trial evaluated the efficacy of 1 gram/day OM3 supplementation for the prevention of recurrent AF, finding no significant differences between study groups.[49] However, this study was stopped early and was underpowered, with 63% of patients receiving prophylaxis with amiodarone at inclusion, and did not use trans-telephonic monitoring for identification of recurrent AF.[49]

The AFFORD trial used a higher dose of OM3 (4 grams/day) and monitored AF recurrence via trans-telephonic monitoring, finding no reduction in AF recurrence up to 16 months in patients not receiving antiarrhythmic therapy.[48] The AFFORD authors believe that their results provide conclusive evidence that fish oil has no role in rhythm-control management of patients with paroxysmal or persistent AF.

13.1 Postoperative AF

Mozaffarian and colleagues,[50] after publishing a trial showing that perioperative fish oil did not reduce post-operative AF, performed a meta-analysis on the subject. The authors concluded that there was convincing evidence that short-term OM3 use does not appreciably reduce post-operative AF, regardless of the type of cardiac surgery.[50]

13.2 Recommendations

There is currently no compelling evidence for OM3 use in the prevention or treatment of AF. The AHA reports that there is no data from large RCTs regarding effects of OM3 for primary prevention of AF.[4] Regarding secondary prevention of AF, the AHA concluded that overall, high-quality evidence from multiple RCTs does not support OM3 supplementation.[4]

14. Heart Failure

In a small 18-week pilot study of 14 patients with class III-IV HF randomized to 5.1 grams/day of EPA and DHA, we showed marked improvements in inflammatory cytokines and percent body fat in advanced HF, suggesting that fish oil may be beneficial in decreasing inflammation and cachexia in advanced HF.[51] Diets rich in unsaturated fatty acids have been associated with improved cardiorespiratory fitness, diastolic function and body composition in obese patients with HF,[52] and a meta-analysis of 7 prospective studies found a lower risk of HF with intake of marine OM3.[53]

The GISSI-HF trial suggested that 1 gram/day OM3 showed lower death from any cause (27% vs 29%) and hospitalizations for CV reasons (57% vs 59%) in the OM3 group vs placebo, respectively.[41] This study suggested a number needed to treat of 56 for 3.9 years to avoid one death or 44 needed to treat to avoid one event like death or admission to hospital.[54] This trial showed a reduction of total mortality by 8% ($p = 0.009$), accompanied by significant improvements in left ventricular ejection fraction, when given in addition to maximal modern drug therapies.[8]

There seems to be a "blunting effect", in which the benefit of OM3 is reduced by maximal medical management, which may not be as significant or as prevalent in the HF population, considering these findings. Also, considering that 1 gram/day may be an insufficient dose, more studies using higher doses of OM3 in HF patients will be particularly helpful. However, the potential impact of this therapy over maximal guideline directed therapy is still questionable, considering that although >90% of patients were taking either an angiotensin converting enzyme inhibitor or aldosterone receptor blocker, only approximately 65% of patients were taking a beta blocker in GISSI-HF.[54]

14.1 Heart transplant

Hypertension is a common complication in cyclosporine treatment, present in 60-100% of heart transplant patients,[28] and studies suggest that OM3 can reduce heart rate, mean arterial pressure,

systemic vascular resistance, left ventricular hypertrophy and improve diastolic function in transplant patients with cyclosporine-induced hypertension.[55] In a small study (n=28), Andreassen et al.[28] randomized heart transplant patients to 4 grams/day OM3 vs corn oil placebo from the 4th post-operative day, finding after 6 months that systolic BP decreased 2 ± 4 mmHg in the treatment group and increased by 17 ± 4 mmHg in the placebo group ($p < 0.01$), whereas diastolic BP increased by 10 ± 3 and 21 ± 2 in the treatment and placebo groups, respectively ($p = 0.01$). The authors concluded that post-operative daily OM3 supplementation of 4 grams/day in heart transplant patients is effective as hypertension prophylaxis. Ventura and colleagues[55] have also demonstrated BP and systemic vascular resistance reductions using OM3 3 grams/day in orthotopic cardiac transplant patients receiving cyclosporine therapy, also suggesting that OM3 can be used as an adjuvant for HTN treatment in cyclosporine-treated cardiac transplant patients.

14.2 Recommendations

It appears that the beneficial effects of OM3 in patients with HF and heart transplant are promising. We agree with Fonarow's[56] assertion that OM3 supplementation should join the short list of evidence-based life-prolonging therapy for HF. To date, no published RCTs have assessed the effect of OM3 on primary prevention of HF.[4] Based on the results of GISSI-HF, a single, large RCT of HF patients (91% having HFrEF and Ejection Fraction <40%), OM3 supplementation reduced risk of total mortality by 9% and risk of CVD related hospitalizations or death by 8%,[54] leading to a new recommendation from the AHA that treatment with OM3 is reasonable among patients with HFrEF.[4]

15. Ischemic Stroke

Although meta-analyses suggest that fish consumption reduces the risk of ischemic stroke, stroke incidence has not been significantly affected in fish oil trials, and there are currently not enough appropriately powered RCTs to evaluate the OM3 effects on stroke.[8] There are no RCTs regarding OM3

effect on stroke or other CVD events among patients with a history of stroke, although post hoc analysis of JELIS patients who had a history of stroke had reduced recurrent stroke in the OM3 group.[4] Overall, there is no evidence of OM3 supplementation to reduce the risk of recurrent stroke or other CVD in patients with prior stroke.[4]

16. Peripheral Artery Disease

With regard to peripheral arterial disease, there is very little evidence to produce recommendations for OM3 use. One meta-analysis of 5 trials (n = 396), all of which with unclear or high risk of bias, with most of the study population (n = 213) in a single trial, found no evidence of a protective association of OM3 supplements on MACE or other serious clinical outcomes.[57] There was no evidence to suggest a protective association of OM3 with MI, CVD death, angina, stroke, amputation, revascularization, pain-free walking distance or quality of life.[57]

17. Primary prevention of CVD

There may only be one RCT of OM3 use for the primary prevention of CVD.[58] The Diet and Omega-3 Intervention Trial (DOIT), was a placebo-controlled trial in 563 elderly men at high-risk of CVD. OM3 (2.4 grams/day) caused a borderline significant 47% reduction in all-cause mortality (p=0.063). There is no proven benefit for primary prevention of stroke, HF or AF. The ongoing VITAL trial will test the efficacy of Vitamin D (2000 IU/d) and OM3 (1 gram/day) for prevention of cancer and CVD in a multiethnic primary prevention population of 25,875 patients.[59] The National Institute of Health concluded that the evidence does not support the use of OM3 supplements for people being treated for primary or secondary prevention, people with CKD or DM.[6] However, as reviewed above, this therapy appears to be of at least modest benefit in patients with elevated TGs and /or LDL-C at least in some meta-analyses, and considering the low cost and side effect profile, could be considered for these populations.

18. Secondary prevention of CVD

The AHA has concluded that "treatment is reasonable" for (1) secondary prevention of CHD and SCD among patients with prevalent CHD; and (2) secondary prevention of adverse outcomes in patients with HF.[4] Due to a lack of RCTs, there is no recommendation for secondary prevention of stroke, and high quality evidence from multiple RCTs does not support OM3 for prevention of recurrent AF.[4]

19. Safety and Sustainability

19.1 Contaminants and side effects

Due to the concern for methyl mercury in diets high in fish consumption, the FDA advised children and pregnant or nursing women to consume a minimum of two to three servings, or eight to 12 ounces, of low-mercury fish every week, and to specifically avoid fish with potentially high mercury content, such as swordfish, tile fish, king mackerel and shark.[7] Nevertheless, a study of almost 12,000 British women found that women who exceeded the FDA recommendation for fish intake actually had offspring with better cognitive and behavioral development than women who consumed less fish during pregnancy.[60] For the general population of adults, risk-benefit analyses conclude that the health benefits of modest fish consumption significantly outweigh the potential risks.[5,8]

The most commonly consumed dietary sources of marine OM3 include salmon, sardines, trout, oysters and herring, which are quite low in mercury content.[61] Because mercury is water soluble and protein bound, it is present in the muscle of fish but not in the oil, and therefore, fish oil supplements contain negligible amounts of or no mercury.[7,8] Fish oil supplements also contain low absolute quantities of dioxins and polychlorinated biphenyls.[8] The FDA concluded that marine OM3 doses of up to 3 grams/day are "generally recognized as safe",[62] and the most common adverse effects of OM3 supplementation are nausea, gastrointestinal upset and "fishy" burp.[7] The fishy taste or eructation may be minimized by taking the capsule frozen, switching to a different formulation with a low oxidation profile, or taking with meals or at a different time of day.[8]

19.2 Malignancy

Articles in popular media have suggested that OM3 ingestion may increase the risk of prostate cancer and many have advised against the use of supplemental fish oil.[63] However, a regular high intake of fish has been linked to a marked increase in survival in prostate and other cancer patients, and Japan has a many-fold lower prostate mortality rate than the US, despite Japanese men typically consuming approximately 8 times more fish than American men.[63] The American Cancer Society also reports that most men diagnosed with prostate cancer do not die from prostate cancer,[64,65] therefore, considering that CVD is a leading cause of morbidity and mortality, a therapy that can potentially reduce CVD risk such as OM3 therapy should not be discredited without substantial evidence of risks. With regards to cancer in general, many large randomized trials of fish oil supplementation have never found an increase in cancer incidence or mortality in those receiving OM3 supplements.[63,66] Also, a recent major study suggested that a diet relatively high in OM3 compared with OM6 was associated with lower risks of several adenocarcinomas, and that DHA specifically may serve as an important adjunct to improving the efficacy of several chemotherapeutic agents.[9] Other studies have shown benefits with regards to maintaining weight and muscle mass, potential to chemosensitise tumors and improve quality of life in patients with various cancers.[67-69]

19.3 Sustainability

The supply of seafood from global capture fisheries has plateaued and is unlikely to supply adequate amounts of additional seafood to the world's growing population.[70] Global fish stocks have declined rapidly over the past 50 years; populations of some commercially popular fish species have collapsed to only 10% of their historic maximum, with over 100 confirmed extinctions of marine species.[71] The catch from wild fish stocks is generally considered to be at or near the biological maximum, with approximately 90% of the fish stocks globally rated as fully or overexploited.[70]

Some researchers have argued that wild fish populations are collapsing and blanket recommendations to increase OM3 from marine sources will only exacerbate this problem.[71] Although predictions from experts stating that worldwide fish stocks could be depleted within 40 years at the current harvest rate have been severely criticized and possibly overly pessimistic, the pressure on fish stocks is likely to increase with recommendations for increased consumption of fish and fish oil.[71] According to some authors, it is clear that fish and vegetable oil sources will not be sufficient to meet the future needs of the world population.[72]

Production of single-cell oil (yeast or microalgae) comes as a sustainable alternative with less environmental impact.[72] However, these alternatives have significant limitations; plants rich in SDA are expensive, metabolic engineering is unfavorably accepted by consumers in many countries, cultivation of microalgae is very expensive, and Antarctic Krill harvest must be restricted.[73] There are significant ecological impacts that will likely result from an initiative to increase fish or fish oil consumption for the general population. Alternative sources of OM3 such as those from single-cell oils or "stealth health" methods mentioned previously need to be further explored in an attempt to satisfy OM3 intake recommendations and lessen the burden of commercial fishing on marine ecosystems in order to achieve sustainability.

Table 3 Patients who may benefit from OM3

Those not meeting recommended dietary fish intake
CHD or other ASCVD
Secondary prevention of CHD death or SCD
Recent CHD event (e.g. post-MI)
Following PCI
HFrEF

Heart Transplant
Aspirin Resistance
Clopidogrel Resistance
Hypertriglyceridemia (>150 mg/dl)
High LDL-C (>130 mg/dl)
Hypertension
ASCVD = Atherosclerotic Cardiovascular Disease; CHD = Coronary Heart Disease; HFrEF = Heart Failure with Reduced Ejection Fraction; LDL-C = Low-density Lipoprotein Cholesterol; MI = Myocardial Infarction; PCI = Percutaneous Coronary Intervention; SCD = Sudden Cardiac Death

20 Conclusion

While dietary intake of oily fish is currently recommended, fish oil supplementation is certainly a safe and reasonable alternative. There is no convincing evidence that OM3 increases risk of malignancy, and may in fact be protective. While OM6 has been associated with increased inflammation and pathogenesis of various disease processes, the AHA currently recommends an OM6 intake of at least 5-10% of total energy, which would seem to lower CHD risk.

Favorable CV effects found in older studies, such as GISSI-P, have been difficult to replicate in modern trials, likely due to the use of modern maximal medical therapy for CVD. Also, the use of 1 gram/day OM3 intervention in early landmark trials is often still used in current trials, despite possibly being an insufficient dose. We recommend that future research (I) focus on higher dose interventions using OM3 (II) in patients already receiving maximal medical therapy for CVD, (III) incorporate an objective measure of OM3 status, such as the OM3 index, to assess treatment efficacy and aid in the comparison of future trials, and (IV) implement early intervention following events such as MI or cardiac transplantation.

OM3 promote a favorable lipid profile that reduces levels of RLP, possibly reducing atherogenicity of LDL-C. OM3 may consequently prevent plaque development and contribute to plaque stabilization, and therefore may be beneficial when added to standard lipid-lowering therapy. We look forward to the results of the ongoing REDUCE-IT trial.

Resistance to antiplatelet agents is associated with increased risk of CHD events, and although this resistance may be reduced by: (I) triple therapy with ASA + clopidogrel + cilostazol, (II) high-dose ASA use, or (III) OM3 supplementation, the use of OM3 may be the safer option. OM3 does not seem to increase risk of bleeding.

The best evidence for the use of OM3 and CV health is for CHD mortality, SCD, post-MI and HFrEF. The AHA now recommends treatment for patients with HFrEF with OM3 to reduce mortality and hospitalizations.[4] Some of these studies have shown favorable results with higher OM3 dosage (4 grams/day) and treatment early following MI or heart transplant, despite being used in patients receiving optimal medical therapy. OM3 use is reasonable for patients with CHD, such as recent MI, according to the AHA.[4]

There is insufficient evidence for recommendations regarding ischemic stroke and peripheral arterial disease, although there has been some evidence of benefit for secondary prevention of ischemic stroke with the use of OM3 in the JELIS trial. Currently, OM3 appear to play no role in the prevention of new or recurrent AF.

According to the AHA, the evidence does not support the use of OM3 supplementation in the general population who are not at high CVD risk, and there was a lack of consensus about the treatment of those at high risk.[4] Treatment is also considered reasonable for secondary prevention of CHD death, and does not appear to have any role in treatment or prevention of AF. The AHA has no class I recommendations for the use of OM3, and our findings indicate that there is currently insufficient

evidence for OM3 use in the primary prevention of CVD in general, which is in agreement with recommendations from the AHA and National Institute of Health.[4,6]

A recurring argument for proponents of OM3 use is that even modest reduced risk of CVD or CV events should encourage the use of a largely innocuous therapy. Although the majority of authors from the AHA concluded that treatment with OM3 is not indicated for patients at high CVD risk, the AHA concluded that a potential reduction of CHD death by 10% would justify the use of OM3.[4] The AHA acknowledges that the lack of evidence of benefit differs from evidence of a lack of effect,[4] however, the magnitude of benefit from OM3 for CV health remains largely undetermined. However, in patients with even moderately elevated LDL-C and /or TGs, this therapy could be strongly considered based on potential benefits and low cost and toxicity.

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