Circulation

AHA SCIENCE ADVISORY

Omega-3 Fatty Acids for the Management of Hypertriglyceridemia

A Science Advisory From the American Heart Association

ABSTRACT: Hypertriglyceridemia (triglycerides 200–499 mg/dL) is relatively common in the United States, whereas more severe triglyceride elevations (very high triglycerides, ≥500 mg/dL) are far less frequently observed. Both are becoming increasingly prevalent in the United States and elsewhere, likely driven in large part by growing rates of obesity and diabetes mellitus. In a 2002 American Heart Association scientific statement, the omega-3 fatty acids (n-3 FAs) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) were recommended (at a dose of 2–4 g/d) for reducing triglycerides in patients with elevated triglycerides. Since 2002, prescription agents containing EPA+DHA or EPA alone have been approved by the US Food and Drug Administration for treating very high triglycerides; these agents are also widely used for hypertriglyceridemia. The purpose of this advisory is to summarize the lipid and lipoprotein effects resulting from pharmacological doses of n-3 FAs (>3 g/d total EPA+DHA) on the basis of new scientific data and availability of n-3 FA agents. In treatment of very high triglycerides with 4 g/d, EPA+DHA agents reduce triglycerides by ≥30% with concurrent increases in low-density lipoprotein cholesterol, whereas EPA-only did not raise low-density lipoprotein cholesterol in very high triglycerides. When used to treat hypertriglyceridemia, n-3 FAs with EPA+DHA or with EPA-only appear roughly comparable for triglyceride lowering and do not increase low-density lipoprotein cholesterol when used as monotherapy or in combination with a statin. In the largest trials of 4 g/d prescription n-3 FA, non–high-density lipoprotein cholesterol and apolipoprotein B were modestly decreased, indicating reductions in total atherogenic lipoproteins. The use of n-3 FA (4 g/d) for improving atherosclerotic cardiovascular disease risk in patients with hypertriglyceridemia is supported by a 25% reduction in major adverse cardiovascular events in REDUCE-IT (Reduction of Cardiovascular Events With EPA Intervention Trial), a randomized placebo-controlled trial of EPA-only in high-risk patients treated with a statin. The results of a trial of 4 g/d prescription EPA+DHA in hypertriglyceridemia are anticipated in 2020. We conclude that prescription n-3 FAs (EPA+DHA or EPA-only) at a dose of 4 g/d (>3 g/d total EPA+DHA) are an effective and safe option for reducing triglycerides as monotherapy or as an adjunct to other lipid-lowering agents.

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Elevated plasma triglycerides are the result of an excess of triglyceride-rich lipoproteins of several different types, most commonly very-low-density lipoproteins (VLDLs) but also intermediate-density lipoproteins (or VLDL remnants), chylomicrons, or chylomicron remnants. The classification, epidemiology, and pathophysiology of elevated triglycerides were reviewed in depth in a 2011 American Heart Association (AHA) scientific statement, along with detailed discussion of diet and lifestyle treatment options, as well as a brief mention of medications.[1] The 2011 statement cited epidemiological evidence that a moderate elevation in triglycerides is often associated with increased atherosclerotic cardiovascular disease (ASCVD) risk. More recent evidence from mendelian randomization studies has shown that elevated triglycerides associated with genetic variants may be a causal factor for ASCVD and possibly for premature all-cause mortality.[2–7]

Fasting plasma triglyceride concentrations may be categorized as normal (<150 mg/dL*), borderline (150–199 mg/dL), high triglyceride (HTG; 200–499 mg/dL), and very HTG (VHTG; ≥500 mg/dL).[1,8] Risk of acute pancreatitis is increased in patients with VHTG, especially those with triglycerides ≥1000 mg/dL.[9] For VHTG, the primary goal of therapy is to reduce triglycerides to <500 mg/dL,[10] whereas there is no specific treatment goal for HTG. For all degrees of triglyceride elevation, treatment or elimination of secondary causes and intensive diet and lifestyle changes are recommended before direct pharmacotherapy.[11] Such changes include weight loss, increased physical activity, limited alcohol consumption, and adoption of various healthy dietary practices such as decreased consumption of refined carbohydrates and simple sugars, substitution of saturated and *trans* fats with unsaturated fats, and increased consumption of seafood (especially species high in omega-3 fatty acids [n-3 FAs]).

The 2002 AHA scientific statement on fish and n-3 FAs recommended increased dietary omega-3 intake plus dietary supplements to achieve 2 to 4 g/d n-3 FA (referring to the total amount of eicosapentaenoic acid [EPA] plus docosahexaenoic acid [DHA]) for triglyceride-lowering treatment (ie, medical management of HTG) under the supervision of a physician. (No prescription n-3 FAs were available at the time).[12] A recent AHA science advisory has addressed the use of n-3 FA supplementation to reduce ASCVD risk.[13] This advisory focuses specifically on the use of n-3 FA agents to treat HTG and VHTG.

Since 2004, several types of prescription n-3 FA agents have been approved by the US Food and Drug Administration (FDA) for the treatment of VHTG. The typical dose is four 1-g capsules daily, providing >3 g/d EPA+DHA. Dietary supplements containing n-3 FA are also widely available in a variety of chemical forms (triglycerides, phospholipid, free fatty acid, or ethyl esters). However, because these supplements are neither reviewed nor approved by the FDA, they are not indicated for triglyceride lowering in patients with any degree of triglyceride elevation.

FDA-approved prescription n-3 FA products include Lovaza and its generic (n-3-acid-ethyl esters [O3AEE]; EPA 0.465 g and DHA 0.375 g/capsule), Omtryg (a similar O3AEE product but not clinically available), Vascepa (an ethyl ester product consisting of EPA without DHA, chemical term icosapent ethyl [IPE]; EPA 0.98 g/capsule), and Epanova (n-3-carboxylic acid [O3CA]; EPA 0.55 g and DHA 0.2 g/capsule, not clinically available). For ethyl ester agents (O3AEE and IPE), the EPA+DHA content is in ethyl ester form rather than free fatty acid. Therefore, the dose of free n-3 FA is slightly less (explained in No. 3 of the Appendix). For consistency with the majority of scientific publications, this advisory uses the convention of expressing grams per day of EPA+DHA as equivalent to the amount of grams per day of EPA+DHA ethyl esters, without adjustment for the ethyl ester moiety. More details on these products and a discussion of n-3 FA dietary supplements are presented in the Appendix.

The purpose of this advisory is to summarize available clinical evidence related to the effects of n-3 FA on plasma concentrations of triglycerides and other lipids and lipoproteins in individuals with elevated triglycerides. Summary information provided in this advisory is intended to inform healthcare providers about prescription n-3 FA newly approved since the 2002 AHA statement and to elaborate on the effects of n-3 FA as an adjunctive lipid-lowering therapy, particularly in combination with statins.

MODIFIABLE CAUSES OF ELEVATED TRIGLYCERIDES SHOULD BE ADDRESSED BEFORE PHARMACOTHERAPY IS INITIATED

As extensively reviewed and discussed in the 2011 "Triglycerides and Cardiovascular Disease: A Scientific Statement From the American Heart Association"[1] (summarized in Table 1), several factors such as medications, genetics, health conditions, lifestyle, and diet can be significant contributors to elevations in triglycerides. Before triglyceride-lowering therapy is initiated, reversible secondary causes of HTG such as hypothyroidism or poorly controlled type 2 diabetes mellitus should be identified and treated. In addition, dietary factors that are established causes of triglyceride elevations such as excessive alcohol or sugar intake (or excessive total dietary fat in the case of severe VHTG or chylomicronemia) warrant intervention. When HTG or VHTG appears to be caused, at least in part, by the medications noted in Table 1, treatment options include eliminating or lowering the dose of

*To convert mg/dL to mmol/L, divide the former by 88.6.

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Table 1. Clinical Conditions and Drugs Associated With HTG

Clinical conditions
Overweight or obesity*
Insulin resistance or metabolic syndrome*
Diabetes mellitus, especially with poor glycemic control*
Alcohol consumption, especially if in excess*
Excess sugar intake, especially if added in food processing
High saturated fat intake
Hypothyroidism†
Chronic kidney disease
Nephrotic syndrome*
Sedentary lifestyle
Pregnancy (especially third trimester)*
Lipodystrophy*
Systemic inflammatory diseases (eg, rheumatoid arthritis, systemic lupus erythematosus, many infections)
Drugs
Oral estrogen* (contraceptives or postmenopausal replacement)
Tamoxifen*
Systemic glucocorticoids*
Retinoic acid derivatives*
Nonselective β-blockers
Thiazide and loop diuretics
Antiretroviral protease inhibitors*
Atypical antipsychotics (eg, clozapine, olanzapine, risperidone)
Sirolimus,* cyclosporine A,† and tacrolimus
Cyclophosphamide

HTG indicates high triglyceride.
*May cause a major increase in triglycerides.
†More commonly causes increased low-density lipoprotein cholesterol with little impact on triglycerides.
Data derived from Miller et al,[1] Yuan et al,[14] and Herink and Ito.[15]

the inciting agent (eg, dose reduction or elimination of a thiazide diuretic or a retinoid), substituting within the same drug class (eg, carvedilol in place of metoprolol for post–myocardial infarction cardioprotection), or switching to a different drug class (eg, angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker in place of metoprolol for congestive heart failure).

If these changes are not possible or not effective, initiating triglyceride-lowering pharmacotherapy may be required. Table 2 summarizes the triglyceride-lowering options for HTG and VHTG other than prescription n-3 FAs.[1] Fibrates, the most commonly used drug class (especially fenofibrate), lower triglycerides by 15% to 60%, with efficacy depending primarily on the baseline triglyceride level.[16] High-intensity statins and niacin also may have substantial triglyceride-lowering effects, which are proportional to baseline triglycerides. Safety and tolerability considerations for these products have been reviewed in detail elsewhere.[17,18] Ezetimibe and proprotein convertase subtilisin kexin type 9 monoclonal antibodies have minimal to modest effects and are not indicated for triglyceride lowering.

Table 2. Triglyceride-Lowering Efficacy of Non–n-3 FA Agents

Drug	Approximate Efficacy, % Triglyceride Lowering
Fibrates	30–50
Immediate-release niacin	20–50
Extended-release niacin	10–30
Statins	10–30
Ezetimibe	5–10

n-3 FA indicates omega-3 fatty acid.
Adapted from Miller et al.[1]

EFFECTS OF PRESCRIPTION N-3 FA AT FDA-APPROVED DOSES IN INDIVIDUALS WITH VHTG (≥500 MG/DL)

Detailed results from the 4 published studies of prescription n-3 FA in patients with VHTG are shown in Table 3. All 3 FDA-approved agents, O3AEE,[19,20] IPE,[21] and O3CA,[22] have been tested at 4 g/d in affected patients. Plasma triglyceride levels were reduced by 30% to 35% in individuals with baseline triglycerides of 600 to 800 mg/dL. In a subanalysis of the IPE study, the placebo-corrected triglyceride-lowering effect in patients with triglycerides >750 mg/dL (mean, ≈900 mg/dL) was 45% (control, 19%; active, –27%).[21] In the only study examining effects in patients with overall mean triglycerides of ≈900 mg/dL, a placebo-adjusted triglyceride reduction of 60% was observed.[19] The degree of triglyceride lowering with full-dose prescription n-3 FA (4 g/d providing >3 g/d EPA+DHA) appears to be similar to that of fibrates, although studies directly comparing these 2 drug classes in patients with VHTG are lacking.

Changes in other lipoprotein classes are also important considerations for evaluating the effects of n-3 FA products; however, it should be noted that measurement of low-density lipoprotein (LDL) cholesterol (LDL-C) in the context of elevated triglycerides may not be accurate, as discussed further in the Appendix. In patients with VHTG treated with prescription EPA+DHA products, LDL-C increased by ≈15% to 36%† (similar to fenofibrate; Table 3).[19,20,22] However, there was no increase in apo B (apolipoprotein B) in the 1 study in which it was reported,[22] suggesting that the increase in LDL-C may reflect an increase in the average size of the LDL particles rather than an increase in LDL particle concentration. In-

†The prescribing information for Lovaza reports a placebo-adjusted median 49% increase in LDL-C and 52% reduction in triglycerides based on a pooled secondary analysis of Harris et al[19] and Pownall et al[20] reported by Sadovsky and Kris-Etherton.[23]

deed, such an effect on LDL particle size is supported by the results of more recent studies of HTG.[24–26] In patients with VHTG (triglycerides, 500–2000 mg/dL), treatment with IPE did not raise LDL-C, and apo B decreased, suggesting differing effects from those of EPA+DHA.[21] With regard to high-density lipoprotein cholesterol (HDL-C), 2 studies from the 1990s using O3AEE[19,20] reported net increases of ≈12%. In contrast, neither IPE[21] nor O3CA[22] significantly changed HDL-C. Trials with head-to-head comparisons of these 3 prescription n-3 FA agents are not available. The studies of O3AEE in VHTG were of monotherapy with no background statin use, whereas more recent studies of IPE and O3CA in VHTG included subjects taking statins (25% and 33% of the study population, respectively).[21,22]

Many patients with VHTG will require multiple medications to reduce triglycerides to acceptable levels (in addition to diet, lifestyle, and potentially medication changes). Limited evidence is available from randomized controlled trials on the effects of n-3 FA in combination with nonstatin therapy for the treatment of VHTG. In patients treated with a combination of 130 mg/d fenofibrate and 4 g/d O3AEE, triglyceride lowering of 61% was observed, which was only marginally better (P=0.06) than the 54% reduction achieved with fenofibrate alone. In an open-label extension phase of the group randomized to fenofibrate monotherapy, the addition of 4 g/d O3AEE reduced triglyceride concentrations by an additional 18%, resulting in a total reduction of 71%, which was not significantly different from the combined therapy arm in the initial randomized phase of the study.[27] Relative to baseline, the combination of fenofibrate and O3AEE resulted in LDL-C increases of 52%, although non–HDL-C significantly decreased by 7% and apo B was unchanged. Potential explanations for the relative lack of additive efficacy may be overlapping mechanisms (eg, peroxisome proliferator-activated receptor-α agonism) and the possibility that drug-induced triglyceride reduction exceeding 60% to 70% (>400 mg/dL median absolute reduction in this study) is unachievable with currently available pharmacotherapy in the absence of concomitant weight loss and substantial lifestyle modifications.

EFFICACY OF N-3 FA AT FDA-APPROVED DOSES IN INDIVIDUALS WITH HTG (200–499 MG/DL)

To evaluate and summarize the existing clinical evidence for n-3 FA effects on HTG, we identified and compared studies meeting the following criteria: administration of 4 g/d prescription n-3 FA or an equivalent amount of EPA+DHA from dietary supplements (>3 g/d EPA+DHA), mean/median baseline triglyceride values between 200 and 499 mg/dL, results reported from at least 20 people per study arm, and inclusion of a placebo-control group. Detailed information about

Table 3. Lipid and Lipoprotein Effects of 2 to 4 g/d n-3 FAs in Individuals With VHTG (Triglycerides ≥500 mg/dL) for Included Studies*

Study Characteristics							
Author, Year (Country)	Design	Treatment Period Duration, wk	Concurrent Lipid-Lowering Medications‡	Prescription Agent	EPA+DHA, g/d	Placebo	No. per Arm
Harris et al,[19] 1997 (United States)	Parallel	16	None	O3AEE	3.4	Corn oil	22 (O3AEE) 20 (placebo)
Pownall et al,[20] 1999 (United States)	Parallel	6	None	O3AEE	3.4	Corn oil	19 (O3AEE) 21 (placebo)
Bays et al,[21] 2011, MARINE (International)	Parallel (dose response: 4 (high) and 2 (low) g/d)	12	25% on statins	IPE	3.8 (High) 1.9 (low)	Light liquid paraffin	74 (High) 70 (low) 71 (placebo)
Kastelein et al,[22] 2014, EVOLVE (United States, Europe, India)	Parallel (dose response: 4 (high), 3 (mid), and 2 (low) g/d)	12	34% on statins	O3CA	3 (High) 2.3 (mid) 1.5 (low)	Olive oil	99 (High) 97 (mid) 99 (low) 98 (placebo)

(*Continued*)

the design and results of these studies is presented in Table 4. Studies evaluating lower doses (typically 2 g/d) are discussed in the section Dosing Considerations.

n-3 FA as Monotherapy

Six published trials in which 3 to 4 g/d n-3 FA was administered to people with HTG not taking other lipid-lowering medications were identified as meeting the inclusion criteria listed above.[28,29,33,36,44–46]‡ Four studies used 4 g/d O3AEE (providing 3.4 g/d EPA+DHA), and 2 studies used similar doses of EPA+DHA from an n-3 FA medical food (n=1) or dietary supplement (n=1).§ Because statins are considered to be first-line lipid treatment in patients with HTG,[11] there have been no published monotherapy studies of the more recently available IPE or O3CA in this population. On average, the triglyceride reduction was ≈27% (range, 21%–35%), apart from the study of a medical food (3.2 g/d EPA+DHA), which specifically recruited people with very low blood levels of n-3 FA and reported a 48% reduction.[45] In 4 trials, 4 g/d O3AEE averaged a 26% reduction in triglycerides, whereas the reduction in a dietary supplement study of 3 g/d EPA+DHA was 35%.[44] An earlier study of a dietary supplement that used a higher dose (4.5 g/d EPA+DHA) reported a 39% reduction in triglycerides after 6 months.[42]

‡One trial had 2 publications that reported lipid results.[44,45] The first publication[44] is discussed here and included in Table 4.

§As noted earlier, dietary supplements are not FDA approved for the treatment of HTG.

n-3 FA Added to Other Lipid-Lowering Therapies

Eight trials evaluated 4 g/d prescription n-3 FA in people with HTG on background statin therapy.[26,30–32,38–41] Five of these trials tested O3AEE; 2 trials used IPE; and 1 trial used O3CA. The triglyceride decrease was ≈21% (range, 15%–25%). Of the 5 O3AEE studies, 2 administered O3AEE in combination with statin therapy as part of the trial design,[26,32] and triglycerides were reduced 17% to 19% beyond the reduction achieved by statins, non–HDL-C was decreased 5% to 7%, and LDL-C was unchanged versus the statin-only control.[26,32] In a third study, in which all patients were on a stable dose of statin before beginning O3AEE treatment, there was a 25% reduction in triglycerides and a marginally significant increase in LDL-C relative to placebo (median, 3.5% increase; P=0.052).[31] In this study and another of O3AEE, there was a modest increase in LDL particle size.[25,26] When IPE (4 g/d) was administered with statins, there were placebo-adjusted decreases of 22% in triglycerides, 5% in HDL-C, 14% in non–HDL-C, 9% in apo B, and 6% in LDL-C,[39] and LDL particle size was modestly increased.[47] In the recently published results of REDUCE-IT (Reduction of Cardiovascular Events With EPA Intervention Trial), similar effects on lipids were reported, with placebo-adjusted decreases of

Table 3. Continued

Baseline Lipids, mg/dL†				Net Effect of Omega-3			
Triglycerides	LDL-C	HDL-C	Non–HDL-C and apo B	Triglycerides	LDL-C	HDL-C	Non–HDL-C and apo B
919	79	30	Non–HDL-C and apo B not reported	↓61%	↑36%	↑13%	Non–HDL-C and apo B not reported
801§	43§	17§	Non–HDL-C and apo B not reported	↓31%§	↑21%§	↑12%§	Non–HDL-C and apo B not reported
680 (High)§ 657 (low)§	91 (High)§ 84 (low)§	27 (High)§ 26 (low)§	225 (High)§ 210 (low)§	↓33% (High)§ ↓20% (low)§	↔	↔	↓Non–HDL-C 18% (high) and 8% (low)§ ↓apo B 9% (high)§
655 (High) 728 (mid) 717 (low)	90 (High) 81 (mid) 77 (low)	29 (High) 28 (mid) 27 (low)	Non–HDL-C: 225 (high), 215 (mid), and 205 (low) apo B: 118 (high), 112 (mid), and 114 (low)	↓27% (High) ↓21% (mid) ↓22% (low)‖	↑16% (Low and high); NS for mid‖	↔	↓Non–HDL-C 13% (high), 9% (mid), and 10% (low)‖ ↔ apo B

apo B indicates apolipoprotein B; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; EVOLVE, Evaluation of Cinacalcet Hydrochloride (HCl) Therapy to Lower Cardiovascular Events; HDL-C, high-density lipoprotein cholesterol; IPE, icosapent ethyl; LDL-C, low-density lipoprotein cholesterol; MARINE, Multi-Center, Placebo-Controlled, Randomized, Double-Blind, 12-Week Study With an Open-Label Extension; mid, middle; NS, not significant; n-3 FA, omega-3 fatty acid; O3AEE, n-3-acid-ethyl esters; O3CA, n-3-carboxylic acid; and VHTG, very high triglyceride.

*All values are reported as means and represent a significant change relative to placebo (P≤0.05) unless otherwise noted.

†Values represent n-3 FA group only.

‡Concurrent use of omega-3 products was prohibited in all studies, and consumption of >1 serving per week of cold-water fish was included as an exclusion criterion by Harris et al[19] and Pownall et al.[20]

§Values represent median or median percent change.

‖Values represent least squares geometric means.

Table 4. Lipid and Lipoprotein Effects of ≥3 g/d EPA+DHA in Populations With HTG (Mean/Median Triglycerides 200–499 mg/dL) for Included Studies*

Author, Year (Country)	Design	Treatment Period Duration	Other Lipid-Lowering Medications	Background Omega-3 Intake	EPA+DHA, g/d
FDA-approved formulations					
O3AEE					
Mackness et al,[28] 1994 (United Kingdom)	Parallel	14 wk	Not specified	Not specified	3.4
Grundt et al,[29] 1995 (Norway)	Parallel	12 wk	None	No use of omega-3 dietary supplements or medication Fish consumption not specified; fish intake reported as "stable"	3.4
Durrington et al,[30] 2001 (United Kingdom)¶	Parallel	24 wk	Statin (all; 10–40 mg/d)	Not specified (instructed to follow AHA step 1 dietary advice)	3.4
Davidson et al,[31] 2007 (United States) COMBOS	Parallel	8 wk	Statin (all; 40 mg/d)	No use of n-3 FA supplements Fish consumption not specified; counseled to follow NCEP TLC diet	3.4
Maki et al,[26] 2008 (United States)	Crossover (combination therapy)	6 wk	None (before study-administered statin as combination therapy)	Up to 2 servings/wk of fish No omega-3 supplements or enriched foods	3.4
Bays et al,[32] 2010 (United States)	Parallel (combination therapy)	16 wk	None (before study-administered statin as combination therapy)	Fish consumption not specified; counseled to follow NCEP TLC diet No omega-3 supplement use	3.4
Skulas-Ray et al,[33,34] 2011 (United States)	Crossover	8 wk (6 wk washout)	None	<2 Servings/wk of fish, flaxseed, or walnuts No omega-3 supplement use	3.4
Metkus et al,[35] 2013 (United States)††	Parallel	8 wk	Mixed (71% on statin, some with additional use of fibrate, niacin, and ezetimibe)	No specific recommendations for fish intake; counseled to maintain diet with 25%–35% fat, <10% kcal from SFA	3.4
Oh et al,[36] 2014 (Republic of Korea)	Parallel	8 wk	None	Not specified; counseled to maintain low-fat diet	3.4
Paranandi et al,[37] 2014 (United States)††	Crossover	12 wk (4 wk washout)	Mixed (32%; type not specified)	Not specified	3.4
Hedengran et al,[38] 2015 (Denmark)	Parallel	8 wk	Mix (statin [75%] and ezetimibe [8%])	Maximum of 2 fish meals per week No fish oil use	3.4
IPE					
Ballantyne et al,[39] 2012 (United States) ANCHOR	Parallel	12 wk	Statin (all)	Not specified (counseled to follow NCEP TLC diet)	3.8
Bhatt et al,[40] 2018 (multisite international) REDUCE-IT	Parallel	16 wk§§	Statin (all)	No use of prescription or supplement n-3 Dietary intake not specified	3.8
O3CA					
Maki et al,[41] 2013 (United States) ESPRIT	Parallel	6 wk	Statin (all)	Fish consumption not specified; counseled to follow NCEP TLC diet No fish oil supplements allowed	3
Dietary supplements, fish oil concentrates (not FDA approved)					
Bairati et al,[42,43] 1992 (Canada)¶¶	Parallel	6 mo	Not specified	Not specified	4.5 (2.7 EPA, 1.8 DHA)
Minihane et al,[44] 2000 (United Kingdom)	Crossover	6 wk (12 wk washout)	None	Fish consumption not specified No fatty acid supplements allowed	3 (1.7 EPA, 1.3 DHA)
Shaikh et al,[45] 2014 (Canada)	Parallel	8 wk	Statin (20%)	Omega Score (EPA+DPA+DHA in whole blood) <6%	3.2 (2.7 EPA, 0.4 DHA)

(*Continued*)

Table 4. Continued

No. per Arm	Baseline Triglycerides, mg/dL	Baseline BMI, kg/m²	Baseline Age, y	Placebo	Effect of Omega-3 on Triglycerides	Effect of Omega-3 on LDL-C and HDL-C	Effect of Omega-3 on Non–HDL-C and apo B
41 (O3AEE) 38 (placebo)	353†‡	27‡	54‡	Corn oil	↓≈30%†§	↔LDL-C and HDL-C	Non–HDL-C and apo B not reported
28 (O3AEE) 29 (placebo)	354‡	27‡	45‡	Corn oil	↓≈24%§	LDL-C not reported ↔HDL-Cǁ	Non–HDL-C not reported ↔apo B
29 (O3AEE) 26 (placebo)	407‡	29‡	55‡	Corn oil	↓26%	↔LDL-C and HDL-C	Non–HDL-C not reported ↔apo B
122 (O3AEE) 132 (placebo)	282‡	31	60	Vegetable oil	↓25%	↔/↑LDL-C# 2%–3% ↑HDL-C 5%	↓Non–HDL-C 6% ↓apo B 3%
39 (O3AEE+statin) 39 (placebo+statin)	304	30	58	Vegetable oil	↓17%	↔LDL-C ↑HDL-C 7%	↓Non–HDL-C 5% ↓apo B 2%
108 (O3AEE+statin) 111 (placebo+statin)	348†‡	30‡	56‡	Corn oil	↓19%†	↔LDL-C ↑HDL-C 2%†	↓Non–HDL-C 7%† ↔apo B
26 (O3AEE) 26 (placebo)	223	29	44	Corn oil	↓27%	↔LDL-C and HDL-C	↔Non–HDL-C ↓apo B 6%
24 (O3AEE) 23 (placebo)	327†‡	Not reported	50†	Corn oil	↓24%†	LDL-C not reported ↔HDL-C	↔Non–HDL-C apo B not reported
44 (O3AEE) 42 (placebo)	287‡	26‡	55‡	Not reported	↓21%**	↔LDL-C and HDL-C	↔Non–HDL-C and apo B
36 (O3AEE) 36 (placebo)	269	25†	52†	Corn oil	↓24%	↔LDL-C and HDL-C	Non–HDL-C and apo B not reported
36 (O3AEE) 39 (placebo)	264	29	62	Olive oil	↓22%†	LDL-C not reported ↔HDL-C	↔Non–HDL-C apo B not reported
226 (IPE) 227 (placebo)	259†	33‡	61‡	Light liquid paraffin (mineral oil)	↓22%†‡‡	↓LDL-C 6%†‡‡ ↓HDL-C 5%†‡‡	↓Non–HDL-C 14%†‡‡ ↓apo B 9%†‡‡
4089 (IPE) 4090 (placebo)	216†	31	64	Light liquid paraffin (mineral oil)	↓20%†ǁǁ	↓LDL-C 7%†ǁǁ ↓HDL-C 7%†ǁǁ	↓Non–HDL-C 12%†ǁǁ ↓apo B 10%†ǁǁ
207 (O3CA) 211 (placebo)	287‡	33‡	60‡	Olive oil	↓15%‡	↔LDL-C ↔HDL-C	↓Non–HDL-C 6% ↓apo B 2%
66 (n-3 FA) 59 (placebo)	205	27	54	Olive oil	↓39%	↔/↑LDL-C# 8% ↑HDL-C 10%	Non–HDL-C and apo B not reported
50 (n-3 FA) 50 (placebo)	220	28	56	Olive oil	↓35%	↑LDL-C 7% ↔HDL-C	Non–HDL-C and apo B not reported
20 (n-3 FA) 22 (placebo)	305‡	33‡	54‡	Corn oil	↓48%	↔LDL-C ↑HDL-C 9%	↔Non–HDL-C and apo B

AHA indicates American Heart Association; apo B, apolipoprotein B; BMI, body mass index; COMBOS, Combination of Prescription Omega-3 With Simvastatin; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EPA, eicosapentaenoic acid; ESPRIT, European/Australasian Stroke Prevention in Reversible Ischaemia; FDA, US Food and Drug Administration; HDL-C, high-density lipoprotein cholesterol; HTG, high triglyceride; IPE, icosapent ethyl; LDL-C, low-density lipoprotein cholesterol; NCEP, National Cholesterol Education Program; n-3 FA, omega-3 fatty acid; O3AEE, omega-3 fatty acid ethyl esters; O3CA, omega-3 carboxylic acids; REDUCE-IT, Reduction of Cardiovascular Events With EPA Intervention Trial; SFA, saturated fatty acid; and TLC, Therapeutic Lifestyle Changes.

*All values are reported as means and represent a significant change relative to placebo ($P \leq 0.05$) unless otherwise noted.

†Value represents median or median percent change.

‡Value represents n-3 FA group only.

§Values not reported; estimated from figure.

ǁHDL-C increased ≈5% at 4 and 8 weeks; change was not significant at final 12-week measurement.

¶Participants were individuals with established coronary heart disease.

#Effect marginally significant at P=0.052 to 0.054.

**Significant decrease from baseline in placebo group.

††Participants were individuals with HIV.

‡‡Placebo group: 6% increase in triglycerides, 9% increase in LDL-C, 10% increase in non–HDL-C, and 7% increase in apo B.

§§The first assessment is reported here, which was at 4 months for all measures except LDL-C (derived method, 1 year) and apo B (2 years).

ǁǁPlacebo group: 3% increase in triglycerides, 10% increase in LDL-C, 8% increase in non–HDL-C, and 8% increase in apo B.

¶¶Participants were individuals with established coronary artery disease.

20% in triglycerides, 7% in HDL-C, 12% in non–HDL-C, 10% in apo B, and 7% in LDL-C at 4 months.[40] O3CA as an adjunct to statin therapy decreased triglycerides by 15%, non–HDL-C by 6%, and apo B by 2%, whereas LDL-C was unchanged[41] and LDL particle size was slightly increased.[24] In summary, all 3 prescription agents were effective for reducing triglycerides and atherogenic lipoproteins when combined with statin therapy.

Three studies of dietary supplements evaluated lower doses (2.4–2.7 g/d EPA+DHA) in conjunction with statin or ezetimibe and reported 22% to 31% reductions in triglycerides.[38,48,49] One of these studies directly compared a mixture of triglycerides, diglycerides, and monoglycerides (providing 2.7 g/d EPA+DHA) to O3AEE (3.4 g/d of EPA+DHA) and found no difference in triglyceride reduction between treatments (22% and 28%, respectively) in the context of background statin or ezetimibe therapy.[38] Another of these studies prospectively recruited patients taking and not taking statins and reported an overall 28% reduction in triglycerides resulting from 2.6 g/d EPA+DHA that did not differ between the 2 groups.[49] This result supports the concept that triglyceride reduction achieved by n-3 FA is not affected by concurrent statin use.

Studies of combination therapy of omega-3 agents with fibrates and niacin in patients with HTG are limited. In 1 study of patients with HTG, combination treatment with fenofibrate and 2 g/d O3AEE resulted in a significant 11% greater triglyceride reduction compared with fenofibrate alone.[50] In a smaller study (n<20 per arm), patients with metabolic syndrome and HTG were treated with O3AEE (4 g/d), extended-release niacin (2 g/d), a combination of both, or placebo for 16 weeks.[51] Triglycerides decreased by 13% in the O3AEE group, by 21% in the extended-release niacin group, and by 33% in the combination arm. Niacin alone also reduced both non–HDL-C and apo B, whereas O3AEE did not; however, non–HDL-C was significantly lower at baseline in the O3AEE monotherapy group compared with the niacin and combination therapy groups. Overall, these results demonstrate that in patients with HTG, the combination of n-3 FA with fenofibrate or niacin can result in additive triglyceride reductions, but more research is needed.

COMPARISON OF EPA+DHA VERSUS EPA-ONLY AGENTS ON LIPIDS AND LIPOPROTEINS IN INDIVIDUALS WITH HTG

Head-to-head comparisons of EPA alone and EPA+DHA agents at FDA-approved doses are not available. However, a descriptive comparison of the triglyceride and LDL-C effects in major studies of the 3 n-3 FA agents in patients with HTG is shown in the Figure.[31,39–41] One additional study directly compared O3AEE (2 or 4 g/d)

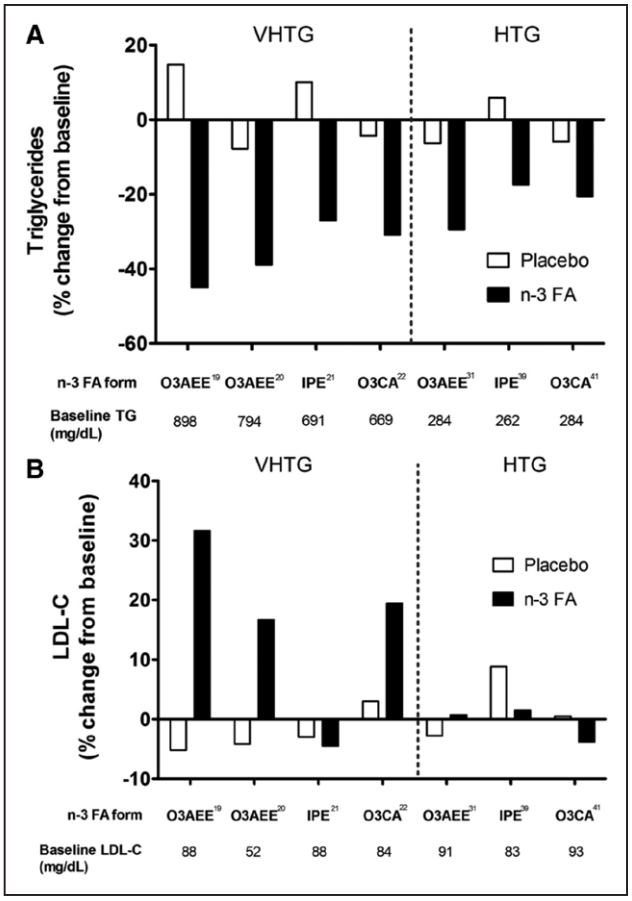

Figure. Effects of long-chain omega-3 fatty acids (n-3 FAs; 4 g/d) provided as omega-3 acid ethyl esters (O3AEE; eicosapentaenoic acid [EPA]+docosahexaenoic acid [DHA]), icosapent ethyl (IPE; EPA-only), or omega-3 carboxylic acids (O3CA; EPA+DHA) vs placebo in patients with very high triglycerides (VHTG; 500-2000 mg/dL) and high triglycerides (HTG; 200-499 mg/dL).
(**A**) Changes in serum triglyceride (TG) concentrations and (**B**) changes in serum low-density lipoprotein cholesterol (LDL-C) concentrations.

with IPE (2 g/d) in ≈600 Japanese patients with HTG, 40% of whom were on background lipid-lowering agents (mostly statins).[52] Triglyceride reductions from baseline were ≈22% in the 4 g/d O3AEE group and ≈11% for both the O3AEE and IPE 2 g/d groups after 12 weeks, and slightly greater reductions were reported in all groups after 1 year.[52] Non–HDL-C decreased by 4% to 6% in all 3 groups at 12 and 52 weeks; however, this trial is excluded from the Figure because it included neither a placebo control nor a full 4-g/d dose of IPE. The lack of studies directly comparing the 3 prescription n-3 FA agents limits firm conclusions about the comparative effects of these agents on triglycerides and other lipid measures.

Concerns have been raised that DHA-containing prescription agents may raise LDL-C in patients with HTG.[53–58] We identified 9 trials of patients with HTG that reported effects on LDL-C with 4 g/d of DHA-containing prescription n-3 FA (8 studies of O3AEE and 1 study of O3CA). In 8 of these 9 studies, there

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was no change in LDL-C versus placebo (4 of which used n-3 FA as an adjunct to statin therapy), whereas in 1 study, the median LDL-C was marginally increased by 3.5% versus placebo (P=0.052).[31] This is similar to the change reported in REDUCE-IT, with a median increase in LDL-C of 3.1% from baseline (P<0.001) for EPA-only.[40] In conclusion, there is no strong evidence that DHA-containing prescription n-3 FA agents used as monotherapy or in combination with statins raise LDL-C in patients with HTG.

For individuals with HTG, the effects of EPA-only products on LDL-C relative to DHA-containing products are unclear. This is illustrated in the Figure (B), where the percent change from baseline in LDL-C for both the active and the placebo arms is shown for the 3 major n-3 FA agents in patients with HTG. When expressed as a percent change from baseline, there was no LDL-C effect of O3AEE, IPE, or O3CA in patients with HTG in these trials. The placebo-corrected LDL-C effect of 4 g/d IPE was −6% (control, 8.8%; active, 2%).[36]‖ A similar finding for LDL-C was reported from REDUCE-IT, in which the effect of IPE was −6.6% (control, 10.2%; active, 3.1%).[40] The unusual placebo effect on LDL-C in the 2 IPE trials and the lack of trials directly comparing the 3 prescription n-3 FA agents prevent the drawing of any firm conclusions about the comparative effects of these agents on triglycerides, LDL-C, and other lipids and lipoproteins.

Effects of n-3 FA agents on other measures of atherogenic lipoproteins such as non–HDL-C and apo B have also been examined in some studies of patients with HTG. Non–HDL-C decreased by 5% to 7% in the 3 largest studies of 4 g/d O3AEE,[22,33,34] and in 2 of these investigations, apo B was also reduced by 2% to 3%.[22,33] O3CA lowered non–HDL-C by 6% and apo B by 2%,[41] and IPE lowered non–HDL-C by 14% (control, 9.8%; active, −5.5%) and apo B by 9% (control, 7%; active, −2.2%).[36] Similarly, in REDUCE-IT, non–HDL-C was reduced by 12.2% (control, 8.2%; active −4.0%) and apo B was reduced by 9.7% (control, 7.8%; active, −2.5%).[40] In summary, prescription n-3 FAs (regardless of whether they contain DHA) have slight or no effect on LDL-C in patients with HTG. Furthermore, modest reductions in the atherogenic lipoproteins non–HDL-C or apo B are likely with n-3 FA treatment in this population.

The magnitude of triglyceride reduction may be a determining factor for whether LDL-C increases in response to EPA+DHA. In 2 older monotherapy studies of dietary supplements (providing 3 and 4.5 g/d total EPA+DHA) that included at least 50 people per arm, a 7% to 8% increase in LDL-C was reported (only marginally significant for the lower dose; P=0.054); however, these studies reported a 35% and 39% reduction in triglycerides.[28,31] Indeed, effects on LDL-C were nonsignificant or marginally significant (1 study, P=0.052) in studies of 4 g/d O3AEE in which triglyceride reductions were ≤30%.[26,28,30–33,36,37] Hence, it may be that an increase in LDL-C occurs with DHA-containing n-3 FA agents when triglyceride reductions exceed those typically observed in HTG (20%–30%) and approach the levels reported for treatment of VHTG (>30%; see Figure).

EFFECTS OF EPA-ONLY VERSUS DHA-ONLY ON LIPIDS AND LIPOPROTEINS

EPA and DHA may have different effects on lipids and lipoproteins,[59] but head-to-head comparisons of EPA-only versus DHA-only agents are not available in patients with HTG or VHTG. A limited number of trials have compared effects in people with above-optimal triglyceride levels (mean values, 100–150 mg/dL) using EPA-only and DHA-only dietary supplements.[60,61] In these studies, DHA consistently increased HDL-C compared with EPA,[60,61] although the clinical implications of this effect remain unknown. In one of the studies, a crossover trial of >100 adults with increased abdominal circumference and moderately elevated C-reactive protein (1–10 mg/L), 10 weeks of supplementation with 2.7 g/d DHA increased both LDL-C and HDL-C more than 2.7 g/d EPA did,[61] whereas DHA was modestly more effective in reducing triglycerides.[61] Effects on apo B did not differ between EPA and DHA. Although this was not specifically a trial of people with HTG (baseline triglycerides, ≈130 mg/dL), it provides one of the few direct comparisons of the effects of EPA and DHA on lipids and lipoproteins. One small additional trial tested 3.8 g/d EPA or 3.7 g/d DHA in individuals with borderline elevated triglycerides (mean triglycerides, 187 mg/dL; n≤20 per study arm) but did not directly compare EPA with DHA (each treatment was compared only with placebo).[62] In this trial, DHA increased LDL-C, LDL particle size, and HDL2, but EPA did not.[62] This trial also reported an inverse relationship between triglyceride values and LDL particle size, whereas HDL-C was positively correlated with LDL particle size. This result is consistent with the observation that reductions in triglycerides and increases in HDL-C induced by n-3 FA can correspond to increased LDL-C values resulting from increased LDL particle size. These data suggest that purified DHA may modestly increase LDL-C and HDL-C more than purified EPA but may also lower triglycerides more than EPA. It is important to note, however, that there are currently no prescription agents that contain DHA only.

‖The apparent difference between placebo-adjusted percent change and calculated percent change is the result of statistical analysis and rounding.

OTHER N-3 FAs FOR MANAGEMENT OF ELEVATED TRIGLYCERIDES

The majority of research has focused on the evaluation of EPA and DHA, which are the 2 predominant n-3 FAs in fish and omega-3 agents. The carbon length of the n-3 FA appears to be important for physiological effects. EPA has a carbon length of 20; DHA has a carbon length of 22; and docosapentaenoic acid, the metabolic intermediate of EPA and DHA, is a 22-carbon n-3 FA (obtained from ruminant animals and some marine sources). Docosapentaenoic acid may have significant potential for treating HTG and VHTG,[63,64] but research on this fatty acid remains limited. In a 2-week open-label crossover comparison of 4 g/d MAT9001 (containing unspecified amounts of free docosapentaenoic acid and EPA) versus 4 g/d IPE in people with HTG, plasma triglycerides were reduced 33% by MAT9001, which was significantly more than the 11% reduction with IPE.[64] α-Linolenic acid, an 18-carbon plant-derived n-3 FA, has not been shown to reduce triglycerides substantially and is not indicated for the treatment of HTG.[65,66]

DOSING CONSIDERATIONS

The 2002 AHA scientific statement recommended 2 to 4 g/d EPA+DHA taken under a physician's supervision to reduce elevated triglycerides.[12] Since then, the FDA has approved prescription n-3 FA agents, and their lipid dose-response data have been published. In studies of O3AEE in patients with HTG, 4 g/d (3.4 g/d EPA+DHA) has demonstrated greater efficacy (20%–30% reduction) than the 2-g/d dose (1.7 g/d EPA+DHA), which resulted in modest reductions of 11% to 15%[50,67] or no significant triglyceride reduction.[36,68] Trials of other prescription n-3 FA agents have reported a similar dose-response effect for triglyceride reduction. For instance, 4 g/d IPE (≈3.8 g/d EPA) resulted in a 22% decrease versus 10% with 2 g/d IPE (≈1.9 g/d EPA).[39] An earlier open-label study of 2 g/d IPE found that triglycerides decreased only 5%.[69] With regard to O3CA, the 2-g/d dose examined in the ESPRIT trial (Epanova Combined with a Statin in Patients with Hypertriglyceridemia to Reduce Non-HDL Cholesterol; ≈1.5 g/d EPA+DHA) reduced triglycerides by 9% versus 15% with 4 g/d.[41] Clinical research has further established that doses of <2 g/d EPA+DHA are not effective for reducing triglycerides compared with higher doses, even in people with HTG.[33] O3CA (alone) is approved by the FDA at 2 g/d. However, doses >4 g/d have not been systematically studied for any of the n-3 FA agents. Regardless of the type of agent, 4 g/d prescription n-3 FA agents (providing >3 g/d EPA+DHA) have consistently reduced triglyceride levels in patients with elevated triglycerides.

TREATMENT OF MEDICATION-INDUCED HTG WITH N-3 FAs

As mentioned previously, several drugs will increase triglyceride concentrations in patients with underlying HTG (Table 1). The effects of n-3 FA on drug-induced HTG have received relatively little attention, but n-3 FAs have uniformly been reported to lower triglycerides when used with interferon-α,[70] antipsychotics,[71,72] L-asparaginase,[73] oral estrogens,[74] protease inhibitors,[35,75] retinoic acid,[76] and sirolimus.[77] Hence, n-3 FAs appear to be effective for lowering triglycerides in patients with drug-induced HTG.

EFFECTS IN CHILDREN AND ADOLESCENTS WITH ELEVATED TRIGLYCERIDES

Prescription doses of n-3 FA appear to be as safe for the management of elevated triglycerides in adolescents and children as young as 10 years of age as they are for adults.[78,79] However, n-3 FAs are little studied in this population, and the FDA-recommended use of n-3 FAs for triglyceride lowering remains limited to adults (≥18 years of age).[80] Compared with the clearly established benefits of n-3 FAs in adults with hypertriglyceridemia, the few studies of n-3 FA supplementation in children/adolescents with HTG have not shown a significant triglyceride-lowering effect.[78,79,81] However, these trials used lower doses (<2 g/d EPA+DHA)[81] or had relatively small sample sizes (<20 participants per study arm)[79,81] that in some cases included patients with only mildly elevated triglycerides.[81] To establish the efficacy, safety, and tolerability in children/adolescents with HTG, larger trials that use a higher dose of EPA+DHA (>3 g/d) and recruit children/adolescents with HTG (200–499 mg/dL) are needed.

SUMMARY OF LIPID EFFECTS FOR N-3 FA AT FDA-APPROVED PRESCRIPTION DOSES

Prescription n-3 FA at a dose of 4 g/d has consistently produced significant reductions in triglyceride levels in patients with HTG or VHTG, and this effect is greater in patients with VHTG than in those with HTG (as for triglyceride-lowering agents in general). Statin treatment does not appear to influence the degree of triglyceride reduction with n-3 FA administration in patients with HTG (≈20%–30% triglyceride reduction), although this has not been thoroughly evaluated. Increased LDL-C with prescription n-3 FA treatment is uncommon in individuals with HTG, regardless of the agent used. When triglyceride reductions exceed 30% with n-3 FA

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prescription therapy, as is more common in the treatment of VHTG, increases in LDL-C have been reported for products that contain DHA. Modest reductions in non–HDL-C (5%–14%) and apo B (2%–9%) have been reported with n-3 FA therapy in HTG, which may reflect improved atherogenic risk. The dearth of studies directly comparing the 3 prescription n-3 FA agents precludes any firm conclusions on the comparative effects of these agents on triglycerides, as well as other lipids and lipoproteins. Prescription n-3 FAs at doses of 2 g/d provided roughly one-half the triglyceride-lowering efficacy of 4 g/d, the former in some cases not differing significantly from placebo.

MECHANISMS OF N-3 FA EFFECTS ON LIPOPROTEIN METABOLISM

Various mechanisms have been proposed and investigated with regard to n-3 FAs and lipoprotein metabolism.[82,83] Kinetic studies have demonstrated that n-3 FAs reduce hepatic secretion of triglyceride-rich lipoproteins, the molecular mechanisms of which have not been fully characterized.[82] Inhibition of diacyl-glycerol acyl transferase, the major triglyceride-synthesizing enzyme in the liver, has also been reported with n-3 FA use.[83] Others have suggested inhibition of phosphatidic acid phosphatase.[84] Furthermore, EPA reduces de novo lipogenesis by inhibiting transcription of the gene for SREBP (sterol regulatory element binding protein)-1c.[85] Treatment with n-3 FA may also reduce triglyceride synthesis via suppression of SREBP-1 activity,[86] inhibition of its activation via posttranslational mechanisms,[87,88] and degradation of its active form.[89] In addition, n-3 FAs lead to intracellular degradation of apo B, which may be a result of decreased triglyceride availability or autophagic destruction of apo B via post-Golgi oxidation,[90] thereby diminishing the assembly of VLDL particles in the hepatocyte and decreasing VLDL secretion.[91,92] Other potential mechanisms include increased peripheral triglyceride clearance (by upregulation of lipoprotein lipase) and a reduction in intrahepatic fatty acid pools, which are the primary source for hepatic triglyceride synthesis.[82]

SAFETY AND TOLERABILITY OF PRESCRIPTION N-3 FA PRODUCTS

General

All forms of n-3 FA products have relatively benign side-effect profiles and are generally safe; however, the evidence for safety of FDA-approved prescription n-3 FA agents comes primarily from short-term randomized clinical trials. In clinical trials of prescription n-3 FA agents, tolerability issues have generally been relatively minor (see sections titled Gastrointestinal, Bleeding, Fish/Seafood Allergies, and Glycemic Control) and resulted in drug discontinuation in only a small percentage of subjects (usually <5%).

Gastrointestinal

Side effects of n-3 FA can include fishy taste, eructation, diarrhea, and nausea. Absorption of the ethyl ester formulations (O3AEE and IPE), although low in a fasting state, is greatly increased by taking them with food, and they are so labeled.[93] Although head-to-head comparisons of the 3 prescription agents are not available, the product inserts suggest substantial differences in the rates of gastrointestinal side effects for each agent relative to placebo: O3CA, 27% versus 8%; O3AEE, 3% to 4% versus <1% to 2%; and IPE, <1% to 7% versus 4% to 7% for active agent compared with placebo, respectively.

Bleeding

Because of the known antiplatelet effect of all n-3 FA products, FDA prescribing information suggests that patients taking both n-3 FAs and an anticoagulant or antiplatelet agent should be monitored periodically. However, no specific monitoring is suggested. It is also stated that n-3 FAs in combination with such agents do not produce clinically significant bleeding episodes. This is consistent with trials reporting no increased risk of bleeding with n-3 FA added to either anticoagulants or antiplatelet drugs.[94,95] However, it should be noted that in JELIS (Japan EPA Lipid Intervention Study), in which 18645 individuals were randomly assigned to 1.8 g/d EPA plus statin or statin only, there was a small but statistically significant increase in total hemorrhagic events (cerebral, fundal, epistaxis, or subcutaneous; 1.1% for EPA versus 0.6% for control; P=0.0006), although no significant increase was reported for cerebral hemorrhage as a single hemorrhagic outcome.[96] Similarly, REDUCE-IT reported a trend toward an increase in bleeding events (2.7% vs 2.1%; P=0.06) but no significant increase for any site (gastrointestinal, central nervous system, or other), and there were no fatal bleeding events in the trial.[40]

Fish/Seafood Allergies

n-3 FAs are highly purified oils and do not appear to be allergenic.[97] Patients allergic to seafood need not avoid these products, although the FDA labels state to use with caution.

Glycemic Control

Early reports suggested that using n-3 FA worsened glycemic control, but meta-analyses of older studies and more recent publications have shown that 4 g/d

prescription n-3 FA does not adversely affect glucose metabolism.[98–100] REDUCE-IT did not find an increase in hemoglobin A_{1c} or in new-onset diabetes mellitus.[40]

CARDIOVASCULAR OUTCOME TRIALS OF N-3 FA IN STATIN-TREATED INDIVIDUALS WITH HTG

A large randomized placebo-controlled clinical trial was recently completed and an additional study is currently in progress testing the effects of 4 g/d n-3 FA on ASCVD outcomes in patients with HTG on background statin therapy. REDUCE-IT[101] reported the effects of 4 g/d of the FDA-approved ethyl ester formulation of EPA (IPE) in 8179 patients across 11 countries. Eligibility for enrollment in REDUCE-IT required fasting triglycerides of 150 to 499 mg/dL, but subjects were allowed to have a triglyceride level within 10% of 150 mg/dL, and roughly 1/10th of the subjects had a baseline triglyceride level of 135 to 150 mg/dL. The baseline triglyceride level for trial inclusion was not raised to 200 mg/dL until roughly halfway through recruitment (May 2013). The median triglyceride level for all subjects was only 216 mg/dL. Subjects also were required to be ≥45 years of age with preexisting ASCVD (71% of subjects) or ≥50 years of age with diabetes mellitus and at least 1 other major risk factor (29% of subjects). All patients were receiving a stable dose of statin and had an LDL-C of 41 to 100 mg/dL at baseline. Subjects randomized to IPE had a 25% reduction in the primary end point, which was a 5-point composite of major adverse cardiovascular end points consisting of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, and unstable angina requiring hospitalization.[40] Risk for each of the individual components of the primary composite end point was also significantly reduced, including a 20% reduction in cardiovascular death. Notably, lipid effects were consistent with earlier IPE trials, with a placebo-adjusted triglyceride reduction of 20% at assessments at 4 months to 3 years and changes in non–HDL-C of –12.2% (control, 8.2%; active, –4.0%), in LDL-C of –6.6% (control, 10.2%; active, 3.1%), in apo B of –9.7% (control, 7.8%; active, –2.5%), and in HDL-C of –7.2% (control, 4.7%; active, –2.8%).

Cardiovascular disease risk reduction did not differ between patients, with on-study triglycerides >150 or <150 mg/dL at 1 year. However, the subset of patients (≈20% of the total cohort) who began the trial with triglycerides >200 mg/dL and HDL-C ≤35 mg/dL experienced a significantly greater risk reduction of the primary end point than those not meeting these criteria: 38% (95% CI, 23–49) versus 21% (95% CI, 12–29), respectively (*P*=0.04 for interaction). Nevertheless, there was no difference between those with and those without these criteria for the secondary composite end point consisting of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke (*P*=0.5). Secondary post hoc analyses of previous trials of triglyceride-lowering pharmacotherapy support the finding with the primary but not the key secondary REDUCE-IT end point.[102,103] Together, these results suggest that HTG (particularly in combination with low HDL-C) could be a useful biomarker for identifying patients who may experience the greatest benefit from prescription n-3 FA. However, the reduction in ASCVD risk may be independent of achieving a specific target for fasting triglycerides.

The potential cardiovascular disease benefit from 4 g/d of a DHA-containing prescription n-3 FA, O3CA, is being tested in the ongoing STRENGTH trial (Statin-Residual Risk Reduction With Epanova in High Cardiovascular Risk Patients With Hypertriglyceridemia)[104] in ≈13 000 patients across 21 countries. Results are expected in 2020 and are likely to further inform prescribing decisions.

Table 5. Summary Statements About the Effects of n-3 FA in Managing HTG

	Summary Statements
Triglycerides 200–499 mg/dL	≈20%–30% reduction in triglycerides and no LDL-C increase with 4 g/d prescription n-3 FA
Triglycerides ≥500 mg/dL	≥30% reduction in triglycerides with 4 g/d prescription n-3 FA, LDL-C increase with DHA-containing agents
Children/adolescents	Apparently safe but more research needed to further evaluate efficacy
Use with other lipid therapy	Safe and apparently additive triglyceride reduction with statin therapy; apparently safe with fibrates or niacin but more research needed to evaluate efficacy
Prescription n-3 FA agent	On the basis of available data, all prescription agents appear comparably effective, but head-to-head comparisons are lacking

DHA indicates docosahexaenoic acid; HTG, high triglycerides; LDL-C, low-density lipoprotein cholesterol; and n-3 FA, omega-3 fatty acid.

SUMMARY AND CONCLUSIONS

Prescription n-3 FAs at the FDA-approved dose of 4 g/d are safe and generally well tolerated. At this dose, triglyceride lowering of ≥30% has been reported in clinical trials of subjects with VHTG (triglycerides ≥500 mg/dL), in whom these agents are FDA approved. In VHTG, the goal of therapy is to reduce triglyceride levels to <500 mg/dL and to lessen the risk of pancreatitis, although this may not be achieved with n-3 FA monotherapy, so additional triglyceride-lowering pharmacological treatment may be indicated. In the context of HTG (triglycerides, 200–499 mg/dL), 4 g/d prescription n-3 FA effectively lowers triglycerides by ≈20% to 30% and does not significantly increase LDL-C. In all patients, established recommendations for diet and lifestyle should also be followed.[11] In the largest

studies of 4 g/d EPA+DHA or EPA-only as adjuncts to statin therapy, non–HDL-C and apo B were modestly decreased, suggesting reductions in total atherogenic lipoproteins. Use of n-3 FA may be accompanied by mild gastrointestinal complaints (such as "fishy burps" or nausea), but taking n-3 FA with meals may reduce gastrointestinal side effects and improve absorption of O3AEE and IPE. In clinical trials completed to date, <5% of subjects have discontinued omega-3 agents because of side effects. The triglyceride-lowering efficacy and generally excellent safety and tolerability of n-3 FAs make them valuable tools for healthcare providers. The use of n-3 FAs (4 g/d) for improving ASCVD risk in patients with HTG is supported by a 25% reduction in major adverse cardiovascular end points in REDUCE-IT, a randomized placebo-controlled trial of EPA-only in high-risk patients on statin therapy. Results from the STRENGTH trial, a randomized placebo-controlled cardiovascular outcomes trial of 4 g/d prescription EPA+DHA in patients with HTG and low HDL-C on statins, are anticipated in 2020. We conclude that prescription n-3 FAs, whether EPA+DHA or EPA-only, at a dose of 4 g/d, are clinically useful for reducing triglycerides, after any underlying causes are addressed and diet and lifestyle strategies are implemented, either as monotherapy or as an adjunct to other triglyceride-lowering therapies (Table 5).

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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Terry A. Jacobson	Emory University	Amarin (Steering Committee-REDUCE-IT Trial)*	None	None	None	None	None	None

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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

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Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/ Honoraria	Expert Witness	Ownership Interest	Consultant/ Advisory Board	Other
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This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

APPENDIX

1. FDA-approved n-3 FA products as of February 2018
   - A. O3AEE (EPA+DHA)
     - i. Lovaza (GlaxoSmithKline)
     - ii. Generic O3AEE (Teva)
     - iii. Omtryg (Tyrgg Pharma; not clinically available)
   - B. IPE (also n-3 FA ethyl esters but consisting solely of EPA)
     - i. Vascepa (Amarin)
   - C. O3CA (EPA+DHA)
     - i. Epanova (AstraZeneca; not clinically available)
2. FDA-approved indication for all prescription n-3 FA products
   - A. The treatment of adult patients with VHTG (≥500 mg/dL)
3. FDA-approved doses of prescription n-3 FA products
   - A. For all products currently available to patients, four 1-g capsules per day (2 g twice daily with food for O3AEE products). The EPA-only product is also available in 0.5-g capsules for dosing as 4 capsules twice daily with food. The carboxylic acid product is also approved at 2 g/d, both doses being taken without regard to food intake.
   - B. The usual listing of percentage content of EPA and DHA in all prescription omega-3 agents helps to accurately assess the non–EPA+DHA content of those products. For example, the IPE product is ≥96% EPA; thus, ≤4% of the content is not EPA. The actual amount of EPA and DHA fatty acids provided by the ethyl ester agents, however, is significantly less than the total stated amount of n-3 FA–containing material as a result of the mass of the ethyl ester moiety. The actual amount of free fatty acid as EPA and DHA provided by each ethyl ester agent, which is an accurate expression of their content of active ingredients, is lower as follows:
     - i. Lovaza: 425 mg EPA and 345 mg DHA fatty acid per 1000-mg capsule (ie, 77% rather than 84% EPA+DHA), 3.1 g EPA+DHA per 4-g dose
     - ii. Omtryg: 425 mg EPA and 345 mg DHA fatty acid per 1200-mg capsule (ie, 70% rather than 76% EPA+DHA), 3.1 g EPA+DHA per 4-g dose
     - iii. Vascepa: 876 mg EPA fatty acid per 1000-mg capsule (ie, 88% rather than 96% EPA), 3.5 g EPA per 4-g dose

iv. Epanova: 550 mg EPA and 200 mg DHA fatty acid per 1000-mg capsule (ie, 75% EPA+DHA; no correction necessary for this non–ethyl ester, carboxylic acid product), 3 g EPA+DHA per 4-g dose

4. Omega-3 dietary supplements:

There are numerous advantages to the use of prescription n-3 FA agents compared with nonprescription products for the treatment of elevated triglycerides. First, with regard to proper terminology, there are no over-the-counter n-3 FA products; that is, no FDA-regulated n-3 FA preparations are available without a prescription. The potency, quality, and efficacy of dietary supplements are not initially reviewed or approved, nor are they subsequently monitored or assured by the FDA; thus, they are not indicated for the treatment of disease. Prescription n-3 FA agents, in contrast, are reviewed, approved, monitored, and assured by the FDA.

The formulations of commercially available long-chain n-3 FA dietary supplements include triglycerides (naturally occurring), ethyl esters, free fatty acids, and re-esterified triglycerides. Apparently independently of formulation, some omega-3 dietary supplements contain cholesterol, oxidized fatty acids, saturated fatty acids, or other contaminants that can affect their net risk-benefit relationship.[57,105] In extreme cases, dietary n-3 FA supplements may have up to 37% saturated fat content.[106] This is undesirable, especially if ≥10 capsules of these products are required to achieve ≥3 g/d EPA+DHA. The calorie burden of this many capsules (≈100 kcal/d) is also undesirable. Some,[107] but not all,[108] supplements also contain unacceptable levels of oxidation products that have been shown to interfere with the beneficial effects of n-3 FAs in some,[109,110] but not all,[111] studies. Furthermore, the EPA+DHA content of dietary supplements is not always confirmed by independent analysis.[112]

Dietary supplement omega-3 preparations are considerably less expensive (per 1 g EPA+DHA) than pharmaceutical products, although the out-of-pocket expense may be less for prescription n-3 FAs, depending on the copay for a given agent and insurance plan. The price per 1 g EPA+DHA for dietary supplements varies widely but is typically much less than the cash price of prescription O3AEE. Although many n-3 FA dietary supplements meet all their label claims and do not contain oxidation products or environmental contaminants, these products are not indicated for the treatment of HTG or VHTG because they are not approved by the FDA for this purpose.

5. Lipid measurements in individuals with HTG:

Factors influencing triglyceride measurement have been reviewed extensively in the 2011 AHA scientific statement on triglycerides and cardiovascular disease.[1] Key points are summarized here.

Variability in lipid levels: Plasma lipid concentrations, particularly triglycerides, fluctuate day to day within individuals in response to diet, alcohol, physical activity, and other factors.[113] Therefore, interpretation of treatment responses based on a single measurement before and after treatment has not been recommended. Ideally, 3 to 4 independent testing occasions would be used to evaluate the response to treatment. With regard to the clinical trials evaluated for this advisory, results were most commonly based on a single fasting triglyceride measurement. Only 3 of the trials presented in Table 4 specified that results were based on 2 independent measurements separated by at least 1 day.[32,33,39]

Measurement and reporting of LDL-C and non–HDL-C: Response to lipid-altering interventions is typically assessed with a standard lipid profile in which total cholesterol, HDL-C, and triglycerides are directly measured. These values are then used to calculate non–HDL-C (total cholesterol minus HDL-C) and to estimate LDL-C with the Friedewald equation (non–HDL-C minus triglycerides divided by 5).[114] Although it is widely recognized that the Friedewald estimation of LDL-C is inappropriate with triglycerides >400 mg/dL, this estimation progressively loses accuracy even at more modest triglyceride elevations. For instance, of 11 116 patients with triglyceride values of 200 to 399 mg/dL who were estimated to have LDL-C values of <70 mg/dL according to the Friedewald calculation, only 40% met this clinical target when LDL-C was measured directly.[115] As total plasma triglyceride increases, the triglycerides carried by VLDL increase disproportionately to its cholesterol content. The Friedewald equation assumes a constant triglycerides/cholesterol ratio of 5 in VLDL, regardless of the plasma triglyceride concentration. Thus, use of the Friedewald estimation for LDL-C becomes increasingly problematic as triglyceride concentrations increase in the 100- to 400-mg/dL range.[115] Unfortunately, homogeneous assays of LDL-C (so-called direct measurements of LDL-C) also lose accuracy in patients with HTG and in nonfasting samples.[116] Furthermore, as a result of inevitable decreases in average LDL particle size with increasing plasma triglycerides, even an accurately determined LDL-C level will tend to progressively underestimate the concentration of LDL particles for triglycerides levels in the 100- to 400-mg/dL range.

The error introduced by either the use of the Friedewald equation or direct measurements of LDL-C may confound the interpretation of clinical trial results. Although most trials presented in Table 4 specified direct LDL-C measurement in cases when triglycerides >400 mg/dL (as is standard for clinical practice), only 3 trials reported LDL-C results obtained from direct LDL measurement throughout the triglyceride range.[28,30,45] Because of the problems with typical measurement and interpretation of LDL-C levels in clinical care, non–HDL-C is preferred over LDL-C as a parameter of atherogenic lipids to guide therapy in patients with HTG and VHTG. Such an approach has been recommended by the National Lipid Association[10] and International Atherosclerosis Society[117] for patients with HTG or VHTG.

Short-term effects of alcohol and diet on triglyceride measurement: As reviewed in the 2011 AHA statement on triglycerides and cardiovascular disease,[1] alcohol consumption just before testing may elevate fasting triglyceride measurements.[118,119] Only 2 trials presented in Table 4 specified avoiding alcohol for at least 48 hours before testing.[29,33] In addition, because patients with HTG (in addition to VHTG) may have delayed postprandial clearance of chylomicrons, consumption of a high-fat meal before a standard fasting period (12 hours) may still influence triglyceride results in this population. Some authors have advocated for the use of nonfasting triglycerides in standard clinical practice because postprandial lipemia appears to contribute to atherogenesis and nonfasting triglycerides are reported to be more strongly linked to ASCVD than are fasting triglycerides.[120,121] However, there are several problems with this approach. First, no published data directly compare fasting and nonfasting triglycerides in the same patients, so potentially greater prediction of ASCVD risk with nonfasting triglycerides can be claimed only for averages of large populations, not for individual patients. Second, triglycerides vary significantly over time in the postprandial period after any significant amount of fat intake, and there are no nomograms for assessing triglyceride concentrations at a given time even after a standardized test meal. Third, it is difficult to know the fat content of any nonstandard meal. Fourth, it is extremely difficult to predict the rate of gastric emptying, fat absorption, and hence chylomicron production or to know the rate of chylomicron clearance. Finally, standard reference ranges do not currently exist for nonfasting triglyceride values; therefore, the interpretation of these values in individual patients in clinical practice is not straightforward.

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