Journal of Cardiovascular Pharmacology and Therapeutics
2021, Vol. 26(6) 524-532

DOI: 10.1177/10742484211023715
journals.sagepub.com/home/cpt

Omega-3 Fatty Acids and Cardiovascular Disease: A Narrative Review for Pharmacists

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Abstract

Background: Atherosclerotic cardiovascular disease is a significant cause of morbidity and mortality worldwide. While use of statin therapy has improved management of lipids, an unmet need in reducing residual atherosclerotic cardiovascular disease risk and ischemic events persists. We provide an overview of the pharmacology of omega-3 fatty acids, omega-3 fatty acid cardiovascular outcomes trials, landmark clinical data and pharmacology of icosapent ethyl (a stable and highly purified ethyl ester of eicosapentaenoic acid), and the critical differences between fish oil supplements and prescription omega-3 fatty acids. **Method:** A PubMed literature review was conducted in April 2020 to identify articles discussing omega-3 fatty acid cardiovascular outcomes trials, pharmacology of icosapent ethyl, and the evaluation of fish oil dietary supplements and prescription omega-3 fatty acids. **Results:** Both eicosapentaenoic acid and docosahexaenoic acid have been widely associated with positive health benefits; however, data are inconsistent regarding the benefit of combination eicosapentaenoic acid and docosahexaenoic acid in patients with cardiovascular disease. Eicosapentaenoic acid, and specifically icosapent ethyl, has demonstrated atherosclerotic cardiovascular disease risk reduction among statin-treated patients. Important clinical differences exist between dietary supplement and prescription omega-3 fatty acid products. **Conclusions:** As research regarding the optimal management of dyslipidemia continues, additional therapy beyond statins is necessary to reduce atherosclerotic cardiovascular disease risk. In large cardiovascular outcomes trials, eicosapentaenoic acid has demonstrated cardiovascular benefit. Icosapent ethyl possesses a favorable efficacy and safety profile and should be considered as an adjunct to statin therapy to reduce ischemic event risk.

Keywords

triglycerides, fatty acids, omega-3, fish oils, eicosapentaenoic acid, icosapent ethyl

Introduction

Atherosclerotic cardiovascular disease (ASCVD) is the most common cause of morbidity and mortality worldwide.[1-3] Although statin therapy has been shown to decrease the risk of cardiovascular (CV) events by 25% to 45%,[4] residual risk remains despite achieving target low-density lipoprotein cholesterol (LDL-C) levels.[5]

Hypertriglyceridemia is associated with increased risk of ASCVD, independent of LDL-C control.[6-10] Approximately 25% of adults in the United States (US), including up to one-third on statin therapy, have elevated (≥150 mg/dL) triglyceride (TG) levels.[11] Management of high TG levels can be derived from diet and lifestyle interventions, including weight loss, physical activity, and changes in diet.[12-15] Pharmacologically, the impact of statin therapy on lowering TG levels is modest.[16] Current therapies available for lowering TG levels include niacin, fibrates, ezetimibe, and mixed omega-3 (OM-3) fatty acids. However, these therapies have not demonstrated consistent ASCVD risk reduction in large CV outcome trials (CVOTs) as an adjunct to statin therapy.[5,14,17]

Icosapent ethyl (IPE) is a highly purified, stable ethyl ester of eicosapentaenoic acid (EPA), an OM-3 fatty acid. IPE was originally approved by the US Food and Drug Administration (FDA) as an adjunct to dietary modifications to reduce TG levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia.[18] The Reduction of Cardiovascular Events with Icosapent Ethyl-Interventional Trial (REDUCE-IT) found that the addition of IPE to statin therapy in adults with elevated TG levels (≥150 mg/dL) and at high risk for ASCVD events resulted in a significant risk reduction compared to statin treatment alone.[19] As a result, the US FDA expanded IPE's indication to also be used as an adjunct to maximally tolerated statin

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Manuscript submitted: March 06, 2021; **accepted:** May 17, 2021.

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therapy to reduce the risk of myocardial infarction (MI), stroke, coronary revascularization, and unstable angina requiring hospitalization in adult patients with elevated TG levels (≥150 mg/dL) and established cardiovascular disease or diabetes mellitus and 2 or more additional risk factors for CV disease.[18]

Aim of the Review

We aimed to review important CVOTs of OM-3 fatty acids including EPA, the unique pharmacological properties of IPE, and the key differences between fish oil dietary supplements and prescription OM-3 fatty acids.

Methods

We conducted a PubMed search in April 2020 for peer-reviewed articles in the English language discussing OM-3 fatty acid CVOTs, the pharmacology of IPE, and the differences between fish oil dietary supplements and prescription OM-3 fatty acids. Primary articles were included when possible. Articles evaluating therapies and therapeutic areas other than OM-3 fatty acids for CV disease were excluded.

Results

Pharmacology of OM-3 Fatty Acids

The term OM-3 (or n-3) is a structural description of a specific family of polyunsaturated fatty acids (PUFAs).[20] The n-3 descriptor denotes the location of the fatty acid's first double bond from the methyl end, which is between the third and fourth carbons.[20,21]

OM-3 PUFAs must be obtained from dietary sources.[21] The simplest OM-3 PUFA is α-linolenic acid (ALA), which is found in plants.[20,22] After ingestion, ALA can be metabolized, predominantly in the liver, to form EPA.[20,22] EPA then undergoes further metabolism through multiple enzymatic actions and β-oxidation to yield docosahexaenoic acid (DHA).[20,21] Conversion of ALA to EPA and eventually DHA is generally poor in humans.[20,23]

Both EPA and DHA have been widely associated with health benefits, including potential anti-inflammatory properties.[20] However, data have been inconsistent with respect to the benefit of mixtures of EPA and DHA in CV disease treatment.[21]

Important Combination EPA+DHA CVOTs

Considering the anti-inflammatory properties of OM-3 fatty acids, multiple studies have evaluated their potential benefit in CV disease. CVOTs evaluating combination EPA+DHA have been inconsistent in the demonstration of ASCVD risk reduction in addition to contemporary medical management.[13,14,24,25] These conflicting results may be due to differences in patient populations, formulations used, dosages evaluated, inconsistencies in baseline statin use, and variability in follow-up duration.[13,14,17]

The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico-Prevenzione (GISSI-P) trial evaluated recent MI patients who were given 850-882 mg/day OM-3 ethyl esters.[26] The study resulted in a significant reduction in the primary endpoint of death, nonfatal MI, and nonfatal stroke in patients treated with OM-3 versus placebo.[26] However, only 5% of patients included in the study were on concomitant statin therapy, limiting its generalizability in the modern era of dyslipidemia management.[26]

The OMEGA trial studied the use of 1 gram daily OM-3 ethyl ester versus placebo in patients post-MI.[27] The study found no significant difference in occurrence of the primary endpoint (sudden cardiac death) between the treatment and placebo groups.[27]

The Alpha Omega Trial randomized patients with a prior MI to 1 of 4 groups—EPA+DHA 400 mg daily, ALA 2 g daily, EPA+DHA and ALA, or placebo.[28] The trial did not demonstrate a significant reduction in major CV adverse events, defined as fatal and nonfatal CV events and cardiac interventions.[28]

One arm of the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial evaluated the use of at least 900 mg/day OM-3 ethyl ester in patients at high risk for CV events who also had impaired fasting glucose, impaired glucose tolerance, or diagnosed diabetes.[29] The study found no significant difference in death from cardiac causes versus placebo in this specific patient population.[29]

The ASCEND (A Study of Cardiovascular Events in Diabetes) trial assessed the use of 840 mg/day EPA+DHA in patients with diabetes mellitus but without known evidence of CV disease.[30] At the conclusion of the trial, no significant difference was found in the rates of serious vascular events versus placebo, or in the rate of all-cause mortality over a mean follow-up time of 7.4 years.[30] Of note, 75% of patients enrolled in the study were also on concomitant statin therapy.[30]

The Vitamin D and Omega-3 Trial (VITAL) was a primary prevention trial evaluating the use of 840 mg/day EPA+DHA with or without vitamin D in healthy patients with no baseline CV disease.[31] The study demonstrated no significant difference in rates of MI, stroke, or CV death versus placebo during a median follow-up of 5.3 years.[31] In this patient population, 37% of patients were also on concomitant statin therapy.[31]

The Outcomes Study to Assess Statin Residual Risk Reduction with Epanova in High CV Risk Patients with Hypertriglyceridemia (STRENGTH) evaluated the use of 4 g daily OM-3 carboxylic acids (CA) versus a corn oil placebo in 13,078 patients on statin therapy, with elevated TG levels, a low high-density lipoprotein cholesterol (HDL-C) level, and an elevated risk for ASCVD.[32] There was no difference in the composite primary endpoint, which consisted of CV death, MI, stroke, coronary revascularization, or unstable angina that required hospitalization (hazard ratio [HR] 0.99, 95% confidence interval [CI] 0.90-1.09, $P = 0.84$). There was also no difference in both secondary composite endpoints of MI, stroke, and CV death (HR 1.05, 95% CI 0.93-1.19, $P = 0.40$) and of MI infarction, coronary revascularization, hospitalization

for unstable angina, and cardiac death (HR 0.91, 95% CI 0.81-1.02, $P = 0.09$). Furthermore, the trial reported an increased rate of new-onset atrial fibrillation (AF) in the OM-3 CA group compared with the corn oil group (2.2% vs 1.3%, HR 1.69, 95% CI 1.29-2.21, $P < 0.001$). As a result, the trial was terminated per recommendation of the Data Monitoring Committee due to a low probability of conferring CV benefit and the increased risk of AF in the OM-3 CA group.[32]

The Omega-3 Fatty Acids in Elderly Patients with Myocardial Infarction (OMEMI) study investigated the use of 1.8 g/day EPA+DHA on elderly patients (age 70-82) who have experienced an acute MI.[33] The primary endpoint of the trial was incidence of the first major CV adverse event, which was represented as a composite endpoint of all-cause mortality, nonfatal MI, stroke, revascularization, and hospitalization due to heart failure.[33] The results showed no difference in the primary endpoint between the EPA+DHA- and placebo-treated patients (21.0% vs 19.8%, HR 1.07, 95% CI 0.82-1.40, $P = 0.62$), including no difference in all-cause mortality (5.5% in both groups, HR 1.01, 95% CI 0.60-1.71, $P = 0.97$).[33] Furthermore, patients in the EPA+DHA group had a higher, though non-statistically significant, incidence of AF compared with patients in the placebo group (HR 1.84, 95% CI 0.98-3.44, $P = 0.056$).

Important EPA-Only CVOTs

The Japan EPA Lipid Intervention Study (JELIS) was an open-label trial that studied the use of 1.8 g/day of a purified EPA formulation in addition to statin therapy.[34] After 5 years, the EPA treatment group demonstrated a significant 19% reduction in the primary endpoint of any coronary event versus statin therapy.[34] This was the first major CVOT to demonstrate benefit in CV outcomes using EPA.[34,35]

However, the results from JELIS should be interpreted with caution. The trial did not specifically enroll patients with elevated TG levels. A subset analysis of patients with elevated TG levels (≥150 mg/dL) and low HDL-C levels (<40 mg/dL) found that treatment with EPA plus statin therapy demonstrated a significant 53% reduction in major ASCVD events versus statin therapy.[35] Statin intensity was low in the trial, with the majority of patients (90%) taking simvastatin 5 mg or pravastatin 10 mg.[34] These doses are appropriate for the Japanese population but limit the generalizability of the study's results to a contemporary population.[34] The mean LDL-C attained in the trial was approximately 136 mg/dL.[34] Rates of sudden cardiac death, MI, unstable angina, or stroke were not significantly improved with EPA in the overall population, although the study was not powered to analyze these endpoints individually.[34]

REDUCE-IT was a randomized, placebo-controlled, double-blind, international, multicenter trial evaluating the use of a prescription, stable, and purified ethyl ester of EPA, IPE, 4 g/day versus placebo.[19] Eligible patients included those taking statins with elevated (150-499 mg/dL) TG levels at baseline with (1) established CV disease or (2) type 2 diabetes and one additional risk factor for CV disease.[19] The primary efficacy composite endpoint consisted of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina. The trial had a median follow-up of 4.9 years.[19]

The study found that IPE significantly reduced the primary composite endpoint by 25% (17.2% treatment group vs 22% placebo, HR 0.75, $P < 0.001$).[19] There was also a 30% relative risk reduction in total ischemic events with IPE versus placebo.[36] The IPE group also exhibited significantly lower rates of individual CV endpoints versus placebo, including a 20% reduction in death due to CV causes, 31% reduction in MI, and 28% reduction in stroke.[19]

In a prespecified separate analysis of the 3146 patients randomized in the US, IPE therapy also demonstrated a significant 31% relative risk reduction and 6.5% absolute risk reduction in the primary composite endpoint (18.2% vs 24.7%, HR 0.69, $P = 0.000001$).[37] This analysis found that treatment with IPE reduced the key secondary composite endpoint of CV death, nonfatal MI, or nonfatal stroke by 31% versus placebo (12.1% vs 16.6%, HR 0.69, $P = 0.00008$).[37] All-cause mortality was also significantly reduced in this analysis in the IPE group compared with placebo (7.2% vs 9.8%, HR 0.70, 95% CI 0.55-0.90, $P < 0.01$).[37] These benefits occurred independent of baseline TG levels.[19]

In a cost-effectiveness analysis of REDUCE-IT, IPE was reported to be a dominant strategy (ie, cost saving) in 70% of simulations, offering the rare finding of better outcomes at lower healthcare costs. In probabilistic sensitivity analysis, >85% of simulations indicated that IPE would be cost-effective (ie, below $50,000 per quality-adjusted life-year [QALY] gained).[38] A separate independent analysis by the Institute for Clinical and Economic Review reported the incremental cost-effectiveness ratio to be $18,000 per QALY for IPE versus medical management alone.[39]

Subsequent prespecified analyses of REDUCE-IT have further elucidated IPE's benefits in certain high-risk populations. A recent prespecified analysis of REDUCE-IT found that administration of IPE significantly reduced both first and total revascularization events by 34% and 36%, respectively.[40] Another recent prespecified analysis of REDUCE-IT found that in patients with diabetes, IPE reduced the risk of the first and total occurrence of the primary composite endpoint by 23% and 24%, respectively.[41]

Based on all of the available data, the US FDA approved an expanded indication for IPE ethyl to include its use as an adjunct to maximally tolerated statin therapy to reduce the risk of MI, stroke, coronary revascularization, and unstable angina requiring hospitalization in adults with elevated TG levels (≥150 mg/dL) and established CV disease or diabetes mellitus and two or more additional risk factors for CV disease.[18] A generic formulation of IPE is now approved by the FDA and available in the US. However, it is only indicated as an adjunct to diet to reduce TG levels in adults with severe (≥500 mg/dL) hypertriglyceridemia and does not have an indication for CV risk reduction.[42]

The Randomized Trial for Evaluation in Secondary Prevention Efficacy of Combination Therapy—Statin and Eicosapentaenoic Acid (RESPECT-EPA; conducted in Japan) is an open-label trial including approximately 3900 patients with established coronary artery disease on statin therapy.[43] Patients are randomized to statin therapy + 1.8 g/day EPA versus statin therapy alone. The primary endpoint is the occurrence of a major adverse cardiac event, defined as CV death, nonfatal MI, nonfatal cerebral infarction, unstable angina requiring emergent hospitalization and coronary revascularization, and coronary revascularization based on clinical findings.[43,44] The trial is expected to finish enrolling in 2022.[5] A summary of recent OM-3 fatty acid CVOTs is shown in Table 1.[5,19,30-33,43,44]

Pharmacology of IPE

Both EPA and DHA are OM-3 fatty acids that can reduce TG levels; however, they have differing effects on membrane structure, formation of cholesterol domains, platelet activity, and LDL-C levels.[17] In particular, DHA may increase LDL-C levels.[24,45,46] These differing actions may impact the efficacy of therapies meant to lower LDL-C levels.[17]

IPE is a highly purified, stable ethyl ester of EPA.[18,45] Following oral administration, IPE is de-esterified to EPA before being absorbed in the small intestine.[18] The compound then enters the systemic circulation through the lymphatic system.[18] EPA achieves peak plasma concentrations approximately 5 hours after dose administration.[18] A linear dose-dependent relationship has been demonstrated with IPE and EPA levels; however, it does not impact DHA levels.[45,47]

IPE has a mean volume of distribution of approximately 88 L at steady-state.[18] In all studies IPE was administered with or following a meal.[18] Metabolism of IPE primarily occurs in the liver via beta-oxidation, similar to the process for dietary fatty acids.[18] Cytochrome P450-mediated metabolism is a minor elimination pathway.[18] IPE does not undergo excretion through the kidneys and possesses a half-life ($t_{1/2}$) of approximately 89 hours.[18]

Studies suggest that IPE decreases TG levels through 2 conceptual mechanisms. IPE is hypothesized to reduce hepatic very low-density lipoprotein TG synthesis and/or secretion while enhancing TG clearance from circulating very low-density lipoprotein (VLDL).[18] These mechanisms are hypothesized to be achieved through increased β-oxidation, inhibition of acyl-CoA:1,2-diacylglycerol acyltransferase, decreased hepatic lipogenesis, increased plasma lipoprotein lipase activity, and inhibition of VLDL oxidation.[18,48] In addition to lowering TG levels, IPE has also been shown to have anti-inflammatory, anti-coagulant, and endothelial- and plaque-stabilizing pleiotropic effects, which may further explain the CV benefits seen with IPE therapy.[17,45,49]

The recently completed REDUCE-IT EPA analysis evaluated patients in REDUCE-IT to examine EPA levels prior to randomization and during therapy for patients receiving IPE and placebo.[50] Serum EPA levels while on IPE therapy demonstrated a strong correlation with the primary composite endpoint of the study (CV death, MI, stroke, coronary revascularization, and unstable angina), the key secondary endpoint (CV death, MI, and stroke), as well as with the individual components of each endpoint.[50] Dose-response analyses also revealed that a higher serum EPA level while on IPE therapy was significantly associated with a greater reduction in ASCVD events, including CV death. Time-varying covariate analyses revealed that changes in EPA concentration, not lipid biomarkers, accounted for most of the relative risk reduction seen in the IPE group in REDUCE-IT.[50]

The Effect of Vascepa on Improving Coronary Atherosclerosis in People With High Triglycerides Taking Statin Therapy (EVAPORATE) trial evaluated the progression of coronary plaque over 18 months in 80 patients with hypertriglyceridemia (TG levels 135-499 mg/dL) taking IPE 4 g/day versus placebo, in addition to diet and statin therapy. The study found that changes in low-attenuation plaque at baseline and at 18 months were significantly reduced with IPE versus placebo (-0.3 ± 1.5 vs 0.9 ± 1.7 mm^3, $P = 0.006$).[51] In addition, changes in volume were significantly different for total plaque (-9% with IPE vs 11% with placebo; $P = 0.002$), total noncalcified plaque (-19% vs 9%; $P = 0.0005$), fibrofatty plaque (-34% vs 32%; $P = 0.0002$), and fibrous plaque (-20% vs 1%; $P = 0.003$). This study provides evidence that IPE plus statin therapy is associated with slowed plaque progression and provides additional mechanistic data to support IPE's clinical effects.[51]

IPE Safety and Tolerability

IPE is generally well tolerated, although side effects found in postmarketing experience include diarrhea, abdominal discomfort, and pain in the extremities.[18] The risk of an allergic reaction in response to IPE administration in patients with known fish allergies has not been definitively investigated. As such, these patients should be advised to discontinue therapy and seek urgent medical attention if any reactions occur.[18]

In REDUCE-IT, there was a trend toward increased major bleeding in the IPE group compared with the placebo group (2.7% vs 2.1%, $P = 0.06$).[19] However, there were no differences in fatal bleeding events attributable to IPE, no differences in rates of adjudicated hemorrhagic stroke, and a significantly lower rate of anemia in patients given IPE versus placebo.[19] The rate of AF was significantly higher in patients receiving IPE versus placebo (5.3% vs 3.9%, $P < 0.01$).[19] However, the risk of typical sequalae of AF and/or atrial flutter such as stroke, MI, cardiac arrest, and sudden cardiac death was significantly lower in patients given IPE versus placebo.[19] After evaluating the data, the FDA determined that the risk-benefit assessment favors the use of IPE according to its approved label, and to use with caution regarding a potential increase in the risk of AF.[18]

Important Differences Between Dietary Supplements and Prescription OM-3 Fatty Acids

Interest in the potential health benefits of DHA and EPA has increased over the last several years, leading to increased

Table 1. Summary of Recent Omega-3 Fatty Acid Cardiovascular Outcome Trials.

Trial	Omega-3 therapy studied	Dose	Number of patients	Study length	Patient population studied	Primary endpoint	Primary results	Reduction of ASCVD events?
ASCEND[30]	EPA+DHA	840 mg/day	15,480	7.4 years	Patients with diabetes but without known ASCVD	First serious vascular event	No significant difference in rates of serious vascular events	No
VITAL[31]	EPA+DHA	840 mg/day	25,871	5.3 years	Healthy patients with no CV disease, primary prevention trial	Major CV events and invasive cancer of any type	No significant difference in rates of major CV events	No
REDUCE-IT[19]	EPA	4 g/day	8179	4.9 years	Patients with established CV disease or diabetes and 1 CV risk factor; also elevated TG levels and on statin therapy	Composite of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina	Significantly reduced composite primary endpoint of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina	Yes
STRENGTH[32]	EPA+DHA	4 g/day	13,086	Median follow-up 42 months, trial terminated early due to futility	Patients with mixed dyslipidemia at high risk for CV disease and on statin therapy	Composite of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina requiring hospitalization	No significant difference in primary and secondary CV benefits; increased risk of atrial fibrillation in the omega-3 carboxylic acid group vs placebo group	No
OMEMI[33]	EPA+DHA	1.8 g/day	1027	2 years	Elderly patients who experienced an acute MI	Composite of nonfatal MI, unscheduled revascularization, stroke, all-cause death, and heart failure hospitalization	No difference in the primary endpoint between the EPA+DHA- and placebo-treated patients, including no difference in all-cause mortality	No
RESPECT-EPA[5,43,44]	EPA	1.8 g/day	Approximately 3900	Planned 5 years (ongoing)	Patients with coronary artery disease on statin therapy	Major adverse cardiac events	Ongoing	Ongoing

Abbreviations: ASCEND, A Study of Cardiovascular Events in Diabetes; ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; MI, myocardial infarction; OMEMI, Omega-3 Fatty Acids in Elderly Patients with Myocardial Infarction; REDUCE-IT, Reduction of Cardiovascular Events with Icosapent Ethyl-Interventional Trial; STRENGTH, Outcomes Study to Assess Statin Residual Risk Reduction with Epanova in High CV Risk Patients with Hypertriglyceridemia; TG, triglycerides; VITAL, Vitamin D and Omega-3 Trial; RESPECT-EPA, Randomized Trial for Evaluation in Secondary Prevention Efficacy of Combination Therapy—Statin and Eicosapentaenoic Acid.

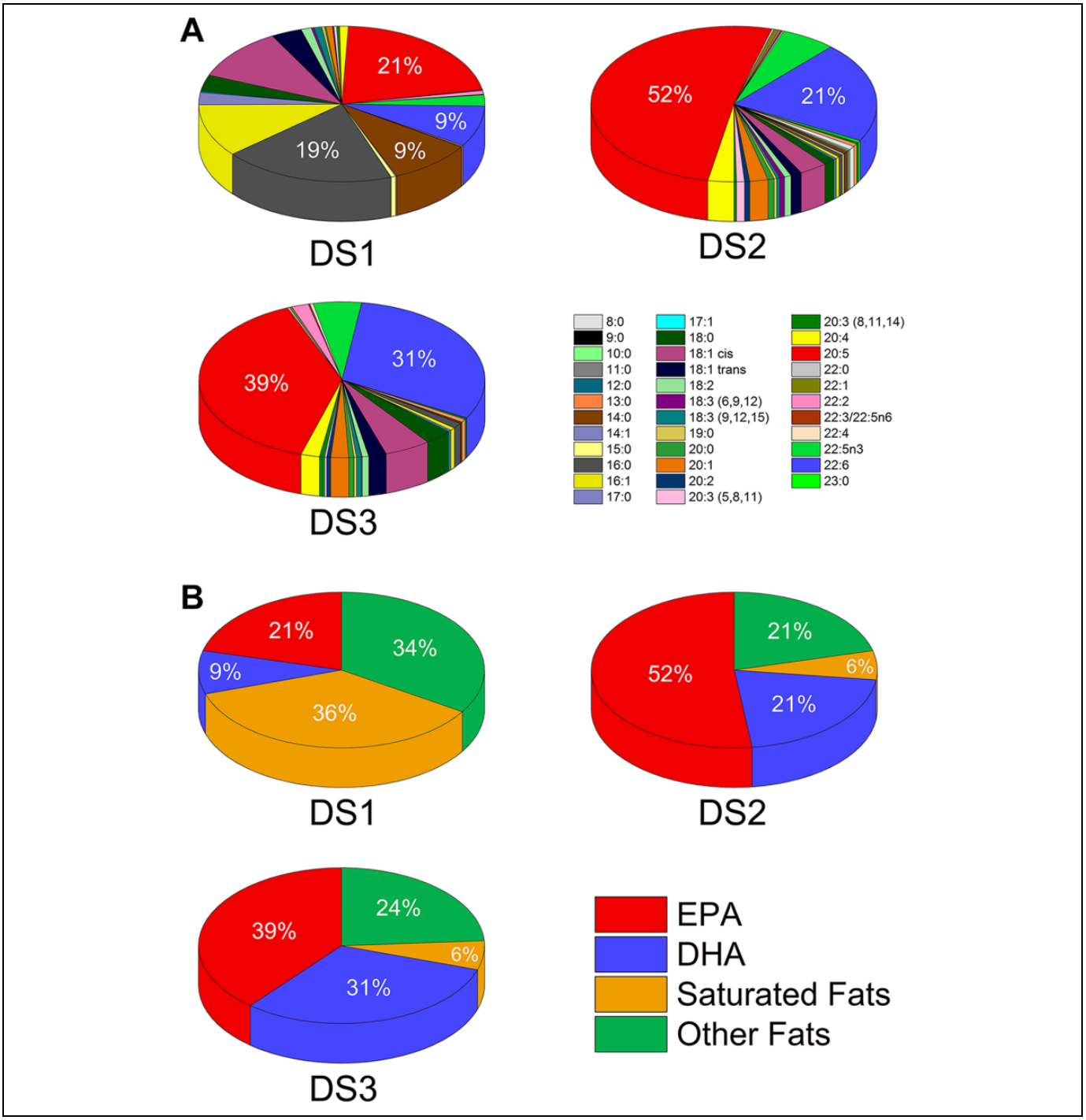

Figure 1. Fatty acid (FA) content of 3 top-selling fish oil dietary supplements (DS1, DS2, and DS3) in the United States. A, The content of individual FAs within each DS was determined by GC-FID analysis and are shown using the carbon nomenclature. Each DS contained more than 30 different FAs, including 10 to 14 different saturated fat species comprising up to 36% of the total FA content. Levels of total omega-3 FAs (ALA [18:3], EPA [20:5], DPA [22:5], and DHA [22:6]) also varied widely among the DS (33%-79%). Data are presented as % of total FA (for a given DS sample) by weight. B, EPA, DHA, saturated fats, and other fats (consisting of mono- and polyunsaturated FAs). Data are presented as % of total FA (for a given DS sample) by weight. ALA indicates alpha linolenic acid; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; DS, dietary supplement; EPA, eicosapentaenoic acid; GC-FID, gas chromatography with flame ionization detection. Reproduced with permission from Mason and Sherratt,[57] noncommercial 4.0 international (CC BY-NC 4.0), https://creativecommons.org/licenses/by-nc/4.0/legalcode.

Table 2. Comparison of Rx and Dietary Supplement Omega-3 Products.[a]

Features	Rx pure EPA	Rx DHA+EPA	Dietary supplements
Highly purified, quality controlled	✓	✓	May contain unwanted/harmful ingredients
Contains EPA	✓	✓	Usually/highly variable
Contains DHA	x	✓	Usually/highly variable
Not expected to affect LDL-C	✓	x	x
Approved to treat TG >500 mg/dL	✓	✓	Not FDA approved to treat any disease or medical condition
Proven CVOT efficacy on background statin therapy	✓	x	x
Substitution/equivalence	–	Not equivalent to Rx pure EPA and should not be substituted	Not equivalent to and should not be substituted for Rx

Abbreviations: CVOT, cardiovascular outcomes trial; DHA, docosahexaenoic acid; FDA, Food and Drug Administration; EPA, eicosapentaenoic acid; LDL-C, low-density lipoprotein cholesterol; Rx, prescription; TG, triglycerides.

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availability of fish oil dietary supplements (FODS).[24] However, patients often do not include their providers in the decision to select and take FODS.[52]

Dietary supplements serve as products intended to further augment nutritional value gained from diet.[53] This includes vitamins, minerals, herbs/botanicals, and amino acids.[53] It is important to note that while dietary supplements are intended to be used for general consumer health, they are not intended or approved to treat diagnosed medical conditions.[53] Dietary supplements are also not required to undergo placebo-controlled trials to demonstrate safety and efficacy.

FODS are considered dietary supplements and therefore do not fall under the same FDA regulatory requirements as prescription products.[54] Due to the lack of oversight and consistency, FODS may contain inconsistent amounts of EPA and/or DHA, which can often be incongruent with labeled quantities.[55] The purity of FODS is also unregulated, and products have been found to contain contaminants such as oxidation lipids, saturated fats, and cholesterols, which may have the unintended effect of contributing to CV disease risk (Figure 1).[54,55] FODS typically provide small amounts of EPA and/or DHA per capsule and would require an unreasonable quantity of capsules to achieve similar doses to prescription therapies.[24] Patients may be inclined to substitute FODS for a prescription product due to perceptions regarding potential cost, convenience, or equivalence. This is an important area for patient education and intervention. Table 2 highlights important clinical considerations regarding differences among FODS, prescription DHA+EPA products, and prescription EPA products. In light of efficacy, safety, and regulatory considerations, FODS should not be substituted for prescription OM-3 therapies.[56]

Conclusion

As research continues in the optimal management of dyslipidemia, additional therapies beyond statin therapy are warranted. The OM-3 fatty acids DHA and EPA each have unique chemical properties and exhibit different pharmacologic effects that may be important in understanding risk reduction in CV disease. However, only EPA has been shown to reduce ASCVD risk in large CVOTs. Combination EPA+DHA formulations have not consistently demonstrated CV benefit in addition to statin therapy.

REDUCE-IT revealed that the addition of IPE to statin therapy reduced the risk of ASCVD events. While initially approved as a TG-lowering drug, IPE possesses unique pharmacologic characteristics and effects beyond TG lowering that may contribute to understanding its ability to reduce the risk of ASCVD. Clinicians should consider this unique emerging therapy and educate their patients at risk for CV disease on its important benefits.

Author Contributions

All authors provided direction, critical review, and revision of the manuscript and approved the final version for submission.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article. Dhiren Patel: Speakers Bureau—Amarin, AstraZeneca, Boehringer Ingelheim, Dexcom, Lilly, Merck, Novo Nordisk, Xeris, Zealand; Consultancy—Amarin, Bayer, Dexcom, Lilly, Insulet, Sanofi. Robert Busch: Speakers Bureau—Amarin, AstraZeneca; Research Support—Amarin, AstraZeneca.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Medical writing assistance was provided to the authors by Mona Shah, PharmD, Rohan Shah, MD, MPH, and Jim Wood from Peloton Advantage LLC, an OPEN Health company, and was funded by Amarin Pharma, Inc.

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