View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Elsevier - Publisher Connector

Atherosclerosis 230 (2013) 381–389

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Review

Update on marine omega-3 fatty acids: Management of dyslipidemia and current omega-3 treatment options

Howard Weintraub*

New York University School of Medicine Center for the Prevention of Cardiovascular Disease, 530 First Avenue, Suite 9U, New York, NY 10016, United States

ARTICLE INFO

Article history:
Received 5 December 2012
Received in revised form
18 July 2013
Accepted 19 July 2013
Available online 31 July 2013

Keywords:
Eicosapentaenoic acid
Docosahexaenoic acid
Dyslipidemia
Fish oil
Omega 3 fatty acid

ABSTRACT

Low-density lipoprotein cholesterol (LDL-C) is currently the primary target in the management of dyslipidemia, and statins are first-line pharmacologic interventions. Adjunct therapy such as niacins, fibrates, bile acid sequestrants, or cholesterol absorption inhibitors may be considered to help reduce cardiovascular risk. This review discusses the need for alternative adjunct treatment options and the potential place for omega-3 fatty acids as such. The cardiovascular benefits of fish consumption are attributed to the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and a variety of omega-3 fatty acid products are available with varied amounts of EPA and DHA. The product types include prescription drugs, food supplements, and medical foods sourced from fish, krill, algal and plant oils or purified from these oils. Two prescription omega-3 fatty acids are currently available, omega-3 fatty acid ethyl esters (contains both EPA and DHA ethyl esters), and icosapent ethyl (IPE; contains high-purity EPA ethyl ester). A pharmaceutical containing free fatty acid forms of omega-3 is currently in development. Omega-3 fatty acid formulations containing EPA and DHA have been shown to increase LDL-C levels while IPE has been shown to lower triglyceride levels without raising LDL-C levels, alone or in combination with statin therapy. In addition, recent studies have not been able to demonstrate reduced cardiovascular risk following treatment with fibrates, niacins, cholesterol absorption inhibitors, or omega-3 fatty acid formulations containing both EPA and DHA in statin-treated patients; thus, there remains a need for further cardiovascular outcomes studies for adjunct therapy.

© 2013 The Author. Published by Elsevier Ltd. Open access under CC BY-NC-ND license.

Contents

* Tel.: +1 212 599 5030; fax: +1 212 599 2918.
E-mail address: Howard.Weintraub@nyumc.org.

0021-9150 © 2013 The Author. Published by Elsevier Ltd. Open access under CC BY-NC-ND license.
http://dx.doi.org/10.1016/j.atherosclerosis.2013.07.041

Abbreviations

ACCORD Action to Control Cardiovascular Risk in Diabetes
AHA American Heart Association
AIM-HIGH Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes;
ALA alpha linoleic acid;
Apo B apolipoprotein B;
CHD coronary heart disease;
CI confidence interval;
COMBOS Combination of Prescription Omega-3 with Simvastatin study;
CV cardiovascular;
DHA docosahexaenoic acid;
ECLIPSE Epanova Compared to Lovaza in a Pharmacokinetic Single-dose Evaluation;
ENHANCE Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression trial;
EPA eicosapentaenoic acid;
ESPRIT Efficacy and Safety of Add-on Epanova to Statin in Subjects With Persistent Hypertriglyceridemia and High Risk for Cardiovascular Disease study;
EVOLVE Epanova for Lowering Very High Triglycerides study;
FIELD Fenofibrate Intervention and Event Lowering in Diabetes;
GISSI Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza cardiaca;
GISSI-HF Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza cardiaca Heart Failure;
HDL-C high-density lipoprotein cholesterol
HPS2-THRIVE Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events;
HR hazard ratio;
IPE icosapent ethyl;
IMPROVE-IT Improved Reduction of Outcomes: Vytorin Efficacy International Trial;
JELIS Japanese EPA Lipid Intervention Study;
LDL-C low-density lipoprotein cholesterol;
Lp-PLA_2 lipoprotein-associated phospholipase A_2;
MARINE Multi-center, Placebo-controlled, Randomized, Double-blind, 12-week study with an Open-label Extension;
NHANES National Health and Nutrition Examination Survey;
NKO Neptune Krill Oil;
OM3EE omega-3 acid ethyl esters;
OMEGA Omega 3 Fatty Acids on Top of Modern Guideline-adjusted Therapy;
OM3FFA omega-3 free fatty acids;
OPERA Omega-3 Fatty Acids for Prevention of Post-operative Atrial Fibrillation trial;
ORIGIN Outcome Reduction with Initial Glargine Intervention;
PUFA polyunsaturated fatty acid
REDUCE-IT Reduction in Cardiovascular Events with EPA-Intervention Trial;
T2DM type 2 diabetes mellitus;
TC total cholesterol;
TG triglycerides;
TRIFECTA Trial for Efficacy of CaPre on Hypertriglyceridemia;
US FDA United States Food and Drug Administration;
VA-HIT Veterans Affairs High-density Lipoprotein Intervention Trial;
VLDL-C very-low-density lipoprotein cholesterol;
VLDL-TG very-low-density lipoprotein triglycerides.

1. Introduction

The relationship between low-density lipoprotein cholesterol (LDL-C) levels and the risk of coronary heart disease (CHD) in a broad patient population was firmly established by landmark studies conducted in the 1980s [1–4]. As a result of widespread adoption of strategies to lower LDL-C levels over the ensuing three decades, including the development of statins, mean LDL-C levels have declined in the United States [5]. Atherogenic dyslipidemia is characterized by elevated triglycerides (TG) and small LDL particles with reduced levels of high-density lipoprotein cholesterol (HDL-C) and often elevated apolipoprotein B (Apo B) and non-HDL-C [6,7]. While LDL-C levels have declined, results from the National Health and Nutrition Examination Survey (NHANES) showed that 31% of US adults have high fasting TG levels (≥150 mg/dL [1.70 mmol/L]), 16% have high TG levels (≥200 mg/dL; 2.26 mmol/L), and 1% have very high TG levels (≥500 mg/dL; 5.65 mmol/L) [8,9]. Substantial progress has been made in the last decade in understanding the effects of omega-3 fatty acids on cardiovascular (CV) disease [10] and lipid parameters including TG and LDL-C [11,12]. The purpose of this review is to provide an update on omega-3 fatty acid treatment options for patients with dyslipidemia.

2. Management of dyslipidemia: guidelines and treatment options

LDL-C remains the primary target for lipid-lowering therapy in the management of dyslipidemia [6,13]. Current recommendations specify that the LDL-C goal is <100 mg/dL (2.59 mmol/L) for high-risk patients (CHD or CHD equivalents, including those with diabetes; 10-year risk >20%) and <70 mg/dL (1.81 mmol/L) for very-high-risk patients (multiple major risk factors, severe and poorly controlled risk factors, multiple risk factors of the metabolic syndrome and acute coronary syndrome) [13]. Non-HDL-C is the secondary target in patients with TG ≥ 200 mg/dL (5.18 mmol/L) [6]. Therapeutic lifestyle changes are an essential first-line modality for clinical management of dyslipidemia in all patients [6,13]. For individuals who cannot attain target LDL-C levels with diet and exercise alone, statins are first-line pharmacotherapy [6]. In patients with dyslipidemia and elevated LDL-C, fibrates and niacins can be

used as adjunctive therapy to statins [6]. Furthermore, non-HDL-C is the secondary target in patients with TG ≥ 200 mg/dL (2.26 mmol/L) and TG-lowering agents such as fibrates or niacins can be considered in addition to statins [6]. In patients with dyslipidemia and low LDL-C, fibrates can be used as monotherapy if CHD is present and niacins can be used as monotherapy if higher risk is present [6]. The use of bile acid sequestrants is recommended in specific populations including patients who require modest reductions in LDL-C to achieve target goals or have moderate elevations in LDL-C, young persons with elevated LDL-C, women with elevated LDL-C who are considering pregnancy, and in patients with very high LDL-C who require combination therapy with statins [6]. Cholesterol absorption inhibitors may be used to reduce elevated total cholesterol (TC), LDL-C, Apo B, and non-HDL-C in patients with primary hyperlipidemia (alone or in combination with statins) or in patients with mixed hyperlipidemia (alone or in combination with fenofibrate) [14]. To reduce CV risk, the American Heart Association (AHA) recommends consumption of two servings of fatty fish per week for all adults [15]; dietary consumption of fish has long been associated with reduced CV risk/outcomes and TG lowering [16–18]. The beneficial effects of fish consumption are attributed to the omega-3 fatty acids eicosapentaenoic acid (EPA; C20:5n-3) and docosahexaenoic acid (DHA; C22:6n-3) [15]; thus, the AHA also recommends that individuals with CHD consume a combined 1000 mg/day of EPA and DHA [15].

2.1. Fibrates, niacins, bile acid sequestrants, cholesterol absorption inhibitors and the need for other options

Trials assessing the efficacy of fibrates in lowering CV risk have yielded mixed results. CV risk was significantly lower in patients receiving gemfibrozil versus those receiving placebo in the Veterans Affairs High-density Lipoprotein Intervention Trial (VA-HIT; $N = 2531$) [19]. The same results were seen in a subpopulation of patients from the VA-HIT trial with diabetes [20]. However, in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial ($N = 9795$) [21] involving patients with diabetes, fenofibrate monotherapy did not significantly reduce the likelihood of reaching the composite end point of CHD death or nonfatal myocardial infarction, although the lack of efficacy could be attributed to statin use in the placebo group [21]. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial ($N = 5518$) [22] involving high-risk patients with type 2 diabetes mellitus (T2DM), addition of flexible-dose fenofibrate or placebo to simvastatin therapy resulted in statistically similar annual rates of nonfatal myocardial infarction, nonfatal stroke, or CV death (hazard ratio [HR], 0.92; 95% confidence interval [CI]: 0.79–1.08; $p = 0.32$). Median TG levels decreased from 1.85 mmol/L at baseline to 1.38 mmol/L in the fenofibrate group and from 1.81 mmol/L at baseline to 1.63 mmol/L in the placebo group over an average follow-up of 4.7 years, and more patients in the fenofibrate group had either a dose reduction or discontinuation due to reduction in glomerular filtration rates [22]. As has been observed in other fenofibrate trials, small increases in mean serum creatinine levels (from 91 to 92 μmol/L) occurred during the first year of fenofibrate therapy. Notwithstanding mixed results from the aforementioned individual trials, a meta-analysis of studies involving patients with atherogenic dyslipidemia (TG > 200 mg/dL [2.26 mmol/L] and/or HDL-C < 40 mg/dL [1.04 mmol/L]) suggested addition of fenofibrate to statin therapy may be beneficial [23]. In patients with both hypertriglyceridemia and reduced HDL-C ($N = 5068$), the relative risk ratio for occurrence of vascular events compared with placebo was 0.71 (95% CI: 0.62–0.82, $p < 0.001$).

Similar results were found with the addition of niacin to simvastatin. The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) study ($N = 3414$) [24] was stopped early because of lack of efficacy of niacin (1500–2000 mg/day) added to simvastatin therapy in patients with established CV disease and low LDL-C levels (<1.81 mmol/L). Despite improvement in HDL-C (15% greater increase with niacin vs placebo, $p < 0.001$) and TG levels (21% greater decrease with niacin vs placebo), the HR for the primary CV outcome was 1.02 (95% CI: 0.87–1.21, $p = 0.80$) for simvastatin plus niacin vs simvastatin alone. Moreover, in the combination treatment group, significantly more patients discontinued the study drug than in the simvastatin-only group (25.4% vs. 20.1%, $p < 0.001$). Flushing or itching resulted in discontinuation in 6.1% in the combination treatment group. Flushing, a common side effect of niacin, is reported by 75% of patients [25]. More recently, the Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) study reported reductions in TG and LDL-C levels of 0.37 mmol/L and 0.26 mmol/L, respectively, with an increase in HDL-C of 0.16 mmol/L following treatment with extended-release niacin/laropiprant; baseline lipids while on statin-based therapy in this group were: TC, 3.32 mmol/L; LDL-C, 1.63 mmol/L; HDL-C, 1.14 mmol/L; and TG, 1.43 mmol/L [26]. However, preliminary outcomes results indicated that the combination of extended-release niacin/laropiprant with statin therapy did not significantly further reduce the risk of major vascular events compared with statin therapy alone (risk ratio = 0.96 [95% CI 0.90–1.03]; $p = 0.29$).

Trials assessing the effects of adding a bile acid sequestrant to a statin regimen have demonstrated improvements in patient lipid profiles. Total cholesterol and LDL-C were significantly lower with the combination of colesevelam 3.8 g plus simvastatin 10 mg or colesevelam 2.3 g plus simvastatin 20 mg versus placebo compared with any of the individual agents alone [27]. Despite the improvements in lipid profiles, use of bile acid sequestrants is limited by an inconvenient mode of administration and frequency of gastrointestinal adverse effects, with constipation reported in 10% and 28% of patients who receive colestipol and cholestyramine, respectively [28]. Additionally, bile acid sequestrants can increase TG levels, and use is contraindicated in patients with TG levels ≥500 mg/dL (5.65 mmol/L) [29].

While the lipid-lowering efficacy and safety of the cholesterol absorption inhibitor ezetimibe were established through a range of clinical studies including investigations of combination use with statins [14], controversy emerged with regard to ezetimibe's vascular and clinical benefit due to the disappointing results of the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial [30]. In this double-blind, 24-month trial, 720 patients with familial hypercholesterolemia received 80 mg of simvastatin with placebo or 10 mg of ezetimibe and were assessed for intima-media thickness of the walls of the carotid and femoral arteries (primary end point; a commonly used risk surrogate for vascular disease). The study results indicated that while combined therapy with ezetimibe and simvastatin reduced LDL-C, it did not result in significant differences in the primary end point. A currently ongoing trial, Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), is an event-driven study with a minimum of 5250 subjects experiencing a primary end point event and seeking to compare the effect of ezetimibe and simvastatin to simvastatin monotherapy on death due to cardiovascular events, nonfatal coronary events, and nonfatal strokes [31].

The mixed and disappointing results of clinical studies investigating CV outcomes and/or the associated adverse events of fibrates, niacins, bile acid sequestrants, or cholesterol absorption inhibitors highlight the need for alternative treatment options such as omega-3 fatty acids.

Table 1
Omega-3 fatty acid products.

Product	Brand name	Active ingredient(s)	Dose	Clinical studies/reviews
Approved prescription drugs				
Omega-3-acid ethyl esters	Lovaza®	Ethyl esters of omega-3 fatty acids sourced from fish oils [37]	Each 1-g capsule contains at least 900 mg of ethyl esters of omega-3 fatty acids: EPA ethyl ester (~465 mg) and DHA ethyl ester (~375 mg) taken as 4 capsules once daily or 2 capsules twice daily [37]	Harris et al. [39] Pownall et al. [40] Davidson et al. (COMBOS) [41]
Icosapent ethyl	Vascepa®	IPE, the ethyl ester of the omega-3 fatty acid EPA [75]	Each capsule contains 1 g of IPE; daily oral dose of 4 g taken as 2 capsules twice daily [75]	Bays et al. (MARINE) [45] Ballantyne et al. (ANCHOR) [46]
Emerging prescription agents and dietary supplements				
Free fatty acids	Epanova®	Free fatty acid forms of EPA and DHA	Each 1-g capsule contains 75% EPA and DHA free fatty acids; studies have included 2 g/day to 4 g/day doses [47]	Davidson et al. (ECLIPSE) [48] EVOLVE: NCT01242527 [49] ESPRIT: NCT01408303 [51] Reviewed by Katoaka et al., 2013 [76]
Fish oil supplements	Various	EPA and DHA; other components	Purity and amount of EPA and DHA varies; median (25–75 percentile) amount per serving: EPA, 216 (160–360) mg; DHA, 200 (120–240) mg taken as 1–3 soft gels, capsules, or packets per serving; liquid forms also available [77]	Reviewed by Zargar 2011 [77] and Tur et al., 2012 [58]
Krill oil supplements	Neptune Krill Oil (NKO®), Superba™, CaPre®	EPA and DHA; other components	30% EPA and DHA, 40% phospholipids (primarily phosphatidyl choline) and astaxanthin, vitamin A, vitamin E, and other fatty acids [78]; studied doses have included 1 g/day to 3 g/day [53]	Bunea et al. [53] NCT01415388 [55] TRIFECTA: NCT01455844 [54]
Algal oil supplements	Various	DHA; other fatty acids; other components; some may also contain EPA	Purity and amount of DHA varies; EPA may also be present [56]; median DHA dose in meta-analysis of 11 RCTs: 1.68 g/day [57]	Reviewed by Bernstein et al., 2012 [57] and Tur et al., 2012 [58]
Plant oil supplements	Various	ALA; other components	Purity and amount of ALA varies and can be sourced from flaxseed and other plant sources [58]	Reviewed by Pan et al., 2012 [59] and Tur et al., 2012 [58]

ALA = alpha-linolenic acid; COMBOS = Combination of Prescription Omega-3 with Simvastatin study; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; ESPRIT = Efficacy and Safety of Add-on Epanova to Statin in Subjects With Persistent Hypertriglyceridemia and High Risk for Cardiovascular Disease study; EVOLVE = Epanova for Lowering Very High Triglycerides study; IPE = icosapent ethyl; MARINE = Multi-center, Placebo-controlled, Randomized, Double-blind, 12-Week Study with an Open-label Extension; RCT = randomized controlled trial; TRIFECTA = Trial for Efficacy of CaPre on Hypertriglyceridemia.

2.2. Omega-3 fatty acids

The potential CV benefits of EPA and DHA have been well recognized, and both have potent TG-lowering effects [15]. While the TG-lowering effects of DHA and EPA have been established, evidence is accumulating as to the differential effects of these two omega-3 fatty acids on other lipoprotein parameters, particularly LDL-C. Results of several small trials in varied populations of patients with mild to moderate TG elevations have suggested that EPA does not raise LDL-C [32–35]. Recently, these observations have been supported by two separate meta-analyses using data from 21 and 22 randomized controlled trials, respectively [11,12]. Wei et al. [11] found that while both EPA and DHA lowered TG, DHA raised LDL-C but EPA did not. Jacobson et al. [12] also found that DHA treatment was associated with LDL-C increases and noted that EPA treatment was associated with reductions or smaller increases in LDL-C. In addition to differential effects on LDL-C, both analyses found that DHA was associated with increases in HDL-C while EPA was not. Jacobson et al. also found that EPA was associated with greater average reductions in non-HDL-C than was DHA. Since the publication of these meta-analyses, a randomized, double-blind, double-dummy, head-to-head study in Japan reported the lipid-lowering effects of 2 g/day or 4 g/day of EPA ethyl ester plus DHA ethyl ester (0.465 g EPA ethyl ester plus 0.375 g DHA ethyl ester per 1-g capsule) versus 1.8 g/day of pure EPA ethyl ester alone [36]. In 611 patients with hypertriglyceridemia (TG $\geq$ 150 mg/dL [1.70 mmol/L] and <750 mg/dL [8.48 mmol/L]), all 3 treatments produced substantial decreases in TG levels, small increases in HDL-C levels and small decreases in LDL-C levels compared with baseline. However, EPA ethyl ester produced numerically greater reductions in LDL-C levels than either dose of EPA ethyl ester plus DHA ethyl ester. While noting that the study was limited to Japanese patients undergoing lifestyle modification, the authors also pointed out that increased LDL-C levels have been observed in other studies of omega-3 fatty acids. Roughly 43% of these patients were taking a statin at baseline; LDL-C changes in the nonstatin subgroups were not published. Together, the available evidence suggests that EPA monotherapy may have clinical benefit, as such therapy may not interfere with reaching or maintaining target LDL-C levels.

Omega-3 fatty acids are available in the form of prescription drugs, dietary supplements from fish oil, krill oil, algal oil, and plant oil as well as emerging options such as free fatty acids (Table 1).

2.3. Prescription omega-3 treatment options

Until recently, the only United States Food and Drug Administration (US FDA)-approved prescription marine omega-3 fatty acid formulation was Lovaza® (omega-3 acid ethyl esters [OM3EE]; GlaxoSmithKline, Research Triangle Park, NC; marketed outside the US as Omacor® [Europe], Zodin® [Germany], or Lotriga® [Japan]) [37]. Each 1-g capsule of Lovaza contains 465 mg of EPA ethyl ester and 375 mg of DHA ethyl ester derived from fish oil [37]. OM3EE is

indicated as an adjunct to diet to reduce TG levels in adult patients with TG levels ≥500 mg/dL (5.65 mmol/L). Icosapent ethyl (IPE; Vascepa® [formerly AMR101]; Amarin Pharma Inc., Bedminster, NJ) is a high-purity prescription form of EPA ethyl ester that was approved by the US FDA in 2012 as an adjunct to diet to reduce TG levels in adult patients with severe (≥500 mg/dL [5.65 mmol/L]) hypertriglyceridemia. A prescription ethyl EPA formulation is also available in Japan as Epadel® [38].

2.3.1. Omega-3 acid ethyl esters (OM3EE)

The pivotal double-blind, placebo-controlled trials by Harris et al. and Pownall et al. [39,40] were designed to assess the effects of OM3EE on lipid profiles in patients with very high TG levels (≥5.65 mmol/L and ≤22.6 mmol/L). Although not specified in the study design, patients did not take statins during the trials. In both trials, TG levels decreased substantially at the first study visit after initiation of active treatment (1 month in the Harris study and 2 weeks in the Pownall study). At the end of both studies, significant reductions were observed in TG and total cholesterol (TC) levels, and significant increases were observed in HDL-C levels. However, notable increases from baseline were observed in LDL-C following OM3EE treatment that were statistically significant compared with placebo (Harris: 32%, $p = 0.0014$; Pownall: 16.7%, $p = 0.013$).

In the Combination of Prescription Omega-3 with Simvastatin (COMBOS) study, Davidson et al. assessed the TG-lowering efficacy and safety of OM3EE in patients with persistent hypertriglyceridemia despite receiving statin therapy [41]. The 8-week study randomized 256 patients with fasting TG ≥ 200 (2.26 mmol/L) and <500 mg/dL (5.65 mmol/L) and mean LDL-C levels ≤10% of their National Cholesterol Education Program–Adult Treatment Panel III goal [41]. Patients received simvastatin 40 mg with 4 g/day OM3EE or placebo, and the primary outcome was the mean change from baseline in non-HDL-C levels at study end. The median percent reduction in TG levels was significantly different between the treatment groups (29.5%, OM3EE plus simvastatin; 6.3%, simvastatin alone; $p < 0.001$). Changes in LDL-C were observed, but there was no significant difference between groups (+0.7%, OM3EE plus simvastatin; −2.8%, simvastatin alone; $p = 0.052$). Percent reductions were significantly different for OM3EE plus simvastatin vs. simvastatin alone for non-HDL-C (9.0% vs. 2.2%; $p < 0.001$), very-low-density lipoprotein cholesterol (VLDL-C; 27.5% vs. 7.2%; $p < 0.001$) and Apo B (4.2% vs. 1.9%; $p = 0.023$). OM3EE has also been studied in patients receiving atorvastatin [42]. Significant reductions were noted for TG, non-HDL-C, and VLDL-C levels, while changes in LDL-C and Apo B levels were not statistically significant [42].

OM3EE was generally well tolerated in clinical trials; adverse events reported by ≥3% of patients that occurred more frequently than in patients receiving placebo were eructation, dyspepsia, and taste perversion [37]. In the pivotal study reporting safety data, treatment did not affect liver function [39]. This may be clinically relevant, as fibrates and niacins are associated with hepatic transaminase elevations [43,44]. Adverse-event rates in the combination therapy trial were similar in the OM3EE plus simvastatin and simvastatin-alone groups, as were study completion rates (94.3%, OM3EE plus simvastatin; 95.5%, simvastatin alone) [41]. While the safety and TG-lowering efficacy of OM3EE have clearly been established, the increases in LDL-C levels could present difficulties for achievement of LDL-C treatment goals.

2.3.2. Icosapent ethyl (IPE)

The pivotal Multi-center, Placebo-controlled, Randomized, Double-blind, 12-Week Study with an Open-label Extension (MARINE) was a large, international trial involving patients with very high TG levels (≥500 [5.65 mmol/L] and ≤2000 mg/dL [22.6 mmol/L]) [45]. This three-arm study randomized 229 patients to IPE 4 g/day, IPE 2 g/day, or placebo. The primary efficacy outcome was the median placebo-adjusted percent change in TG levels from baseline to week 12. Although changes were typically greater in the 4 g/day group, both doses of IPE improved lipid profiles compared with placebo: TG levels were significantly reduced by 33.1% ($p < 0.0001$) and 19.7% ($p = 0.0051$) with IPE 4 g/day and 2 g/day, respectively. Importantly, LDL-C levels were not significantly increased. Reductions were also observed for non-HDL-C, VLDL-C, lipoprotein-associated phospholipase A_2 (Lp-PLA_2), Apo B, TC, and very-low-density lipoprotein triglycerides (VLDL-TG) levels, and all were significant in the IPE 4 g/day group (17.7%, 28.6%, 13.6%, 8.5%, 16.3%, and 25.8%, respectively; all $p < 0.01$); no significant changes were observed for HDL-C levels.

The 12-week ANCHOR study [46] evaluated the efficacy and safety of IPE in patients with persistent high TG levels (≥200 [2.26 mmol/L] and <500 mg/dL [5.65 mmol/L]) despite having well-controlled LDL-C levels while on optimized statin therapy, with ~73% diagnosed with diabetes mellitus. Patients ($N = 702$) were randomized to receive IPE 4 g/day, 2 g/day, or placebo, and the primary outcome measure, as in the MARINE study, was median placebo-adjusted percent change in TG levels from baseline to study end. TG levels were significantly reduced by 21.5% ($p < 0.0001$) and 10.1% ($p = 0.0005$) with IPE 4 g/day and 2 g/day, respectively. As seen in the MARINE study, favorable results were also observed in terms of LDL-C levels compared with placebo. In the ANCHOR population with well-controlled LDL-C levels at baseline, LDL-C levels were not significantly increased with IPE 2 g/day and were significantly decreased with IPE 4 g/day (6.2%; $p = 0.0067$). Significant reductions (all $p < 0.0001$) were also observed for non-HDL-C (13.6%), VLDL-C (24.4%), Lp-PLA_2 (19.0%), Apo B (9.3%), TC (12.0%), and VLDL-TG (26.5%) levels compared with placebo for IPE 4 g/day.

IPE was generally well tolerated in both 12-week studies. Most adverse events in the MARINE and ANCHOR studies were considered unrelated to treatment, with adverse-event rates low and similar between IPE groups and placebo [45,46]. IPE treatment did not affect kidney or liver function evaluations, blood glucose, or Hb_{A1c} levels, even when given in combination with statins. As mentioned earlier, this may offer clinical benefit over fibrates and niacins. While fishy eructations are often reported for other omega-3 fatty acid products, fewer patients receiving IPE reported eructations than patients in the placebo groups. Compliance was high, with more than 90% of patients completing treatment in both trials.

2.4. Other and emerging omega-3 fatty acid treatment options

2.4.1. Omega-3 free fatty acids (OM3FFA)

OM3FFA (Epanova®; Omthera Pharmaceuticals, Princeton, NJ, USA), is a purified mixture of the free fatty acid forms EPA and DHA with amounts of EPA and DHA that are comparable to OM3EE [47]. In the Epanova Compared to Lovaza in a Pharmacokinetic Single-dose Evaluation (ECLIPSE), the bioavailability of OM3FFA was found to be 4-fold greater than that of OM3EE during low-fat consumption periods [48]. The Epanova for Lowering Very High Triglycerides (EVOLVE) study was conducted to ascertain the efficacy of OM3FFA compared with placebo in lowering TG in patients with severe hypertriglyceridemia [49,50]. The 12-week study randomized 399 subjects with TG levels 500 mg/dL (5.65 mmol/L) to 2000 mg/dL (22.6 mmol/L). Patients received 2 g/day, 3 g/day, or 4 g/day of OM3FFA or 4 g/day of olive oil and the primary outcome was percent change in TG level from baseline to week 12. There were significant reductions in median percent change from baseline in TG levels of 25.8% ($p = 0.003$), 21.7% ($p = 0.021$), and 30.7% ($p < 0.001$) and median percent increases from baseline in LDL-C of 21.4% ($p = 0.003$), 15.5% ($p = 0.092$), and 26.2% ($p < 0.001$) in the 2 g/day, 3 g/day, and 4 g/day groups, respectively. Significant reductions

were also observed for non-HDL-C (7.7%; $p < 0.002$) and VLDL-C (34.7%; $p < 0.001$) with nonsignificant increases in HDL-C and Apo B in the 4 g/day group. OM3FFA was also found to be safe and well tolerated. Discontinuations due to adverse events (5–7% in the active treatment arms) were primarily gastrointestinal in nature.

OM3FFA has also been investigated in statin-treated patients in the recently completed ESPRIT trial (Efficacy and Safety of Add-on Epanova to Statin in Subjects With Persistent Hypertriglyceridemia and High Risk for Cardiovascular Disease) [51,52]. This 6-week, double-blind study randomized 647 diet-stable patients with TG levels ≥200 mg/dL (2.26 mmol/L) and <500 mg/dL (5.65 mmol/L) who were on a maximally tolerated dose of statin or statin/ezetimibe therapy with persistently high TG levels and high risk for cardiovascular disease to olive oil, 2 g/day OM3FFA, or 4 g/day OM3FFA. The primary end point was mean percent change in non-HDL-C from baseline to end of treatment. Non-HDL-C was reduced in both the 2 g/day (3.9%; $p = 0.0373$) and 4 g/day (6.9%; $p < 0.0001$) treatment groups. Mean reductions in TG of 14.6% ($p < 0.0001$) and 20.6% ($p < 0.0001$), as well as increases in LDL-C of 4.6% ($p = 0.0247$) and 1.3% ($p = 0.6470$) were also reported for the 2 g/day and 4 g/day groups, respectively. Significant reductions were observed for VLDL-C (21.5%; $p < 0.0001$), Apo B (2.1%; $p = 0.0352$), and Lp-PLA_2 (10.7%; $p < 0.0001$), with a nonsignificant increase of 3.3% in HDL-C in the 4 g/day group.

2.4.2. Krill oil

Krill oil, as provided by Antarctic krill, is a rich source of phospholipids containing long-chain omega-3 polyunsaturated fatty acids (PUFAs; primarily EPA and DHA) along with antioxidants such as vitamins A and E and astaxanthin [53]. A double-blind, randomized trial assessed the effect of krill oil (Neptune Krill Oil [NKO]; Neptune Technologies & Bioresources, Laval, Quebec, Canada), on TC, TG, LDL-C, and HDL-C [53]. The 12-week study randomized 120 patients with at least a 6-month diagnosis of mildly high to very high cholesterol (193.9 mg/dL [5.02 mmol/L] −347.9 mg/dL [8.93 mmol/L]) and TG (203.8 mg/dL [2.30 mmol/L] −354.4 mg/dL [4.00 mmol/L]). Patients received krill oil (1, 1.5, 2, or 3 g/day) as determined by body mass index, fish oil (3 g once daily: 180 mg EPA and 120 mg DHA per gram), or placebo (3 g once daily). Significant changes were observed in TC, LDL-C, and HDL-C in all the krill oil groups (−18.1%, −37.4%, +55.3% in the 2 g/day group and −17.9%, −39.2%, and +59.6% in the 3 g/day group, respectively); significant reductions in TG were observed in the 2 g/day group (27.6%) and 3 g/day (26.5%), but not in lower-dose groups [53]. Currently, the 12-week TRIFECTA study (Trial for Efficacy of CaPre on Hypertriglyceridemia) [54] is assessing whether 1 g/day or 2 g/day of a krill oil product (CaPre®; Acasti Pharma, Laval, Quebec, Canada) has an effect on fasting plasma TG in patients with mild to high hypertriglyceridemia compared with placebo (stable statin dose is permitted). In addition, a 12-week study [55] investigating the effects of Superba™ krill oil (Aker BioMarine ASA, Oslo, Norway) on change from baseline in fasting serum TG and the omega-3 index was recently completed.

2.4.3. Algal oil

Algal oil is another potential resource for omega-3 fatty acids [56]. The clinical literature describing the relationship between algal oil use and CV risk factors comprises a few small studies. As such, a meta-analysis conducted by Bernstein et al. examined the impact of algal oil supplementation on TG, HDL-C, and LDL-C. This analysis of randomized controlled trials dating from 1996 to 2011 included a total of 485 patients [57]. The mean age of patients across the included trials ranged from 24 to 59 years. The studies were mostly 6 weeks in duration. TG decreased with algal oil supplementation, whereas LDL-C and HDL-C increased (TG, −15% [95% CI: 10–20%]; LDL-C, +8% [95% CI: 6–10%]; HDL-C, +5% [95% CI: 4–7%]) [57].

2.4.4. Plant oil

Plant oil from food sources such as flaxseed and walnuts is a resource for the omega-3 fatty acid alpha-linoleic acid (ALA) [58]. The relationship between ALA exposure and risk of CV disease was examined in a systematic review and meta-analysis by Pan et al. [59]. This analysis included 27 studies with 251,049 patients and 15,327 CV disease events. Taking into consideration both dietary intake of ALA and biomarker concentration, the overall relative risk of CV disease event was 0.86 (95% CI: 0.77–0.97). Recently, a meta-analysis of omega-6 linoleic acid studies by Ramsden et al. was updated by incorporating recovered data from the Sydney Diet Heart Study [60]. Analysis of the recovered data from 458 men aged 30–59 years demonstrated higher rates of CV mortality (HR: 1.7 [95% CI: 1.03–2.80]; $p = 0.037$) and mortality from CHD (HR: 1.74 [95% CI: 1.04–2.92]; $p = 0.036$) in the intervention group (wherein dietary saturated fats from animal fats and common margarines and shortenings were replaced with omega-6 linoleic acid from safflower and sunflower oils) compared with the control group. Incorporating these results into the meta-analysis resulted in no evidence of CV benefit for omega-6 linoleic acid.

2.5. Omega-3 cardiovascular outcome studies

The Japanese EPA Lipid Intervention Study (JELIS) investigated the effects of purified EPA for prevention of major coronary events [61]. A total of 18,645 Japanese individuals with hypercholesterolemia (TC ≥ 6.5 mmol/L) were randomized to receive 1800 mg/day EPA plus a statin (pravastatin or simvastatin) or statin only over 5 years. In 2007, the JELIS study reported that the risk of major coronary events was reduced by 19% in the EPA group compared with the statin-only group ($p = 0.011$). Moreover, a subgroup analysis of patients from the JELIS study demonstrated that those with TG ≥ 150 mg/dL (1.70 mmol/L) and HDL-C <40 mg/dL (1.04 mmol/L) had a significantly higher risk of major coronary events (combined HR: 1.71 [95% CI: 1.11–2.64]; $p = 0.014$) at the time of study registration compared with patients with TG < 150 mg/dL (1.70 mmol/L) and HDL-C ≥40 mg/dL (1.04 mmol/L) [62]. However, EPA treatment lowered the risk of major coronary events by 53% in the group with TG ≥ 150 mg/dL (1.70 mmol/L) and HDL-C <40 mg/dL (1.04 mmol/L) (HR: 0.47 [95% CI: 0.23–0.98]; $p = 0.043$). In 1999, the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione study of 11,324 patients with recent myocardial infarction demonstrated a significant relative decrease of 10% ($p = 0.048$) in the risk of the combined end point of death, nonfatal myocardial infarction, and nonfatal stroke in patients treated with 850–882 mg/day of combined EPA and DHA ethyl esters [63]. The later Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza cardiaca Heart Failure (GISSI-HF) study ($N = 7046$) demonstrated a risk reduction of 1.8% (95% CI: 0.3–3.9) for all-cause mortality in patients with clinical evidence of heart failure who had been treated with omega-3 fatty acids [64].

While these earlier studies of CV outcomes reported favorable effects of omega-3 fatty acids, recent CV outcomes studies of EPA and DHA combination therapy have been disappointing. In the randomized, double-blind, placebo-controlled Alpha Omega trial ($N = 4837$), the CV benefits of omega-3 fatty acid supplementation were evaluated [65]. Patients with previous myocardial infarction who were receiving state-of-the-art antihypertensive, antithrombotic, and lipid-modifying therapy were assigned to use margarine containing a combination of EPA plus DHA; the plant-based omega-3 fatty acid ALA; a combination of EPA, DHA, and ALA; or placebo for 40 months. Active treatment groups had an average additional daily intake of 226 mg EPA combined with 150 mg DHA, 1.9 g ALA, or both. At the end of the study, there were no statistically significant differences in the incidence of the

combination of fatal or nonfatal CV events across treatment groups (HR, EPA plus DHA: 1.01 [95% CI: 0.87–1.17]; $p = 0.93$; HR, ALA: 0.91 [95% CI: 0.78–1.05]; $p = 0.20$) [65]. In this trial, the beneficial effects of low-dose EPA plus DHA therapy may have been difficult to prove because the patients were receiving state-of-the-art clinical care.

In the randomized, placebo-controlled Omega 3 Fatty Acids on Top of Modern Guideline-adjusted Therapy (OMEGA) trial, patients with acute myocardial infarction ($N = 3851$) received 1-g capsules containing either 460 mg EPA and 380 mg DHA or placebo daily in addition to guideline-adjusted therapy and were followed for 1 year [66]. Rates for the primary efficacy outcome of sudden cardiac death were 1.5% in both study arms ($p = 0.84$) Differences in secondary end points such as major CV or cerebrovascular events were also statistically similar. Interpretation of the results from the OMEGA trial was limited because the study lacked sufficient statistical power. The sample size and event rates used in the OMEGA study were based on prior studies, but the patient population was receiving considerably improved guideline-adjusted treatment of acute myocardial infarction, and thus the number of sudden death events was lower than expected. The Alpha Omega and OMEGA trials may have both been limited by insufficient duration; the relatively low dose of omega-3 fatty acids may also have been a limiting factor in the Alpha Omega trial.

The effects of long-term treatment with 1-g capsules containing 465 mg EPA and 375 mg DHA on CV events was examined in the Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial in patients with T2DM, impaired fasting glucose, or impaired glucose tolerance ($N = 12{,}536$) [67]. The study found that 1 g/day of EPA/DHA did not prevent death or any CV outcomes in this patient population. As with the Alpha Omega trial, the ORIGIN trial may have been limited by concomitant cardioprotective therapies which may have reduced the statistical power to detect any effect of omega-3 fatty acid intervention. Other limitations may have included relatively low-dose supplementation and low dietary intake of omega-3 fatty acids. It may be worth noting that in the JELIS study, where cardiovascular outcomes were improved in patients who received both statins and EPA as compared with patients who received statins alone, the omega-3 therapy contained EPA without DHA and the dose was nearly 2 g/day.

In the Omega-3 Fatty Acids for Prevention of Post-operative Atrial Fibrillation (OPERA) trial, the effects of perioperative omega-3 PUFA supplementation on the occurrence of post-operative atrial fibrillation was assessed in patients who underwent cardiac surgery ($N = 1516$) [68]. No significant difference was observed between patients who received the perioperative omega-3 PUFA supplementation and those who received placebo (omega-3 PUFA, 30.0% vs. placebo, 30.7%; $p = 0.74$; odds ratio: 0.96 [95% CI: 0.77–1.20]). Of note, stroke incidence (secondary end point) occurred less frequently in patients treated with omega-3 PUFA supplementation (omega-3 PUFA, 0.5% vs. placebo, 1.1%; odds ratio: 0.45 [95% CI: 0.13–1.51]), although the difference was not statistically significant ($p = 0.18$). In response, a meta-analysis conducted by Larsson et al. assessed the relationship between omega-3 PUFAs and stroke risk [69]. The 8 prospective studies that met the inclusion criteria included 242,076 participants who reported 5238 stroke events. The overall relative risk of stroke was 0.90 (95% CI: 0.81–1.01) and did not indicate a clear association between long-chain omega-3 PUFA intake and total stroke risk. Limitations of this study included the presence of measurement error in the assessment of long-chain omega-3 intake, confounding risk factors, and publication bias.

Further studies are needed to assess omega-3 therapies in the context of current standards of clinical care in sufficiently large patient populations and at higher doses. The ongoing, prospective, randomized, double-blind Reduction in Cardiovascular Events with EPA-Intervention Trial (REDUCE-IT; NCT01492361) will assess CV outcomes with lipid-lowering doses of IPE in high-risk patients with hypertriglyceridemia in addition to statin therapy [70].

2.6. Omega-3 considerations

Given the high availability of omega-3 fatty acid products to the general public, it is important to consider the potential health benefits and risks; these have been described in a recent review of 147 publications covering various dietary sources of omega-3 fatty acids by Tur et al. [58] and a systematic review and meta-analysis of omega-3 fatty acids and incident T2DM by Wu et al. [71]. Overall, Tur et al. noted no health risks with omega-3 fatty acid products derived from fish, algae, or plant sources with the exception of potential risks in patients with T2DM, which was noted in 2 of the studies reviewed. In addition, they noted that while algal omega-3 fatty acids may be a suitable source for vegetarians, fishy taste and eructations may be a concern [58]. Additional CV and lipid benefits beyond those described herein were also noted by Tur et al. These included decreased blood pressure, heart rate, and oxidative stress (algal sources); protection effects against non-fatal myocardial infarction, improved insulin sensitivity in hyperlipidemic adults and improvement in CV health (plant oil sources); and reduced oxygen demand on the body and myocardium, reduced atherothrombotic risk, reduced CV disease morbidity and mortality, prevention of inflammatory disease development, and reduced CV risk (fish oil sources) [58]. Krill oil products may have added benefits for oxidative damage prevention given their higher levels of antioxidants compared with fish and plant oil products [58]. In analyzing 16 studies, Wu et al. found there was no harmful or beneficial association of dietary EPA and DHA consumption with the development of T2DM, but plant-derived ALA may have been associated with a nonsignificant trend toward lower risk; substantial heterogeneity across findings may have been a limiting factor in the analysis [71].

Further considerations that may have clinical bearing include the differences between dietary supplements and prescription omega-3 fatty acid drugs. Primary among these differences is that manufacturers of dietary supplements are not required to demonstrate the clinical efficacy of their products [72,73]. Moreover, the content, purity and consistency of dietary supplements are not as rigorously regulated as prescription drugs [72]. An independent analysis of 24 dietary fish oil supplements revealed that the actual omega-3 fatty acid content ranged from <20% to >80% more than the concentrations stated on the label; quality issues ranged from spoilage at the time of purchase to premature release of oil from softgel capsules [74]. In addition to uncontrolled/unknown amounts of EPA and DHA, dietary supplements may also contain other fats including cholesterols [10].

3. Conclusions

In the management of dyslipidemia, LDL-C remains the primary target for lipid-lowering therapy. If LDL-C goal cannot be achieved by therapeutic lifestyle changes or statin treatment, fibrates, niacins, bile acid sequestrants, cholesterol absorption inhibitors, and marine omega-3 fatty acids may be considered to help reduce CV risk. For patients who experience adverse events with other options, omega-3 fatty acids offer a safe and well-tolerated alternative, although dietary supplements and prescription drugs containing both EPA and DHA have been shown to increase LDL-C levels, potentially compromising therapy. Recent CV outcomes studies have failed to provide clear support for the use of fibrates, niacins, cholesterol absorption inhibitors, or omega-3 EPA and DHA combinations as adjuncts to statin therapy. The need therefore

remains for alternative treatment options as well as further CV outcomes studies. IPE is a high-purity prescription form of EPA ethyl ester and has been shown to lower TG levels without raising LDL-C levels, alone or in combination with statin therapy. The ongoing IPE REDUCE-IT study will help to address the need for additional CV outcomes data with 4 g/day of an EPA-only omega-3 fatty acid therapy in statin-treated patients with hypertriglyceridemia and established CV disease or at high risk for CV disease.

Conflict of interest and source of funding

Editorial support was provided by Peloton Advantage, LLC, Parsippany, NJ, funded by Amarin Pharma Inc., Bedminster, NJ.

Acknowledgments

Dr. Weintraub acknowledges Beth Daro-Kaftan, PhD of Peloton Advantage, LLC, Parsippany, NJ, supported by Amarin Pharma Inc., Bedminster, NJ. No financial support was received by Dr. Weintraub for manuscript preparation.

References

[1] The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. J Am Med Assoc 1984;251(3):351–64.
[2] The Lipid Research Clinics Coronary Primary Prevention Trial results. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. J Am Med Assoc 1984;251(3):365–74.
[3] Rossouw JE, Lewis B, Rifkind BM. The value of lowering cholesterol after myocardial infarction. N Engl J Med 1990;323(16):1112–9.
[4] Pekkanen J, Linn S, Heiss G, Suchindran CM, Leon A, Rifkind BM, et al. Ten-year mortality from cardiovascular disease in relation to cholesterol level among men with and without preexisting cardiovascular disease. N Engl J Med 1990;322(24):1700–7.
[5] Cohen JD, Cziraky MJ, Cai Q, Wallace A, Wasser T, Crouse JR, et al. 30-year trends in serum lipids among United States adults: results from the National Health and Nutrition Examination Surveys II, III, and 1999–2006. Am J Cardiol 2010;106(7):969–75.
[6] Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106(25):3143–421.
[7] Fruchart JC, Sacks FM, Hermans MP, Assmann G, Brown WV, Ceska R, et al. The Residual Risk Reduction Initiative: a call to action to reduce residual vascular risk in dyslipidaemic patients. Diabetes Vasc Dis Res 2008;5(4):319–35.
[8] Miller M, Stone NJ, Ballantyne C, Bittner V, Criqui MH, Ginsberg HN, et al. Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. Circulation 2011;123(20):2292–333.
[9] Ford ES, Li C, Zhao G, Pearson WS, Mokdad AH. Hypertriglyceridemia and its pharmacologic treatment among US adults. Arch Intern Med 2009;169(6):572–8.
[10] Weitz D, Weintraub H, Fisher E, Schwartzbard AZ. Fish oil for the treatment of cardiovascular disease. Cardiol Rev 2010;18(5):258–63.
[11] Wei MY, Jacobson TA. Effects of eicosapentaenoic acid versus docosahexaenoic acid on serum lipids: a systematic review and meta-analysis. Curr Atheroscler Rep 2011;13(6):474–83.
[12] Jacobson TA, Glickstein SB, Rowe JD, Soni PN. Effects of eicosapentaenoic acid and docosahexaenoic acid on low-density lipoprotein cholesterol and other lipids: a review. J Clin Lipidol 2012;6(1):5–18.
[13] Grundy SM, Cleeman JI, Merz CN, Brewer Jr HB, Clark LT, Hunninghake DB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 2004;110(2):227–39.
[14] Zetia [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; 2013.
[15] Kris-Etherton PM, Harris WS, Appel LJ. Omega-3 fatty acids and cardiovascular disease: new recommendations from the American Heart Association. Arterioscler Thromb Vasc Biol 2003;23(2):151–2.
[16] Bang HO, Dyerberg J. Plasma lipids and lipoproteins in Greenlandic west coast Eskimos. Acta Med Scand 1972;192(1–2):85–94.
[17] Whelton SP, He J, Whelton PK, Muntner P. Meta-analysis of observational studies on fish intake and coronary heart disease. Am J Cardiol 2004;93(9):1119–23.
[18] He K, Song Y, Daviglus ML, Liu K, Van HL, Dyer AR, et al. Accumulated evidence on fish consumption and coronary heart disease mortality: a meta-analysis of cohort studies. Circulation 2004;109(22):2705–11.
[19] Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. N Engl J Med 1999;341(6):410–8.
[20] Rubins HB, Robins SJ, Collins D, Nelson DB, Elam MB, Schaefer EJ, et al. Diabetes, plasma insulin, and cardiovascular disease: subgroup analysis from the Department of Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT). Arch Intern Med 2002;162(22):2597–604.
[21] Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet 2005;366(9500):1849–61.
[22] Ginsberg HN, Elam MB, Lovato LC, Crouse III JR, Leiter LA, Linz P, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med 2010;362(17):1563–74.
[23] Lee M, Saver JL, Towfighi A, Chow J, Ovbiagele B. Efficacy of fibrates for cardiovascular risk reduction in persons with atherogenic dyslipidemia: a meta-analysis. Atherosclerosis 2011;217(2):492–8.
[24] Boden WE, Probstfield JL, Anderson T, Chaitman BR, Desvignes-Nickens P, Koprowicz K, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med 2011;365(24):2255–67.
[25] Capuzzi DM, Guyton JR, Morgan JM, Goldberg AC, Kreisberg RA, Brusco OA, et al. Efficacy and safety of an extended-release niacin (Niaspan): a long-term study. Am J Cardiol 1998;82(12A):74U–81U.
[26] Armitage J. HPS2-THRIVE: randomized placebo-controlled trial of ER niacin and laropiprant in 25,673 patients with pre-existing cardiovascular disease [oral presentation] Presented at the Annual Scientific Session of the American College of Cardiology. San Francisco: CA; 2013. March 9–11.
[27] Knapp HH, Schrott H, Ma P, Knopp R, Chin B, Gaziano JM, et al. Efficacy and safety of combination simvastatin and colesevelam in patients with primary hypercholesterolemia. Am J Med 2001;110(5):352–60.
[28] Ast M, Frishman WH. Bile acid sequestrants. J Clin Pharmacol 1990;30(2):99–106.
[29] Welchol [package insert]. Parsippany, NJ: Daiichi Sankyo Inc.; 2012.
[30] Kastelein JJ, Akdim F, Stroes ES, Zwinderman AH, Bots ML, Stalenhoef AF, et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. N Engl J Med 2008;358(14):1431–43.
[31] IMPROVE-IT: Examining outcomes in subjects with acute coronary syndrome: Vytorin (ezetimibe/simvastatin) vs simvastatin (P04103 AM5) NCT00202878. ClinicalTrials.gov. Available from: http://clinicaltrials.gov/show/NCT00202878, [accessed 06.05.13].
[32] Nestel P, Shige H, Pomeroy S, Cehun M, Abbey M, Raederstorff D. The n-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid increase systemic arterial compliance in humans. Am J Clin Nutr 2002;76(2):326–30.
[33] Ando M, Sanaka T, Nihei H. Eicosapentanoic acid reduces plasma levels of remnant lipoproteins and prevents in vivo peroxidation of LDL in dialysis patients. J Am Soc Nephrol 1999;10(10):2177–84.
[34] Kurabayashi T, Okada M, Tanaka K. Eicosapentaenoic acid effect on hyperlipidemia in menopausal Japanese women. The Niigata Epadel Study Group. Obstet Gynecol 2000;96(4):521–8.
[35] Satoh N, Shimatsu A, Kotani K, Sakane N, Yamada K, Suganami T, et al. Purified eicosapentaenoic acid reduces small dense LDL, remnant lipoprotein particles, and C-reactive protein in metabolic syndrome. Diabetes Care 2007;30(1):144–6.
[36] Tatsuno I, Saito Y, Kudou K, Ootake J. Efficacy and safety of TAK-085 compared with eicosapentaenoic acid in Japanese subjects with hypertriglyceridemia undergoing lifestyle modification: the omega-3 fatty acids randomized double-blind (ORD) study. J Clin Lipidol 2013;7(3):199–207.
[37] Lovaza [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2012.
[38] Epadel [package insert]. Tokyo, Japan: Mochida Pharmaceutical Co., Ltd; 2007.
[39] Harris WS, Ginsberg HN, Arunakul N, Shachter NS, Windsor SL, Adams M, et al. Safety and efficacy of Omacor in severe hypertriglyceridemia. J Cardiovasc Risk 1997;4(5–6):385–91.
[40] Pownall HJ, Brauchi D, Kilinc C, Osmundsen K, Pao Q, Payton-Ross C, et al. Correlation of serum triglyceride and its reduction by omega-3 fatty acids with lipid transfer activity and the neutral lipid compositions of high-density and low-density lipoproteins. Atherosclerosis 1999;143(2):285–97.
[41] Davidson MH, Stein EA, Bays HE, Maki KC, Doyle RT, Shalwitz RA, et al. Efficacy and tolerability of adding prescription omega-3 fatty acids 4 g/d to simvastatin 40 mg/d in hypertriglyceridemic patients: an 8-week, randomized, double-blind, placebo-controlled study. Clin Ther 2007;29(7):1354–67.
[42] Bays HE, McKenney J, Maki KC, Doyle RT, Carter RN, Stein E. Effects of prescription omega-3-acid ethyl esters on non-high-density lipoprotein cholesterol when coadministered with escalating doses of atorvastatin. Mayo Clin Proc 2010;85(2):122–8.
[43] Tricor [package insert]. North Chicago, IL: Abbott Laboratories; 2010.
[44] Niaspan [package insert]. North Chicago, IL: Abbott Laboratories; 2010.
[45] Bays HE, Ballantyne CM, Kastelein JJ, Isaacsohn JL, Braeckman RA, Soni PN. Eicosapentaenoic acid ethyl ester (AMR101) therapy in patients with very high triglyceride levels (from the Multi-center, plAcebo-controlled, Randomized, double-blINd, 12-week study with an open-label Extension [MARINE] trial). Am J Cardiol 2011;108(5):682–90.
[46] Ballantyne CM, Bays HE, Kastelein JJ, Stein E, Isaacsohn JL, Braeckman RA, et al. Efficacy and safety of eicosapentaenoic acid ethyl ester (AMR101) therapy in

statin-treated patients with persistent high triglycerides (from the ANCHOR study). Am J Cardiol 2012;110(7):984–92.
[47] Davidson MH, Kling D, Maki KC. Novel developments in omega-3 fatty acid-based strategies. Curr Opin Lipidol 2011;22(6):437–44.
[48] Davidson MH, Johnson J, Rooney MW, Kyle ML, Kling DF. A novel omega-3 free fatty acid formulation has dramatically improved bioavailability during a low-fat diet compared with omega-3-acid ethyl esters: the ECLIPSE (Epanova compared to Lovaza in a pharmacokinetic single-dose evaluation) study. J Clin Lipidol 2012;6(6):573–84.
[49] Omthera Pharmaceuticals announces positive top-line results from phase 3 EVOLVE study. Omthera Pharmaceuticals. Available from: http://www.omthera.com/pdf/EVOLVE_Data_Final.pdf, [accessed 06.05.13].
[50] Kastelein JJ, Maki KC, Susekov A, Ezhov M, Nordestgaard BG, Kling D, et al. Dose response of a novel free-fatty acid formulation of omega-3 for the management of dyslipidemia in patients with severe hypertriglyceridemia – EpanoVa fOr Lowering Very High TriglycErides (the EVOLVE trial) [abstract 16374]. Circulation 2012;126:A16374.
[51] Efficacy and safety of add-on Epanova® to statin in subjects with persistent hypertriglyceridemia and high risk for cardiovascular disease (ESPRIT). NCT01408303. ClinicalTrials.gov. Available from: http://www.clinicaltrials.gov/ct2/show/NCT01408303?term=nct01408303&rank=1, [accessed 06.05.13].
[52] Maki KC, Orloff D, Nicholls S, Dunbar R, Roth E, Curcio DL, et al. A highly bioavailable omega-3 free-fatty acid reduces non-high density lipoprotein cholesterol in high-risk patients treated with a statin and residual hypertriglycerigemia (ESPRIT trial) [abstract]. J Am Coll Cardiol 2013;61(10 Suppl.):E1468.
[53] Bunea R, El Farrah K, Deutsch L. Evaluation of the effects of Neptune Krill Oil on the clinical course of hyperlipidemia. Altern Med Rev 2004;9(4):420–8.
[54] TRIal For Efficacy of Capre on hyperTriglyceridemiA (TRIFECTA). NCT01455844. Available from: http://clinicaltrials.gov/ct2/show/NCT01455844?term=%28TRIFECTA%29.&rank=1, [accessed 06.05.13].
[55] Study to investigate the effects of krill oil on fasting serum triglycerides. NCT01415388. ClinicalTrials.gov. Available from: http://www.clinicaltrials.gov/ct2/show/NCT01415388?term=NCT01415388&rank=1, [accessed 06.05.13].
[56] Sijtsma L, de Swaaf ME. Biotechnological production and applications of the omega-3 polyunsaturated fatty acid docosahexaenoic acid. Appl Microbiol Biotechnol 2004;64(2):146–53.
[57] Bernstein AM, Ding EL, Willett WC, Rimm EB. A meta-analysis shows that docosahexaenoic acid from algal oil reduces serum triglycerides and increases HDL-cholesterol and LDL-cholesterol in persons without coronary heart disease. J Nutr 2012;142(1):99–104.
[58] Tur JA, Bibiloni MM, Sureda A, Pons A. Dietary sources of omega 3 fatty acids: public health risks and benefits. Br J Nutr 2012;107(Suppl. 2):S23–52.
[59] Pan A, Chen M, Chowdhury R, Wu JH, Sun Q, Campos H, et al. alpha-Linolenic acid and risk of cardiovascular disease: a systematic review and meta-analysis. Am J Clin Nutr 2012;96(6):1262–73.
[60] Ramsden CE, Zamora D, Leelarthaepin B, Majchrzak-Hong SF, Faurot KR, Suchindran CM, et al. Use of dietary linoleic acid for secondary prevention of coronary heart disease and death: evaluation of recovered data from the Sydney Diet Heart Study and updated meta-analysis. Br Med J 2013;346:e8707.
[61] Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet 2007;369(9567):1090–8.
[62] Saito Y, Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Ishikawa Y, et al. Effects of EPA on coronary artery disease in hypercholesterolemic patients with multiple risk factors: sub-analysis of primary prevention cases from the Japan EPA Lipid Intervention Study (JELIS). Atherosclerosis 2008;200(1):135–40.
[63] GISSI Prevenzione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. Lancet 1999;354(9177):447–55.
[64] GISSI-HF Investigators. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet 2008;372(9645):1223–30.
[65] Kromhout D, Giltay EJ, Geleijnse JM. n-3 fatty acids and cardiovascular events after myocardial infarction. N Engl J Med 2010;363(21):2015–26.
[66] Rauch B, Schiele R, Schneider S, Diller F, Victor N, Gohlke H, et al. OMEGA, a randomized, placebo-controlled trial to test the effect of highly purified omega-3 fatty acids on top of modern guideline-adjusted therapy after myocardial infarction. Circulation 2010;122(21):2152–9.
[67] ORIGIN Trial Investigators. n-3 fatty acids and cardiovascular outcomes in patients with dysglycemia. N Engl J Med 2012;367(4):309–18.
[68] Mozaffarian D, Marchioli R, Macchia A, Silletta MG, Ferrazzi P, Gardner TJ, et al. Fish oil and postoperative atrial fibrillation: the Omega-3 Fatty Acids for Prevention of Post-operative Atrial Fibrillation (OPERA) randomized trial. J Am Med Assoc 2012;308(19):2001–11.
[69] Larsson SC, Orsini N, Wolk A. Long-chain omega-3 polyunsaturated fatty acids and risk of stroke: a meta-analysis. Eur J Epidemiol 2012;27(12):895–901.
[70] A study of AMR101 to evaluate its ability to reduce cardiovascular events in high risk patients with hypertriglyceridemia and on statin (REDUCE-IT). Available from: http://clinicaltrials.gov/show/NCT01492361, [accessed 06.05.13].
[71] Wu JH, Micha R, Imamura F, Pan A, Biggs ML, Ajaz O, et al. Omega-3 fatty acids and incident type 2 diabetes: a systematic review and meta-analysis. Br J Nutr 2012;107(Suppl. 2):S214–27.
[72] Collins N, Tighe AP, Brunton SA, Kris-Etherton PM. Differences between dietary supplement and prescription drug omega-3 fatty acid formulations: a legislative and regulatory perspective. J Am Coll Nutr 2008;27(6):659–66.
[73] Food and Drug Administration. Dietary supplements. Food and Drug Administration; Available from: http://www.fda.gov/Food/DietarySupplements/UsingDietarySupplements/ucm109760.htm, [accessed 06.05.13].
[74] Fish oil and omega-3 fatty acid supplements (EPA and DHA from fish, algae, and krill). Consumer Lab; Available from: https://www.consumerlab.com/reviews/fish_oil_supplements_review/omega3, [accessed 06.05.13].
[75] Vascepa [package insert]. Bedminster, NJ: Amarin Pharma Inc.; 2012.
[76] Kataoka Y, Uno K, Puri R, Nicholls SJ. Epanova® and hypertriglyceridemia: pharmacological mechanisms and clinical efficacy. Future Cardiol 2013;9(2):177–86.
[77] Zargar A, Ito MK. Long chain omega-3 dietary supplements: a review of the National Library of Medicine Herbal Supplement Database. Metab Syndr Relat Disord 2011;9(4):255–71.
[78] Krill oil. Monograph. Altern Med Rev 2010;15(1):84–6.