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NONSTATIN DRUGS (E. DEGOMA, SECTION EDITOR)

Review of Cardiometabolic Effects of Prescription Omega-3 Fatty Acids

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Abstract
Purpose of Review Populations with significant dietary fish intake tend to have lower cardiovascular (CV) risk and demonstrable physiologic differences including lower lipid/lipoprotein levels and other direct and indirect effects on the arterial wall and inhibiting factors that promote atherosclerosis. Treatment with high doses of pharmacologic-grade omega-3 fatty acid (*n*-3FA) supplements achieves significant reductions in triglycerides (TG), non-high-density lipoprotein- (non-HDL-) and TG-rich lipoprotein- (TRL-) cholesterol levels. *n*-3FA supplements have significant effects on markers of atherosclerosis risk including endothelial function, low-density lipoprotein (LDL) oxidation, cellular and humoral markers of inflammation, hemodynamic factors, and plaque stabilization. This review summarizes the lipid and cardiometabolic effects of prescription-grade *n*-3FAs and will discuss clinical trials, national/organizational guidelines, and expert opinion on the impact of supplemental *n*-3FAs on CV health and disease.
Recent Findings Clinical trial evidence supports use of *n*-3FAs in individuals with established atherosclerotic cardiovascular disease (ASCVD), but the data either does not support or is lacking for other types of cardiometabolic risk including prevention of stroke, treatment in patients with heart failure, diabetes mellitus and prediabetes, and for primary prevention in the general population.
Summary Despite inconsistent findings to support widespread benefit, there is persistent population-wide enthusiasm for *n*-3FA as a dietary supplement for its cardiometabolic benefits. Fortunately, there are ongoing clinical trials to assess whether the lipid/lipoprotein benefits may be extended to other at-risk populations and whether lower-dose therapy may provide background benefit for primary prevention of ASCVD.

Keywords Dietary supplement · Omega-3 FA (*n*-3FA) · Eicosapentaenoic acid (EPA) · Docosahexaenoic acid (DHA) · Linoleic acid (LA) · Alpha-linolenic acid (ALA) · Triglycerides (TG) · Ethyl ester (EE) · Fatty acid (FA) · Free FA (FFA)

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Introduction

Observational and interventional studies from the 1980s to the early 2000s have confirmed the notion that intake of marine-derived omega-3 polyunsaturated fatty acids (*n*-3FAs), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), reduce cardiovascular (CV) risk [1, 2]. The U.S. Departments of Health and Human Services and Agriculture (USDHHS/USDA) and the American Heart Association (AHA) have issued guidelines recommending regular intake of preferably oily fish as part of a healthy dietary pattern aimed at reducing the population burden of CV disease [3, 4]. This dietary component has multiple favorable cardiometabolic effects accounting for potential CV risk reduction, including impact on lipids and lipoproteins (LP), inflammation,

oxidation, thrombosis, and improving endothelial function, blood pressure, heart rate and heart rate variability, vascular reactivity, plaque stability, cardiac electrical conduction, and CV mortality [1]. These effects explain why fish oil, omega-3, EPA, and/or DHA have together become the most commonly consumed natural dietary supplement in the USA [5]. Nonetheless, recent studies have cast doubt on the clinical benefits of prescription-grade *n*-3FAs for CV risk reduction. The following review of the evidence may reveal an explanation for their attenuated benefits yet provide support for ongoing use of *n*-3FA supplementation for specific medical circumstances.

There are now several prescription-grade EPA/DHA-combined or EPA-alone supplements approved by the Food and Drug Administration (FDA) as an adjunct to diet for treating adults with triglyceride (TG) levels ≥ 500 mg/dL [6]. Clinical trials are ongoing to determine whether they have a role in treating individuals with TG 150–499 mg/dL [7]. Whether fish oil supplementation should be recommended for individuals with established CV disease is a subject of ongoing debate and the AHA has recently reassessed their 2002 recommendations on this topic based on the cumulative evidence from trials with clinical endpoints [8••]. A description of the relative effects and variety of non-prescription fish oil dietary supplements and impact of supplementation on non-CV concerns is outside the scope of this review. We will instead summarize the lipid and cardiometabolic effects of prescription *n*-3FAs that help explain the persistent enthusiasm for this class of therapy and will review completed and ongoing clinical trials, meta-analyses, and expert advice on the impact of supplemental *n*-3FAs on CV health and disease.

Polyunsaturated Fatty Acids: Omega-6 and Omega-3 Fatty Acids

Polyunsaturated fatty acids (PUFAs) are long-chain hydrocarbons containing 18 to 22 carbons with more than one double bond. PUFAs have a carboxylic acid end (*alpha*) and a methane terminal end (*omega*). Historically, English language typewriters did not have Greek lettering, so the letter *n* has come to substitute for *omega* (*Ω*). PUFAs include both *n*-6FAs and *n*-3FAs, which are considered essential since they cannot be synthesized by humans and therefore must be consumed in the diet. Dietary sources of *n*-3 and *n*-6 PUFAs are listed in Table 1 [9]. Linoleic acid (LA) is an essential *n*-6FA found primarily in vegetable oils and is more prevalent than *n*-3FA sources in the Western diet [10]. *n*-3FAs are either plant- or marine-derived. Alpha-linolenic acid (ALA) is a plant-derived essential *n*-3FA, which is found in high concentrations in flaxseed and canola oils. EPA and DHA are marine-derived *n*-3FAs. They are considered non-essential since they can be synthesized from ALA; however, this process is very inefficient in humans, and thus, an inadequate source of either EPA or DHA (< 0.1–7.9% of ALA is converted to EPA and < 0.1–3.8% of ALA is converted to DHA) [1, 11].

Marine-derived PUFAs are found in high levels in fatty fish, especially salmon, mackerel, herring, and sardines. Current dietary intake of EPA and DHA in the USA is about 90 mg/day (30 mg EPA and 60 mg DHA) [12]. Bang and Dyerberg first described the relationship between marine-derived fatty acids and CV disease when they observed that Greenland Inuits, eating a diet rich in *n*-3FAs from whales, seals, and fish, had platelet membranes highly enriched with *n*-3FAs and associated lower atherosclerotic cardiovascular disease (ASCVD) risk compared to their Danish counterparts [13•, 14]. They attributed this risk reduction to the distinct dietary pattern of this cohort and its impact on lipid/lipoprotein and coagulation parameters. Subsequent investigation into the physiologic role of *n*-3FAs, clinical trials with supplements, pharmacologic dosing, and even widespread use in populations has created a body of literature that is complex and worthy of review, particularly as it pertains to CV health.

n-3FAs are incorporated into all tissues of the body but in particular, neurologic, retina, and myocardium [15]. *n*-3FAs are important structural molecules that insert themselves among the phospholipids of plasma membranes and contribute to membrane fluidity, and they are substrates for other functional lipids, including eicosanoid products (e.g., prostacyclin) [16••]. *n*-6FAs are also found in plasma membranes, and they form the chemical foundation of the inflammatory substrate, arachidonic acid (ARA). Because of this, the relative *n*-6/*n*-3 dietary ratio is commonly used to describe the inflammatory potential of a diet, though the clinical relevance of this description is not definitively demonstrated in the medical literature [16••] (see Fig. 1).

Prescription Omega-3 Fatty Acids

Compared to *n*-3FA dietary supplements, prescription-grade *n*-3FA supplements have greater EPA/DHA concentrations and are highly purified. The EPA/DHA content in each capsule is closer to 100%, making it more convenient for patients to obtain the recommended dose with less of a pill burden. There is also more attention paid to exposure to contaminants, oxidized fatty acids, toxins (e.g., mercury), and unwanted ingredients such as cholesterol and saturated fat [17], which takes into consideration the FDA and Environmental Protection Agency advice regarding safety concerns (https://www.fda.gov/Food/FoodborneIllnessContaminants/Metals/ucm393070.htm). Currently, there are three prescription *n*-3FA formulations that are FDA-approved for adults, including (1) combined EPA/DHA ethyl esters (EE) (Lovaza®, Omtryg™, and generic Lovaza® products), (2) icosapent ethyl (IPE) which is an EPA-only ethyl ester (Vascepa®), and (3) combined EPA/DHA free fatty acids (FFA) (Epanova®) (see

Table 1 Dietary sources of *n*-3 and *n*-6 PUFAs

PUFA	Dietary source
n-6 (plant-derived: linoleic acid)	Corn, safflower, sunflower, soybean oils
n-3 (plant-derived: alpha linolenic acid)	Flaxseed oil, canola (rapeseed) oil, English walnuts, soybean oil, flaxseeds, soybeans
n-3 (marine-derived: EPA/DHA)	Oily fish, fortified foods including pasta, cereal, juice, eggs from chickens fed high *n*-3FA diets

Adapted from Gebauer et al. [9]

Table 2) [17, 22]. They are all roughly 1000 mg soft gel capsules approved at a dose of 4 g/day as an adjunct to dietary modification for the treatment of severe hypertriglyceridemia (TG ≥ 500 mg/dL) in adults. These prescription supplements effectively lower TG levels, are generally well-tolerated, and have a good safety profile [22]. Drug-drug interactions have not been reported in patients taking *n*-3FA prescription supplements even when taken in combination with other lipid-lowering or anticoagulant medications [6, 23].

The bioavailability of EPA and DHA has been shown to vary among the different formulations; however, the clinical significance of this property has not been evaluated [6, 12]. Unlike *n*-3FFA, *n*-3EE must be hydrolyzed by pancreatic lipase before they are absorbed. Data from the Epanova® compared to Lovaza® in a Pharmacokinetic Single-dose Evaluation (ECLIPSE) trial showed a fourfold greater increase in plasma concentrations of EPA and DHA for a 4-g dose of *n*-3 FFA compared with the *n*-3EE form when consuming a low-fat diet [24]. Since pancreatic lipase is secreted in response to the fat content of the meal, *n*-3FFA formulations, which do not require lipolytic activity, could potentially benefit patients with severe hypertriglyceridemia requiring a low-fat diet. There are also different physiologic effects from EPA and DHA that may play a role in selecting which agent to prescribe, and pharmaceutical formulary availability, cost, and tolerability may dictate selection as well.

Evidence for Cardiometabolic Effects of EPA and DHA

There are multiple cardiometabolic effects from intake of *n*-3FAs including lowering TG levels, blood pressure, heart rate, heart rate variability, endothelial function, and myocardial oxygen demand [1]. In addition, *n*-3FAs have an impact on inflammation, thrombosis, oxidation, vascular reactivity, cardiac electrical activity, and CV outcomes. We will thus consider the observed and projected net benefit from supplementation.

Triglyceride Lowering

TG-lowering can be accomplished with *n*-3FA supplementation in a characteristic dose–response relationship and

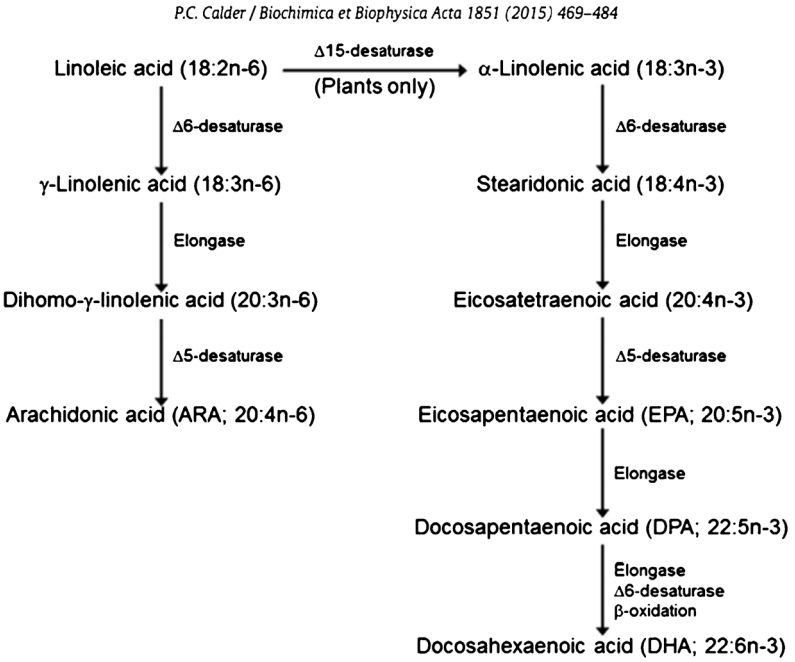

Fig. 1 Pathways of biosynthesis of *n*-6 and *n*-3 fatty acids. Used with permission from Calder [16••]

Table 2 Prescription *n*-3FA products indicated as an adjunct to diet to reduce TG levels in adults with severe hypertriglyceridemia (TG ≥ 500 mg/dL) according to FDA-approved product package inserts [18–21]

	EPA + DHA EE	EPA-only EE	EPA + DHA FFA
Brand name	Lovaza®, Omtryg™[a]	Vascepa®	Epanova®
Generic available	Yes	No	No
EPA/DHA (%)	55/45	100/0	73/27
n-3FA g/capsule	EPA 0.465 g DHA 0.375 g	EPA 1 g	EPA 0.550 g DHA 0.20 g
Regimen, capsules	2 caps twice daily or 4 caps daily with meals	2 caps twice daily with meals	2 caps twice daily or 4 caps daily with or without meals
% Lipid/LP change Rx vs placebo (per PI)			
TG	− 51.6	− 33[b]	− 21[b]
LDL-C	+ 49.3	− 2	+ 15
non-HDL-C	− 10.2	− 18	− 10[b]
TC	− 8.0	− 16	− 9
HDL-C	+ 9.1	− 4	+ 4
VLDL-C	− 40.8	− 29[b]	− 21
apoB	Not reported	− 9[b]	+ 2

Adapted from Sperling and Nelson [7]

TG triglyceride, *LDL-C* low-density lipoprotein cholesterol, *non-HDL-C* non-high-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *VLDL-C* very low-density lipoprotein cholesterol, *apoB* apolipoprotein B, *EE* ethyl ester, *FA* fatty acid(s), *FFA* free FA, *PI* package insert, *Rx* prescription

[a] Omtryg is available as 1.2 g capsule (EPA/DHA ethyl ester)

[b] Refers to analysis for and confirmation of statistically significant result

proportional to the untreated TG level [1]. The primary mechanism of action is in part due to enhanced beta-oxidation of fatty acids resulting in less substrate for □ very low-density lipoprotein (VLDL) synthesis [6]. Upregulation and enhancement of lipoprotein lipase (LPL) activity, inhibition of apolipoprotein C3 (apoC3), activation of peroxisome proliferator-activated receptors (PPARs), hepatic lipase (HL), and cholesteryl ester transfer protein (CETP) [25], and possibly reduction of proprotein convertase subtilisin/kexin type 9 (PCSK9) [26] may also be affected by *n*-3FA intake. There is no consensus on the relative importance of each of the lipoprotein metabolic mechanisms from *n*-3FA consumption.

Table 2 lists the FDA-approved prescription *n*-3FA products including their *n*-3FA content, dosing regimen, and TG and other lipid/LP response from their respective package inserts based on clinical trials on adult patients with severe hypertriglyceridemia [18–21]. Epanova® and Omtryg™ are not currently marketed in the USA. Since head-to-head studies comparing the lipid-modifying effects are lacking, it is not possible to suggest one *n*-3FA formulation is superior to another for TG-lowering. Safety and efficacy have not been established for the pediatric population with any of these products and pregnancy also and lactation safety has not been established.

Karalis reviewed randomized placebo-controlled clinical trials (RCT) with prescription n-3FA (2-4 g/day) and reported the observed lipid-modifying results in published studies on patients with moderate-severe hypertriglyceridemia between 1997 and 2014 [27•]. TG-lowering varied between studies, with the greatest reported reduction of 45% compared to 16% increase in placebo in subjects with moderate-severe hypertriglyceridemia [28]. However, typical reductions of 10–39% were reported in other studies [29–34].

Other Lipid/Lipoprotein Effects

Jacobson et al. reported on the differential effects of DHA and EPA on LDL-C primarily and secondarily TG, HDL-C, and non-HDL-C in trials as of 2012 [35]. This review was based upon a MEDLINE search of available clinical trials with various marine *n*-3FA supplements in a variety of patient types, not limited to prescription supplements. The analysis included 22 high quality studies: 6 studies compared DHA with EPA directly, 12 studied DHA alone, and 4 studied EPA alone. The results from the meta-analysis are summarized in Table 3:

The authors observed that LDL-C increases in DHA, but not EPA-treated study groups, were directly and significantly associated with baseline TG levels. They noted that while there was a wide range of non-HDL-C response, EPA led to reductions in non-HDL-C in 80% of the EPA-treated subjects, compared with only 40% of the DHA-treated subjects. Findings that DHA may downregulate LDL receptor activity may, in part, explain its LDL-C raising effect [17].

Atherogenesis

Endothelial Function/Inflammation/Oxidation

In a 2006 review of the anti-atherosclerotic and anti-thrombotic effects of *n*-3FAs, Robinson and Stone found that the measurable anti-inflammatory effect of *n*-3FA consumption is inconsistent [36]. Taken together with modest lipid-modifying effects, or use in patients with normal TG levels, this may suggest an explanation for blunted ASCVD benefits in clinical trials that include a large percentage of patients with normal lipid profiles. The authors cite several studies in patients with chronic inflammatory disease (e.g., rheumatoid arthritis, lupus) where high sensitivity C-reactive protein (hsCRP) level is reduced and several studies where the level

Table 3 Lipid/lipoprotein effects of *n*-3FA

Mean response to *n*-3FA	EPA (% change)	DHA (% change)
LDL-C	− 0.7	+ 2.6
TG	− 15.6 (− 4.4 to 40.5)	− 22.4 (− 8.9 to 30.3)
HDL-C	+ 1.4 (± 3.5%)	+ 7.3% (± 6.1%)
non-HDL-C	− 2.9 (± 3.3%)	− 1.2 (± 2.9%)

Derived from Jacobson et al. [35]

was not modified by supplementation. They add, however, that ALA-enriched diets, with a lower *n*-6/*n*-3 ratio, are more likely to demonstrate reductions in hsCRP and other soluble inflammatory factors.

Measures of endothelial function are significantly improved with high-dose (≥ 3 g/day) EPA/DHA supplements [37] and with dietary ALA intake as well [38]. Since endothelial dysfunction is a key factor in atherogenesis, it is expected that an *n*-3FA induced improvement from supplemental intake would result in significant ASCVD benefit.

Other features of *n*-3FA atheroprotection include their role as anti-oxidant and anti-inflammatory agents. EPA attenuates nitric oxide synthesis, lipid peroxidation, and generation of reactive oxygen species in human-derived embryonic endothelial cells [39] and has been shown to reduce LDL oxidation in the ANCHOR study [40] and glucose-induced lipid peroxidation [41].

Despite the findings by Robinson and Stone of inconsistent anti-inflammatory effects, there is a database of basic and clinical science evidence demonstrating that intake results in reduction of inflammatory markers associated with ASCVD. Dietary studies on laboratory animals and humans demonstrate significant cell membrane uptake of EPA and DHA, when fed marine-based compared to vegetable-based diets, which results in less membrane expression of ARA. As expected, EPA and DHA contents in cell membranes, particularly white blood cells (lymphocytes, macrophages, neutrophils), increase considerably at the expense of ARA when diets are enriched with marine *n*-3FA. A diet that is rich in EPA will thus result in reduced prostaglandin E_2 (PGE_2) expression, for example, and feeding studies suggest that a minimum intake of 1.35–2.7 g EPA/day is required to achieve an anti-inflammatory effect [16••].

Observational studies have reported reductions in hsCRP from *n*-3FA intake [42, 43]; however, interventional studies with *n*-3FA supplementation in healthy volunteers have not [44, 45]. Micaellef et al. demonstrated a strong inverse relationship between hsCRP and measured plasma *n*-3FA levels in healthy volunteers [46]. A review by Bays and Ballantyne of the MARINE and ANCHOR trials showed that treatment with prescription-grade, high-dose EPA (AMR101 [ethyl icosapentate], Vascepa®) lowered hsCRP and lipoprotein-associated phospholipase A_2 ($LpPLA_2$) in patients with hypertriglyceridemia [40].

Calder and others have concluded that *n*-3FA intake reduces leukotrienes, prostaglandins, and other markers of leukocyte activation (e.g., tumor necrosis factor alpha [TNF-α] and interleukin-1 [IL-1]) and hsCRP [16••, 47–50]. There is additional evidence that eicosanoids derived from marine PUFA precursors have both direct and indirect effect on nuclear factor-kappa beta (NF-κβ), peroxisome proliferator-activated receptor gamma (PPAR-γ), and the nuclear response element retinoid-X-receptor (RXR) [16••].

In addition, EPA is a unique precursor to the family of resolvins, which have anti-inflammatory properties [51]. Experimental models demonstrate that resolvins inhibit transendothelial migration of neutrophils and synthesis of TNF-α and IL-1β. Both EPA and DHA will give rise to resolvins, protectins, and maresins through interaction with cyclooxygenase (COX), lipoxygenase (LOX), and cytochrome P450 (CyP450), and diets rich in *n*-3FA result in higher cellular levels of these anti-inflammatory mediators [16••]. It was shown, however, that a cohort of patients with obesity, type 2 diabetes mellitus (T2DM), and established ASCVD treated with 3 months of *n*-3FA (2 g/day) did not achieve improvements compared to controls when examining platelet function and coagulation, inflammation, and even metabolic health looking at a variety of markers for each function [52].

EPA administration also promotes neovascularization in ischemic models and improves endothelium-derived vasodilation in patients with hyperlipidemia compared to normolipidemic patients when administered in high doses [53]. The pre-surgical administration of *n*-3FA (fish oil) compared to *n*-6FA (sunflower oil) has been shown to limit macrophage infiltration of carotid plaque in endarterectomy specimens [54, 55]. *n*-3FAs also increase atherosclerosis fibrous cap thickness when given to acute coronary syndrome (ACS) patients who are co-administered high doses of EPA with background statin therapy suggesting clinically significant plaque stabilization with supplementation [56]. Thus, plaque morphology and coronary stent restenosis rates are reduced from *n*-3FA supplementation which suggests that endothelial function, anti-oxidation, and/or anti-inflammatory improvements may have a protective role in some patients.

Thrombosis

Remnant LP (from TG-rich chylomicrons, VLDL, and intermediate-density lipoprotein [IDL]), which can be reduced with *n*-3FA intake, contribute to the generation of both tissue factor and thrombin [57]. *n*-3FAs result in reduced levels of fibrinogen, factor V, and thrombin [58]. McEwen et al. noted a greater impact on these parameters in healthy subjects compared to those with ASCVD who were treated with 4 weeks of moderate-dose *n*-3FA supplementation [59]. This is concordant with the early observations by Dyerberg and Bang who

observed prolonged bleeding times in Greenland Inuits in their original work on the subject [14].

Increased bleeding rates are reported in the Japan EPA Lipid Intervention Study (JELIS), raising concern that this may be a harmful effect of *n*-3FA supplementation [60]. This finding and previously recognized anti-thrombotic effects prompted Begtrup et al. to conduct a systematic review of the medical literature assessing surgical bleeding risks in individuals taking fish oil supplements. They found that while fish oil intake may reduce hemostasis in healthy subjects, it does not increase bleeding risk in individuals undergoing surgery or invasive procedures [61]. However, surgical outcomes have not been specifically studied with the current pharmaceutical-grade *n*-3FA supplements, and the authors of the present review caution readers to recognize that it is still the standard of most surgeons to ask patients to discontinue their supplements in the perioperative period to mitigate surgical bleeding.

Effects on Hemodynamics and Vascular Reactivity

Although data is limited, supplementation with *n*-3FAs has been shown to have multiple hemodynamic effects. Most important among these are reductions in resting heart rate and blood pressure, in addition to increased vasodilatation and arterial compliance [62, 63].

Heart Rate

There are multiple mechanisms by which dietary consumption of *n*-3FAs is thought to lead to heart rate-lowering; these include direct effects on the sinus node as well as indirect effects via modulation of the autonomic nervous system by increasing vagal tone or by improved ventricular filling. A meta-analysis of 30 RCTs looking at the effects of heart rate with *n*-3FA supplementation showed a significant reduction in heart rate in the treatment group, especially with longer treatment durations and in those patients with higher baseline heart rates [62]. Despite the heart rate-lowering effects, the data regarding effects on heart rate variability and arrhythmia remain mixed. A recent study by Weisman et al. [64] showed a reduction in frequency of ventricular tachyarrhythmic episodes in patients with automatic implantable cardioverter-defibrillator (AICD) and ischemic cardiomyopathy; however, previous meta-analyses looking at RCT evidence of reduction in arrhythmia (atrial as well as ventricular) and AICD firing in patients treated with *n*-3FAs have been negative [65, 66]. Additionally, in a large, double-blinded, multi-national RCT by Mozaffarian et al. that looked at the effects of fish oil supplementation on preventing atrial fibrillation (the OPERA trial), there was no difference in reducing post-operative atrial fibrillation when compared to placebo [67]. These studies suggest that although *n*-3FA supplementation may well have physiologic benefits in affecting cardiac electrical conduction and heart rate, the clinical significance of this remains unclear.

Blood Pressure

The effects of *n*-3FAs on blood pressure (BP) are favorable, as demonstrated in multiple studies and summarized in meta-analyses. An older meta-regression analysis of RCTs showed significant reductions in both systolic and diastolic BP with high-dose (mean 3.7 g/day) fish oil supplementation, achieving systolic BP reductions of 1.7 mmHg (95% CI = 0.3, 3.1) and diastolic BP reductions of 1.5 mmHg (95% CI = 0.6, 2.3), especially in older (> 45 years) hypertensive patients [68]. A more recent meta-analysis by Miller et al. showed reductions in systolic BP (− 1.52 mmHg; 95% CI = − 2.25 to − 0.79) and diastolic BP (− 0.99 mmHg; 95% CI = − 1.54 to − 0.44) in patients treated with > 2 g/day EPA and DPA compared to placebo, with greater effect seen in those with untreated hypertension [69]. On the other hand, significant BP reductions were observed only in subjects with systolic hypertension in a retrospective analysis of data from the Fish Oil Intervention and Genotype (FINGEN) study, which demonstrated 5 mmHg reductions in systolic BP in this RCT using dietary doses of *n*-3FA (0.7–1.8 g/day combined EPA/DHA) [70].

Glycemia

Multiple studies have examined the impact of *n*-3FA supplementation on glycemic control (hemoglobin A1C) in both type 1 and 2 diabetics, and at doses used in contemporary care, and there is no consistent impact [36]. The original concern was raised by older studies that employed doses > 10 g/day, where there was a significant increase in hemoglobin A1C [71].

Daily fish consumption, as part of a weight loss regimen, resulted in improved insulin and leptin response compared to either intervention alone in one small RCT of overweight, hypertensive adults. This same study also documented substantial BP reductions in the combined daily fish weight loss group [72]. A recent randomized trial of overweight and obese (but otherwise healthy) individuals showed that dietary consumption of fatty fish, but not lean fish, significantly improved post-prandial glucose regulation and significantly increased the content of *n*-3FAs in leukocyte cell membranes [73].

Key Supplemental *n*-3FA Cardiovascular Outcome Studies and Guidelines

AHA Science Advisory on n-3FA Supplementation and the Prevention of Clinical Cardiovascular Disease

The AHA recently released a Science Advisory summarizing the clinical trial data on the net cardiovascular disease (CVD)

impact from *n*-3FA supplementation [8••]. This was a review by a panel of national experts in the field, examining recent RCTs and meta-analyses of supplementation in key clinical scenario, rating the strength and quality of evidence where available using the AHA criteria [74], including:

- Primary prevention of CV disease and stroke
- Secondary prevention of CV disease or for those at high risk
- Diabetes or prediabetes
- Heart failure
- Atrial fibrillation

The AHA panel could not make a recommendation on the use of *n*-3FAs for the *primary prevention of coronary heart disease (CHD)* in the general population because of the lack of clinical trial evidence but did note that the Vitamin D and Omega-3 Trial (VITAL) is ongoing and results from this RCT, which are expected in December 2017, may lead to a change in their conclusion [75]—*no recommendation*.

The panel felt that use of *n*-3FAs is not indicated for *prevention of CHD in individuals at high risk for CHD* based upon the results of multiple RCTs including four large RCTs. Three of the studies (Outcome Reduction With Initial Glargine Intervention [ORIGIN] trial) [76], Risk and Prevention Study [R&P] [77], and Age-Related Eye Disease Study 2 [AREDS2] [78] did not show benefit (although they were individually underpowered to show differences in cardiac death), and one open-label RCT (JELIS) [60] showed a benefit in total CVD. This evidence was rated as class III strength, level B-R for quality of evidence—*not indicated*.

They did conclude, however, that treatment is reasonable for *secondary prevention of CHD and sudden cardiac death (SCD)*, citing class II, A evidence from the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico–Prevenzione [GISSI-Prevenzione] [79] and the negative Alpha Omega trial [80], which are both large RCTs, and three small RCTs, including Diet and Reinfarction Trial (DART) [81], which showed benefit, and two (Effect of Omega 3-Fatty Acids on the Reduction of Sudden Cardiac Death After Myocardial Infarction [OMEGA] [82], Supplementation With Folate, Vitamin B6 and B12 and/or Omega-3 Fatty Acids [SU.FOL.OM3]) [83] that did not. A meta-analysis published in 2012 revealed a risk ratio for cardiac death of 0.9 [84]—*treatment is reasonable*.

As for the *primary prevention of stroke in high risk patients*, the panel concluded that *n*-3FA supplementation is not recommended on the basis of level III, B-R evidence from the same Rizos meta-analysis of stroke as a secondary outcome in RCTs [84]. There was insufficient evidence to make any recommendation for secondary prevention of stroke—*not recommended*.

They concluded that *n*-3FA supplementation is not indicated for the *prevention of CVD mortality in diabetes mellitus and prediabetes* based upon level III, B-R evidence. Cited is the large ORIGIN study [76] as the basis for this conclusion but the panel did note that A Study of Cardiovascular Events in Diabetes (ASCEND; NCT00135226) is ongoing and may provide the rationale for an updated recommendation in this population [85]—*not indicated*.

There is insufficient evidence to support the use of *n*-3FA supplementation for primary prevention of, but consider it a reasonable recommendation for use in patients with diagnosed *heart failure* (class IIa, level B-R), citing the GISSI-HF study as the single supporting trial [86]—*no recommendation (primary prevention); reasonable indication (secondary prevention)*.

Finally, the panel concluded that there is no recommendation for *n*-3FA supplementation for the prevention and treatment of *atrial fibrillation* or for post-thoracic surgery preventive management. These conclusions are on the basis of no RCT data for primary prevention and multiple RCTs and meta-analyses for secondary management (strength of evidence class III, level A)—*no recommendation*.

Meta-Analyses

Since 2012, data from meta-analyses of *n*-3FA supplementation for both primary and secondary prevention of CV disease have yielded mixed results [12]. A recent comprehensive meta-analysis of 18 RCTs and 17 prospective cohort studies by Alexander et al. [87] showed an overall non-significant reduction for any CHD event (6%) with EPA and DHA intake from food or supplements among all RCTs; however, a greater significant benefit was observed among high risk participants with both elevated TG (≥ 150 mg/dL) and LDL-C levels (> 130 mg/dL) of 16 and 14%, respectively. A significant inverse association was observed between EPA and DHA intake and risk of any CHD event in the meta-analysis of prospective cohort studies. Casula et al. presented evidence in a meta-analysis of 11 RCTs that the long-term effect of high-dose *n*-3FA supplementation might have beneficial effects in patients with existing CV disease. Compared to placebo, those patients who received ≥ 1 g EPA and DHA daily for > 1 year showed significant risk reductions for cardiac death (32%), sudden death (33%), and MI (25%). No significant effect was observed for all-cause mortality and stroke [88].

Ongoing Clinical Trials

Two large ongoing outcome trials are evaluating the efficacy of high-dose prescription *n*-3FAs when used in combination with statins on CV events in patients with high TG (200 to 500 mg/dL). The Reduction of Cardiovascular Events with EPA-Intervention Trial (REDUCE-IT; NCT01492361) is assessing the effect of 4 g/day of IPE (Vascepa®) with statin therapy versus statin therapy and placebo in patients with or at

high risk of CV disease. This is the first blinded study to assess high-dose *n*-3FAs added to a statin in a Western population with elevated TG. The endpoint is a composite of CV death, myocardial infarction, stroke, cardiovascular revascularization, and hospitalization for angina. The expected completion date is December 2017 [89, 90]. The Statin Residual Risk Reduction with Epanova® in High Risk Patients with Hypertriglyceridemia (STRENGTH; NCT02104817) trial is investigating the effect of 4 g/day *n*-3FFA (Epanova®) compared to corn oil in statin-treated patients at high risk for CV disease with TG levels ≥ 180 mg/dL. The primary endpoint is the first occurrence of a major adverse coronary event and should be completed by June 2019 [91]. Results from these outcome trials should help clarify the role of high-dose prescription *n*-3FA supplements in reducing residual CV risk in patients with hypertriglyceridemia who are taking statin therapy.

Clinical Guidelines for Treating Hypertriglyceridemia

American Heart Association

Since 2002, the AHA has recommended the intake of at least two servings of fish (preferably oily) per week, with potentially higher doses in those at risk for or who have CV disease. Individuals with CHD may consider getting their *n*-3FAs from prescription dietary supplements, especially if there is hypertriglyceridemia [92]. The 2011 AHA Triglyceride Guidelines suggest specific dose recommendations based upon the TG level [93]. They recommend *n*-3FA daily intake of 0.5–1 g for individuals with TG 150–199 mg/dL (borderline), 1–2 g if TG 200–499 mg/dL (high), and > 2 g as part of the dietary strategy to reduce risk of pancreatitis for individuals with TG > 500 mg/dL (very high).

National Lipid Association

In 2014 and 2016, the National Lipid Association (NLA) published recommendations for the management of dyslipidemia in two parts respectively [94, 95]. The initial publication affirmed the importance of recognizing and managing hyperlipidemia. It was acknowledged that the root cause of atherosclerosis is the accumulation of apoB-containing lipoproteins in the arterial wall and that excess TG-rich lipoproteins (TRL; chylomicron-, VLDL-, IDL-remnant particles) need to be treated to optimally reduce ASCVD risk and to reduce risk of pancreatitis from severe hypertriglyceridemia. Specific dose recommendations for *n*-3FA supplementation are suggested on the basis of serum TG levels, as follows: daily intake of 0.25–2 g *n*-3FA in individuals with TG 150–199 mg/dL, 1–2 g if 200–499 mg/dL, 2–4 g if 500–999 mg/dL, and 3–4 g if > 1000 mg/dL.

Endocrine Society

The 2016 guidelines recommend that non-HDL-C guide therapeutic decision-making in patients with moderate hypertriglyceridemia and patients at risk for pancreatitis due to severe hypertriglyceridemia should use fibrates as first-line pharmacotherapy after appropriate therapeutic lifestyle changes. In individuals with less severe hypertriglyceridemia, they suggest that niacin, fibrates, and *n*-3FAs can be considered as add-on therapy to statin drugs [96].

European Society of Cardiology/European Atherosclerosis Society

The European Society of Cardiology/European Atherosclerosis Society guidelines support using TG and non-HDL-C levels to help estimate ASCVD risk and target therapy and rate this as level I, class C evidence. The workgroup reviewed the available medical literature on lifestyle modification to address high TG (and all of the major lipid/LP parameters) and concluded that the evidence to support use of *n*-3FAs for TG treatment is class A, with a "less pronounced effect" for that purpose. They concluded that *n*-6FA intake should be limited to < 10% of total daily caloric intake but do not believe there is strong enough evidence to support a specific dietary *n*-6/*n*-3FA ratio [97].

Conclusions

n-3FAs are PUFAs with significant cardiometabolic effects and clinical trial evidence supporting pharmacologic supplementation to achieve ASCVD risk reduction in high risk patients. There is also epidemiologic evidence that suggests fish consumption is associated with a reduced risk for ASCVD though the interventional evidence falls short of justifying prescription for primary prevention. Multiple physiologic effects from *n*-3FA intake provide a plausible explanation for their role in protecting CV health and preventing disease. High doses of prescription *n*-3FAs are used in medical practice because of their lipid/lipoprotein effects to treat adults with hypertriglyceridemia to prevent pancreatitis from hyperchylomicronemia. Presently, similar doses are being evaluated as an intervention to augment ASCVD risk reduction in statin-treated patients with moderate hypertriglyceridemia.

Organizational guidelines and recommendations call for regular fish intake and for the use of *n*-3FAs for specific groups most likely to benefit from pharmacologic supplementation. Most recently, the AHA has issued a Science Advisory reviewing the available evidence in various cardiovascular scenarios including ASCVD, diabetes/prediabetes, atrial fibrillation, and heart failure. Readers are encouraged to review

the details of the clinical trials and summary provided in this Advisory.

Dietary supplements are taken by 53% of the US population according to estimates from the 2006 National Health and Nutrition Examination Survey (NHANES) and "fish oil" supplements are presently the most widely used dietary products [98]. Clinicians are often faced with questions from healthy patients about the role of *n*-3FA supplementation for maintenance of good health and disease prevention and that is where the evidence is less clear. The present body of literature does suggest that there are physiologic benefits from intake of *n*-3FAs; however, this does not necessarily translate to an expectation of long-term health benefits or justification for a medical prescription.

While observational data about the population health benefits of *n*-3FA intake are intriguing, prospective RCTs are needed to assess the true health benefits for a representative population before prescribing for primary prevention. Testing hypotheses involving dietary manipulation in populations is complicated because of the heavy reliance upon patient reporting and expectations of dietary variability, but testing pharmacologic doses of *n*-3FAs may be manageable. For example, measured plasma or red blood cell membrane *n*-3FA levels (*omega*-3 index) could distinguish true low-dose treatment (dietary supplement) from controls even if a randomized study is corrupted by high background fish oil intake. It is expected that future study of *n*-3FA supplementation for a healthy population will require a large study population, confirm significant difference in the *omega*-3 index between the treatment and control groups, and be of significant duration to recognize differences between two healthy groups. In the meantime, prescription-grade/dose *n*-3FA supplementation should be reserved for patients most likely to benefit based upon the highest grade evidence and expert panel review of the available literature.

Compliance with Ethical Standards

Conflict of Interest Megan F. Burke and Frances M. Burke declare no conflict of interest.

Dr. Soffer reports that he has participated as a local investigator in pharmaceutical company-sponsored clinical trials that provide program support. He has been an investigator with Akcea, Ionis, Novartis, Pfizer, Regeneron, Sanofi, Amgen, Omthera/Astra Zeneca, Regenex/NIH, and Kowa pharmaceuticals, outside the submitted work. He has also received faculty payment for services as a course director for the National Lipid Association.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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