Strategies to improve bioavailability of omega-3 fatty acids from ethyl ester concentrates

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Purpose of review
To describe recent strategies that have been developed to enhance absorption of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from dietary supplements.

Recent findings
The long-chain omega-3 fatty acids EPA and DHA have important physiologic functions, and numerous potential health benefits have been suggested by results from observational studies and randomized, controlled trials. EPA and DHA intakes in the average American diet are substantially below recommended levels. Dietary supplements are available for consumers wishing to increase their intakes, but many of these are in ethyl ester formulations from which EPA and DHA are poorly absorbed when consumed without a meal containing dietary fat. Technologies have been developed to enhance EPA and DHA absorption through in-situ emulsification, which facilitates bioavailability, even in the absence of a fat-containing meal. Findings from randomized controlled trials of absorption enhancers incorporated into omega-3 fatty acid supplements demonstrate that they can markedly improve the bioavailability of EPA and DHA.

Summary
The development of absorption enhancement technology to increase bioavailability of long-chain omega-3 fatty acids has important implications for studies on the health effects of dietary supplement and pharmaceutical products containing EPA and/or DHA.

Keywords
bioavailability, dietary supplements, docosahexaenoic acid, eicosapentaenoic acid, omega-3 fatty acids

INTRODUCTION

Omega-3 fatty acids are polyunsaturated fatty acids (PUFA) with the first double bond in the omega-3 position on the carbon chain. The most common omega-3 fatty acids in the diet of developed countries are alpha-linolenic acid (alpha-linolenic acid (ALA); 18 : 3 omega-3), eicosapentaenoic acid (EPA; 20 : 5 omega-3) and docosahexaenoic acid (DHA; 22 : 6 omega-3) [1–3]. Common food sources of ALA include flaxseed, walnuts, soy and canola oils, whereas EPA and DHA are mainly consumed in cold-water fish, fish oils and other marine sources. Long-chain omega-3 PUFA, that is, EPA and DHA along with docosapentaenoic acid (DPA; 22 : 5 omega-3), which is an intermediary between EPA and DHA, have numerous physiologic functions and higher intake has potential health benefits [2,4,5]. Some of the benefits that have been suggested by results from observational studies and/or randomized controlled trials (RCTs) include lowering of blood pressure and heart rate, reducing propensity for thrombosis, decreasing plasma triglycerides, reducing systemic vascular resistance, reducing myocardial fibrosis, lessening inflammation, and supporting maintenance of normal neurological function [2,4]. Because of their myriad of potential effects, supplementation of omega-3 fatty acids has been studied in a variety of diseases/conditions, such as cardiovascular disease (CVD) childhood asthma/allergies, depression, attention-deficit/hyperactivity disorder, Alzheimer's disease, dementia and reduced cognitive function, brain trauma, infant health, cancer, age-related macular degeneration, rheumatoid arthritis, inflammatory bowel disease and cystic fibrosis [6].

The US Department of Agriculture, Health and Human Services recommends consumption of 8–12 oz/week of a variety of seafood as the prime

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Curr Opin Clin Nutr Metab Care 2019, 22:116–123

DOI:10.1097/MCO.0000000000000537

KEY POINTS

- Omega-3 fatty acids in ethyl ester form are substantially less bioavailable than triglyceride or phospholipid forms when consumed in a fasting state or with a low-fat meal.
- Failure to demonstrate significant heart disease reduction in a majority of clinical trials of omega-3 fatty acids is likely due, in part, to low EPA and DHA dosages and possibly suboptimal absorption from standard omega-3 ethyl ester products.
- Recent developments with absorption enhancement technology demonstrate markedly improved long-chain omega-3 fatty acid absorption from ethyl esters.
- Development of products containing absorption enhancers can be expected to increase the ability to raise omega-3 tissue status with ethyl ester formulations to levels that have been associated with health benefits in observational studies.

dietary source of EPA and DHA [7]. The American Heart Association encourages the intake of approximately two servings per week of fish rich in EPA and DHA, to achieve an average intake of at least 250 mg/day EPA and DHA [8]. However, the current US diet provides a quantity of omega-3 fatty acids below recommended levels; mean usual intakes of EPA and DHA are 23 and 63 mg/day, respectively [4,8–10]. Thus, omega-3 supplementation may be prudent for some individuals, especially those who do not regularly eat coldwater fish.

There are more than 300 omega-3 products listed in the US National Institutes of Health Dietary Supplement Label Database [3,6,11]. These vary widely in the amount of EPA and DHA they provide. Prescription omega-3 fatty acid products are also available with higher concentrations of EPA and DHA per gram of oil. These are approved as an adjunct to diet to reduce triglyceride levels in adults with severe hypertriglyceridemia (triglycerides $\geq$500 mg/dl) and include omega-3 acid ethyl esters (Lovaza/Omacor or Omtryg) providing 465 mg EPA and 375 mg DHA per 1 g capsule, icosapent ethyl (Vascepa) providing 960 mg EPA ethyl esters per 1 g capsule, and a free fatty acids formulation (omega-3 carboxylic acids; Epanova) providing 850 mg PUFA (EPA and DHA most abundant) per 1 g capsule [11]. Lovaza and Vascepa are approved for 4 g/day capsule dosages, whereas Epanova is approved for use at both 2 and 4 g/day capsule dosages.

Many dietary supplement products and some of the pharmaceuticals currently marketed contain EPA and DHA in ethyl ester formulations. Recently, absorption-enhancing technologies have been developed to increase EPA and DHA bioavailability in omega-3 products. This review will discuss the bioavailability of different omega-3 fatty acid forms, and describe studies conducted using strategies recently developed to enhance EPA and DHA absorption from supplements and pharmaceuticals.

RELATIVE BIOAVAILABILITY OF LONG-CHAIN OMEGA-3 POLYUNSATURATED FATTY ACIDS FORMULATIONS

In pharmacology, bioavailability is a subcategory of absorption and is defined as the fraction of an administered dose of a drug that reaches the systemic circulation and is thus assumed to be available to exert physiologic effects on tissues [12]. The same basic principles apply to bioavailability of nutrients and relative bioavailability is typically assessed by comparing the incremental area under the curve after ingestion of a supplement product compared with a standard reference product [13,14]. There are several factors with the potential to affect the bioavailability of long-chain omega-3 fatty acids including [3,11]:

(1) *Chemical form in which the fatty acids are delivered*: Long-chain omega-3 fatty acids can be formulated as triglycerides, phospholipids, ethyl esters, or free fatty acids (carboxylic acids).
(2) *Form in which the fatty acids are ingested*: Long-chain omega-3 fatty acids can be ingested in foods, capsules, tablets, powders, liquids, or gummies. The main sources of long-chain omega-3 fatty acids include fish oils, oils extracted from crustaceans such as krill, and oils derived from algae.
(3) *Food effects*: The degree to which the long-chain omega-3 fatty acids EPA and DHA are absorbed is influenced by co-ingestion of other foods. When a meal containing fat is ingested, this triggers the release of bile, which emulsifies fats and promotes the formation of mixed micelles. Micelles increase the surface area available to digestive enzymes and assist with the translocation of fatty acids liberated through digestion to the intestinal brush border for absorption. For all food and chemical forms of long-chain omega-3 fatty acids, absorption is lowest when consumed in the fasting state, highest when consumed with a high-fat meal, and intermediate when consumed with a low-fat meal.

In an examination of EPA absorption when administered in different forms to eight patients, Lawson *et al*. demonstrated that, when expressed as a percentage of that for ALA as a reference standard, absorption of free-fatty acid EPA was 95%, EPA from triglycerides was 68% and EPA in ethyl esters was 20% [15,16]. Unlike triglycerides and phospholipids, which are hydrolyzed principally by colipase-dependent pancreatic lipase, ethyl esters require additional digestion with carboxyl ester lipase, also known as bile salt-dependent lipase [14].

In the Epanova Compared to Lovaza in a Pharmacokinetic Single-dose Evaluation (ECLIPSE I) study, a randomized, open-label trial, the relative bioavailability of EPA and DHA from single 4 g doses of omega-3 free fatty acids (carboxylic acids; Epanova) or omega-3 acid ethyl esters (Lovaza) along with a low-fat diet (with the product administered to subjects while fasting) and high-fat diet were compared in 54 overweight adults [17]. The baseline-adjusted area under the curve from 0 to 24 h ($AUC_{0-24\,h}$) for total EPA plus DHA during the low-fat (fasting) period was four-fold greater with the omega-3 free fatty acid form compared with the ethyl ester form (Table 1). During the high-fat period, the $AUC_{0-24\,h}$ was 1.3-fold greater for the free fatty acid vs. ethyl ester form. Notably, for both the free fatty acid and ethyl ester formulations, the $AUC_{0-24\,h}$ were markedly enhanced by the consumption of the high-fat meal, although the meal effect was much larger for ethyl esters (5.4-fold) than for free fatty acids (1.6-fold).

Offman *et al.* [18] extended the results from ECLIPSE I by studying steady-state bioavailability after 14 days of consumption of free fatty acid omega-3 or ethyl ester omega-3 formulations under low-fat dietary conditions in 52 healthy male and female subjects in ECLIPSE II. Baseline-adjusted $AUC_{0-24\,h}$ values were approximately 5.8-fold and 6.5-fold higher for the free fatty acids relative to ethyl esters (Table 1).

Several studies have compared the acute and chronic bioavailability of long-chain omega-3 fatty acids from phospholipids with that from other forms, mainly triglycerides [19,20]. The results have consistently shown greater absorption from phospholipids [19,20]. Thus, the gradient of bioavailability from lowest to highest for different chemical forms is ethyl esters, then triglycerides, phospholipids, and finally free fatty acids (carboxylic acids).

OMEGA-3 ASBORPTION ENHANCERS

An emulsion is a mixture of two or more liquids that are normally immiscible (i.e. unable to be blended), with the prototypical example being oil and water. An emulsifier is a substance that stabilizes an emulsion. These typically have a polar (hydrophilic) portion and a nonpolar (hydrophobic or lipophilic) portion and, in the body, facilitate the formation of microdroplets that allow dispersion of lipid in aqueous media, such as blood and the contents of the intestines.

Coingestion of emulsifiers with fish oil has been shown to enhance the digestion and absorption of its omega-3 fatty acids, which are mainly in triglyceride form [14]. Raatz *et al.* [21] had 10 subjects consume 4 g of an emulsified fish oil supplement or four 1 g capsules of triglyceride fish oil, after which plasma phospholipid fatty acids were measured periodically over 48 h. Total omega-3 phospholipid fatty acid levels were enhanced with the emulsified supplement compared with the fish oil capsules: change from baseline of 0.67% for emulsified product vs. 0.45% with the fish oil capsules ($P \le 0.05$). EPA absorption was also increased: change from baseline of 0.34% for emulsified product vs. 0.23% with the fish oil capsules ($P \le 0.05$).

New technologies have been developed to enhance omega-3 fatty acid absorption including Advanced Lipid Technologies (ALT) and Self-Micro-Emulsifying Delivery System (SMEDS; Accelon). The

Table 1. Total eicosapentaenoic acid plus docosahexaenoic acid baseline-adjusted change after a single 4 g dose of omega-3 carboxylic acids and omega-3 ethyl esters during low-fat (fasting) and high-fat periods in the ECLIPSE I ($n = 51$) and ECLIPSE II trials ($n = 52$)[a]

	Geometric LS mean, h × nmol/ml			
	Carboxylic acids	**Ethyl esters**	**Ratio of LS geometric means**	**90% CI**
ECLIPSE I				
Low-fat	2650	662	4.0	3.3–4.9
High-fat	4604	3589	1.3	1.2–1.4
ECLIPSE II	19 111	3320	5.7	4.5–7.4

Original table based on data from references [17,18].

[a]Carboxylic acid capsules contained 850 mg polyunsaturated fatty acids, including multiple omega-3 fatty acids (EPA and DHA most abundant) per 1 g capsule (Epanova); ethyl ester capsules contained 465 mg EPA and 375 mg DHA per 1 g capsule (Lovaza). In the low-fat period, the product was actually administered in the fasting state, followed by low-fat lunch and dinner meals (after 4 and 12 h, respectively). CI, confidence interval; DHA, docosahexaenoic acid; ECLIPSE, Epanova Compared to Lovaza in a Pharmacokinetic Single-dose Evaluation; EPA, eicosapentaenoic acid; LS, least squares.

ALT platform is a patented formulation engineered to spontaneously form micelles and mimic the natural release of fats and bile salts [22,23,24■]. In an aqueous medium, ALT forms oil micelles that permit consistent absorption of EPA and DHA, even under low-fat feeding conditions. The SMEDS Accelon ingredient enables rapid emulsification and microdroplet formation upon entering the aqueous environment of the gut, thereby enhancing absorption of EPA and DHA [25,26■■].

The bioavailability of SC401 (a product containing 1530 mg EPA and DHA from ethyl esters and the absorption enhancer ALT) was compared with 3600 mg EPA and DHA from ethyl esters (4 g Lovaza) under low-fat feeding conditions in a phase 1, randomized, open-label, single-dose crossover study in 24 healthy subjects [24■]. Dose- and baseline-adjusted analyses showed that SC401 produced an $AUC_{0\text{-last}}$ EPA plus DHA geometric mean value that was higher by a factor of 2.8 compared with the reference product.

Qin *et al.* reported results from two single-dose crossover studies in healthy adults ($n = 20$ and $n = 40$ subjects) that examined the relative bioavailability of a SMEDS formulation of omega-3 ethyl esters (PRF-021) compared with standard omega-3 ethyl esters [26■■]. One study administered lower doses: 630 mg EPA plus DHA in PRF-021 vs. 840 mg EPA plus DHA in standard ethyl esters (1 g Lovaza), and the other study administered higher doses: 1680 mg EPA plus DHA in PRF-021 vs. 3360 mg EPA plus DHA in standard ethyl esters (4 g Lovaza). Total EPA plus DHA absorption based on the ratio of baseline-corrected, dose-normalized $AUC_{0-24\,h}$ from the SMEDS formulation was 6.2 and 9.6 times higher compared with standard ethyl esters in the lower dose and higher dose studies, respectively (Table 2). The relative absorption improvement was more pronounced for EPA than DHA. In the lower-dose study, baseline-corrected, dose-normalized EPA $AUC_{0-24\,h}$ was 24-fold higher for PRF-021 vs. standard ethyl esters. In the higher dose study, EPA $AUC_{0-24\,h}$ was 26-fold higher for PRF-021 vs. standard ethyl esters. For DHA in the lower-dose study, $AUC_{0-24\,h}$ was 3.6-fold higher with PRF-021 vs. standard ethyl esters, and in the higher dose study, it was 5.6-times higher.

Our group recently examined the bioavailability of EPA and DHA from ethyl esters administered in a slightly different proprietary formulation containing SMEDS from that studied by Qin *et al.* [27■]. In this randomized, crossover study, 23 healthy men and women consumed a capsule containing 500 mg EPA plus DHA in a SMEDS formulation and a capsule containing 840 mg EPA plus DHA in a standard ethyl ester formulation (1 g Lovaza) under fasting conditions. The $AUC_{0-24\,h}$ least squares geometric mean ratio for SMEDS:standard ethyl esters was 8.2 [95% confidence interval (CI) 4.3–15.5) indicating markedly higher bioavailability of EPA plus DHA with the SMEDS formulation compared with standard ethyl esters (Table 2). This was also true separately for EPA (geometric mean ratio 18.2, 95% CI 10.3–32.3) and DHA (geometric mean ratio 4.5, 95% CI 2.6–7.7). The average of the absorption multipliers (geometric mean ratios) for EPA plus DHA reported for the Qin studies (6.2 and 9.6) and our study (8.2) is ~8.0, suggesting marked increases in EPA and DHA bioavailability that do not appear to be dose-dependent.

A study by West *et al.* [28■] 'confirmed previous findings from acute investigations of SMEDS and extended them to chronic consumption. Healthy subjects ($n = 80$) were randomly assigned to consume a single dose of one of two EPA plus DHA SMEDS preparations containing 1.2–1.3 g/day of

Table 2. Baseline-adjusted, dose-normalized $iAUC_{0-24\,h}$ for eicosapentaenoic acid plus docosahexaenoic acid after a single dose of self-microemulsifying delivery system or standard ethyl esters formulations in studies by Qin *et al.* [low-dose ($n = 19$) and high-dose ($n = 35$)] and Maki *et al.* ($n = 23$)[a]

	Geometric LS mean, h × μg/ml/g			
	SMEDS	**Standard ethyl esters**	**Ratio of LS geometric means**	**95% CI**
Qin *et al.*				
Low-dose	331	53.2	6.2	4.3–9.0
High-dose	331	35.7	9.6	7.0–13.1
Maki *et al.*	475	58.0	8.2	4.3–15.5

Original table based on data from references [26■■,27■].
[a]In Qin *et al.*, the low-dose study administered 630 mg EPA plus DHA in a SMEDS formulation vs. 840 mg EPA plus DHA in standard ethyl esters (1 g Lovaza); the high-dose study administered 1680 mg EPA and DHA in a SMEDS formulation vs. 3360 mg EPA plus DHA in standard ethyl esters (4 g Lovaza). In Maki *et al.*, the doses used were 500 mg EPA plus DHA in a SMEDS formulation and 840 mg EPA plus DHA in a standard ethyl ester formulation (1 g Lovaza). Dosing was in the fasting state, with lunch provided 4.5 h later. CI, confidence interval; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; $iAUC_{0-24\,h}$, incremental area under the curve from 0–24 h; LS, least squares; SMEDS, Self-Microemulsifying Delivery System.

EPA plus DHA (EPA:DHA ratio in one formulation was ~1.25 and in the other formulation was ~0.44), or standard EPA or DHA ethyl ester formulations without a meal (fasting). EPA and DHA were measured in plasma for 24 h. Subjects also continued to take a single dose of the assigned products each morning before breakfast for 12 weeks. EPA and DHA were measured in fasting plasma, mononuclear cells and red blood cells. Results demonstrated that EPA and DHA concentrations were higher with SMEDS vs. standard ethyl ester products after both acute and repeated dosing. The effects on the omega-3 index, which is the erythrocyte membrane EPA plus DHA as a percentage of total phospholipid fatty acids, were also reported. The omega-3 index serves as a marker of chronic EPA and DHA bioavailability, and its values correlate strongly with levels of EPA and DHA in buccal, cardiac and other tissues [29]. It is also widely available for clinical and research applications [29–31]. Chronic consumption of the SMEDS-containing EPA plus DHA supplements produced larger increases in the omega-3 index than similar dosages of EPA plus DHA in the standard ethyl ester formulations that lacked the SMEDS component [28▪]. Baseline omega-3 index values for the higher EPA SMEDS and non-SMEDS formulations and the higher DHA SMEDS and non-SMEDS formulations were 5.1 ± 0.9, 5.3 ± 1.1, 4.8 ± 0.8 and $5.2 \pm 0.9\%$, respectively. At the end of treatment, the omega-3 index values were significantly higher with the SMEDS formulations compared with the non-SMEDS formulations ($P < 0.001$ for all): SMEDS-EPA, $7.9 \pm 0.9\%$ vs. non-SMEDS-EPA, $6.4 \pm 0.9\%$ and SMEDS-DHA, $9.0 \pm 1.2\%$ vs. non-SMEDS-DHA, $7.2 \pm 1.0\%$.

OMEGA-3 FATTY ACIDS AND REDUCTION OF CARDIOVASCULAR DISEASE RISK

Observational studies have shown that higher long-chain omega-3 PUFA intakes and biomarker status are associated with lower risk for CVD, particularly cardiac death [32–34,35▪,36▪]. However, results from RCTs of the effects of omega-3 supplementation on CVD endpoints have been mixed [1,35▪–37▪,38,39▪]. Different conclusions were reached by the investigators in four recent meta-analyses of RCT data regarding the effects of supplemental omega-3 PUFA intakes on CVD endpoints. However, limitations in the available RCT data need to be acknowledged, including the following:

(1) Low dosages administered in most trials: median of ~840 mg/day of EPA plus DHA in ethyl ester formulations that have poor bioavailability when not consumed with a fat-containing meal;
(2) Failure to assess omega-3 status before and during treatment;
(3) Absence of a clear biological target or pathophysiologic hypothesis for the intervention.

A meta-analysis of 19 cohort studies conducted by Del Gobbo *et al.* [34] investigated the relationships between biomarkers of omega-3 status and cardiovascular outcomes. Results showed that each 1-standard deviation (SD) increase in plasma total long-chain omega-3 fatty acids (EPA plus DHA plus DPA) was associated with reduced risk for fatal coronary heart disease (CHD). The relative risk (RR) for plasma total omega-3 was 0.84 (95% CI 0.72–0.97) and for plasma phospholipids was 0.88 (95% CI 0.80–0.96). Harris *et al.* have shown that levels of plasma and plasma phospholipid long-chain omega-3 fatty acids correlate strongly with the omega-3 index, and regression equations have been published to allow estimation of the omega-3 index from these values [29,40,41]. Conversion of the total plasma and plasma phospholipid values from 10 cohorts in the Del Gobbo analysis to omega-3 index equivalents resulted in weighted mean $\pm$ SD values of $6.1 \pm 2.1\%$ and a RR for fatal CHD of 0.85 (95% CI 0.80–0.91) for each 1-SD increase in omega-3 index [34,40].

In the study by West *et al.* described previously, supplements providing ~1.25 g/day of EPA plus DHA ethyl esters without SMEDS increased the omega-3 index by an average of 1.8%, or 0.86 SDs based on the estimate of 2.1% for the population SD [28▪,40,42]. The estimated effect on omega-3 index would, therefore, be ~1.2% or ~0.57 SDs. Using the estimate of a RR of 0.85 per SD increase in omega-3 index from prospective cohort studies [40], this translates to an expected reduction in fatal CHD of $1 - 0.85^{0.57} = 0.088$, or 8.8% [42]. This is consistent with the results reported in four recent meta-analyses of RCT data for the outcomes of CVD death, coronary death or cardiac death, which reported pooled RR (95% CI) estimates of 7% (0–15%) [39▪], 7% (−9 to 21%) [37▪], 8% (1.6–13.9%) [36▪] and 19% (0–35%) [35▪]. Thus, it is plausible to suggest that higher effective dosages and/or inclusion of an absorption enhancer might result in larger reductions in risk for cardiac death.

Ongoing and recently completed RCTs of long-chain omega-3 PUFA interventions include: Reduction of Cardiovascular Events with EPA – Intervention Trial (REDUCE-IT), Statin Residual Risk Reduction with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia (STRENGTH), A Study of Cardiovascular Events in Diabetes (ASCEND) and Vitamin D and Omega-3 Trial (VITAL) [38]. Among these, only REDUCE-IT and STRENGTH employed higher dosages of long-chain omega-3 PUFAs. These studies also enrolled subjects with elevated triglycerides who were at high risk for a CVD event. Therefore, we have viewed these as trials that did not share the main limitations in the designs of many previous studies.

Recently, the results from REDUCE-IT were published, a global study of 8179-statin treated adults with hypertriglyceridemia and elevated cardiovascular risk followed for a median of 4.9 years. There was a risk reduction of 25% (hazard ratio 0.75, 95% CI 0.68–0.83, $P<0.001$) in the primary composite endpoint of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina among subjects who took 4 g/day EPA ethyl esters (icosapent ethyl) vs. placebo [43■■]. The key secondary composite endpoint of cardiovascular death, nonfatal myocardial infarction and nonfatal stroke also showed a significant benefit with EPA treatment (hazard ratio 0.74, 95% CI 0.65–0.83, $P<0.001$). This confirms that EPA, administered at a higher dosage than employed in most previous trials, did lower risk among statin-treated patients with elevated triglycerides. At present, it is unclear to what degree the benefit can be attributed to lowering of triglycerides and triglyceride-rich lipoproteins vs. other mechanisms. Nevertheless, these results represent an important step forward in understanding the potential for long-chain omega-3 fatty acid administration to lower CVD risk.

The results from VITAL, a trial in which 25 871 subjects at 'usual risk' received 2000 IU/day vitamin D and/or a 1 g/day fish oil concentrate capsule (Omacor/Lovaza containing 840 mg EPA plus DHA ethyl esters) in a two-by-two factorial design, were also recently published [44]. Omega-3 fatty acids did not result in a lower incidence than placebo in the primary cardiovascular composite endpoint of myocardial infarction, stroke or death from cardiovascular causes (hazard ratio 0.92, 95% CI 0.80–1.06, $P=0.24$) during a median follow-up of 5.3 years. However, secondary outcomes of total myocardial infarction (hazard ratio 0.72, 95% CI 0.59–0.90), total CHD (hazard ratio 0.83, 95% CI 0.71–0.97), and death from myocardial infarction (hazard ratio 0.50, 95% CI 0.26–0.97) were significantly lower in the group receiving the long-chain omega-3 fatty acid supplement.

The ASCEND trial employed the same low dosage (1 g/day of Omacor/Lovaza containing 840 mg/day of EPA and DHA as ethyl esters) used in most prior studies [45]. The results were consistent with those from prior studies in that they did not show a benefit for the primary composite CVD outcome variable, but did show a trend toward reduced CHD death (hazard ratio 0.79, 95% CI 0.61–1.02). There was also a statistically significant reduction in vascular death (hazard ratio 0.82, 95% CI 0.68–0.98), which included coronary, sudden, stroke, and pulmonary embolism deaths. Notably, omega-3 index was measured in a subset of ~1% of patients and showed that there was no material change in the placebo group (6.6% at baseline and 6.5% at follow-up), whereas the index increased from 7.1 to 9.1% in the omega-3 fatty acid group, resulting in a net difference of 2.1% in the change from baseline, and a difference between groups of 2.6% at the end of the trial.

Taken together with results from prior studies, the results from VITAL and ASCEND support a modest benefit of low-dosage omega-3 fatty acids (840 mg/day EPA plus DHA from ethyl esters) on risk for CHD death in high-risk patients. Additional research is needed on higher dosages of EPA plus DHA that produce larger differences in measures of omega-3 status, such as the omega-3 index. The lower risk for fatal and nonfatal CVD events in the REDUCE-IT trial with 4 g/day of EPA ethyl esters vs. placebo in statin-treated patients with hypertriglyceridemia underscores the potential for higher dosages of long-chain omega-3 fatty acids to produce cardiovascular benefits. Absorption enhancement technology has the potential to enhance the practicality of achieving larger changes in omega-3 status with omega-3 ethyl esters, with less concern about the need to consume the supplement or pharmaceutical product with a fat-containing meal.

CONCLUSION

In conclusion, findings from RCTs of absorption enhancement technologies demonstrate that they can markedly improve the bioavailability of EPA and DHA from ethyl esters. Some combination of higher omega-3 fatty acid dosage and increased EPA and DHA bioavailability facilitated by absorption enhancers should allow expansion of research to more fully evaluate the ability of long-chain omega-3 fatty acid supplementation to lower CVD risk and facilitate other areas of research into potential benefits of increasing long-chain omega-3 tissue status.

Acknowledgements

The authors would like to thank Kymberley Lanza of Midwest Biomedical Research for administrative assistance during the development of this article.

Financial support and sponsorship

None.

Conflicts of interest

K.C.M. has received research funding and/or consulting fees from AstraZeneca, DSM, GOED, Kowa, Sancilio & Co., Pharmavite and Acasti Pharma. As an employee of

Midwest Biomedical Research, M.R.D. has worked on projects funded by AstraZeneca, DSM, GOED, Kowa, Sancilio & Co., Pharmavite and Acasti Pharma.

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▪ of special interest
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