Journal of Clinical Lipidology (2019) 13, 860–872

Journal of Clinical Lipidology

NLA Scientific Statement

National Lipid Association Scientific Statement on the use of icosapent ethyl in statin-treated patients with elevated triglycerides and high or very-high ASCVD risk

Carl E. Orringer, MD, FNLA*, Terry A. Jacobson, MD, FNLA, Kevin C. Maki, PhD, FNLA

Miller School of Medicine, Cardiovascular Division, University of Miami, Miami, FL, USA (Dr Orringer); Department of Medicine, Emory University, Atlanta, GA, USA (Dr Jacobson); School of Public Health, Department of Applied Health Science, Indiana University, Bloomington, IN, USA (Dr Maki); and Midwest Biomedical Research, Center for Metabolic and Cardiovascular Health, Addison, IL, USA (Dr Maki)

KEYWORDS:
Omega-3 fatty acids;
Icosapent ethyl;
Eicosapentaenoic acid;
Cardiovascular disease;
Triglycerides

Abstract: Representatives from the National Lipid Association (NLA) participated in the development of the 2018 American Heart Association/American College of Cardiology/Multisociety Guideline on the Management of Blood Cholesterol, which reaffirmed that lifestyle changes and statin treatment are therapeutic cornerstones for atherosclerotic cardiovascular disease (ASCVD) risk reduction. It also updated prior recommendations to incorporate newer data demonstrating ASCVD risk reduction with ezetimibe and proprotein convertase subtilisin kexin type 9 inhibitors as adjuncts to statin therapy for patients at high and very-high ASCVD risk. The 2018 Guideline was finalized shortly before full results were available from a randomized, placebo-controlled cardiovascular outcomes trial [Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT)] that examined the effects of icosapent ethyl (IPE) 4 g/d on major adverse cardiovascular events in selected high- or very high-risk, statin-treated patients with elevated triglycerides. The primary outcome variable of first major adverse cardiovascular event (cardiovascular death, myocardial infarction, stroke, coronary revascularization and hospitalization for unstable angina) was reduced by 25% (95% confidence interval 17%–32%, $P < .001$). REDUCE-IT served as the primary basis for the NLA's review of evidence for the use of IPE for ASCVD risk reduction. Based on this review, the NLA position is that for patients aged ≥45 years with clinical ASCVD, or aged ≥50 years with diabetes mellitus requiring medication plus ≥1 additional risk factor, with fasting triglycerides 135 to 499 mg/dL on high-intensity or maximally tolerated statin therapy (±ezetimibe), treatment with IPE is recommended for ASCVD risk reduction (evidence rating: class I; evidence level: B-R).

Introduction

Results from observational studies have suggested lower risks for adverse cardiovascular outcomes associated with higher intakes, or higher biomarker levels of, long-chain omega-3 fatty acids, particularly eicosapentaenoic acid

* Corresponding author. Miller School of Medicine, Cardiovascular Diseases, University of Miami, Clinical Research Building, 1120 NW 14th Street, Suite 1111, Miami, FL 33136, USA.
E-mail address: ceo20@med.miami.edu
Submitted October 21, 2019. Accepted for publication October 25, 2019.

1933-2874/
https://doi.org/10.1016/j.jacl.2019.10.014

(EPA) and docosahexaenoic acid (DHA).[1–4] However, results from randomized, controlled trials (RCTs) of omega-3 fatty acid interventions have shown mixed results, with some suggesting cardiovascular outcomes benefits,[5,6] while others failed to support beneficial effects.[7,8]

Interpretation of results from the previously available RCTs was complicated by several design limitations, chief among these being the low dosages used in most trials (median 840 mg/d of EPA + DHA as ethyl esters),[9] which is substantially lower than those doses recommended by the Food and Drug Administration (FDA) for prescription omega-3 products that lower triglycerides (TGs). For example, the daily dosage of omega-3 ethyl esters available as Lovaza and generic products is 3.36 g of EPA + DHA, that of icosapent ethyl (IPE or EPA ethyl esters, available as Vascepa) is 3.84 g, and that of omega-3 carboxylic acids, approved as Epanova, is 3.40 g of EPA + DHA. Benefits in RCTs were observed more consistently in non–placebo-controlled trials,[5,6] and less frequently in placebo-controlled studies.[7,8] Moreover, as of mid-2018, none of the larger RCTs of omega-3 fatty acids that assessed cardiovascular outcomes had specifically selected a sample with elevated TGs. There are several well-documented effects of long-chain omega-3 fatty acids to modify atherosclerotic cardiovascular disease (ASCVD) risk factors, including lowering the plasma TG concentration, in a dose-dependent manner.[10]

One RCT, the Japan EPA Lipid Intervention Study (JELIS), used a higher dosage (1.8 g/d) of EPA given as ethyl esters than had been used in most prior studies.[5] The trial randomly assigned a group of 18,465 Japanese primary and secondary prevention patients with hypercholesterolemia to receive EPA + statin therapy, or statin therapy alone (no placebo). The results showed a 19% relative risk reduction in the primary outcome of major fatal and nonfatal coronary events: hazard ratio (HR): 0.81 (95% confidence interval [CI] 0.69–0.95, $P = .011$). Of note, there was a modest effect of EPA on the plasma TG concentration, with 5% more lowering of the TG level in the EPA arm (9% in the EPA group compared with 4% in the control group). There was a larger reduction in the primary outcome with EPA in the subset of primary prevention subjects with elevated TGs (≥150 mg/dL) and low high-density lipoprotein cholesterol (HDL-C; <40 mg/dL), HR 0.47 (95% CI 0.23–0.98).[11] Greater ASCVD risk reduction among subjects with the phenotype of elevated TGs plus low HDL-C has been reported previously from subgroup analyses of other agents that lower the plasma TG concentration, such as fibrates.[12–14] Furthermore, an analysis of the relationship between on-treatment plasma EPA concentration and incidence of coronary events suggested a dose-response relationship.[11]

Although subgroup and exploratory analyses should be interpreted with caution, the results from JELIS are consistent with the hypotheses that use of lower dosages of omega-3 fatty acids and selection of groups without the high TG and low HDL-C phenotype may have been factors in the failure of some prior trials to provide evidence of benefit.[9] It should also be noted that most prior large-scale omega-3 RCTs used a mix of EPA and DHA (as well as other minor omega-3 fatty acids), whereas JELIS used a formulation of EPA ethyl esters that is essentially free of other omega-3 fatty acids.

In late 2018, results from the Reduction of Cardiovascular Events with EPA-Intervention Trial (REDUCE-IT) were published.[15] This trial was designed in a manner that avoided many of the limitations of prior RCTs by (1) enrolling a study sample at high or very-high ASCVD risk with elevated TGs while on statin therapy; (2) using a comparatively high dosage of omega-3 fatty acids (3.84 g/d of EPA in the form of IPE); and (3) using a double-blind, placebo-controlled design. REDUCE-IT served as the primary basis for the National Lipid Association's (NLA's) review of evidence for the use of IPE for ASCVD risk reduction. The rationale for the NLA's recommendation is outlined in this Scientific Statement.

2018 American Heart Association/American College of Cardiology/Multisociety Guidelines for treatment of high-risk and very-high-risk patients

Representatives from the NLA participated in the development of the 2018 American Heart Association (AHA)/American College of Cardiology (ACC)/Multisociety Guideline on the management of blood cholesterol, which reaffirmed that lifestyle changes and statin treatment are the therapeutic cornerstones for ASCVD risk reduction.[16] The 2018 Guideline also updated prior recommendations to incorporate the newer data demonstrating ASCVD risk reduction with ezetimibe and proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors as adjuncts to statin therapy for patients at high and very-high ASCVD risk. Very-high-risk individuals were characterized as having a history of two major ASCVD events or one major ASCVD event and two or more high-risk conditions. Major ASCVD events and high-risk conditions are defined in Figure 1. High-risk ASCVD is defined as clinical ASCVD in patients who do not meet the criteria for very-high-risk categorization. Based on RCT data, patients with uncomplicated ASCVD are estimated to have a 20% to 29% 10-year risk of ASCVD events.[17] Those with very-high risk have an estimated 10-year risk ≥30%, and some patients, such as those with clinical ASCVD and either ischemic stroke, peripheral arterial disease, or recurrent cardiovascular events, have a 10-year risk exceeding 40%.[17]

Hypertriglyceridemia, TG-lowering therapies, and ASCVD risk

Epidemiological[18–20] and Mendelian randomization studies[21] have demonstrated that fasting or nonfasting TG elevation is associated with increased ASCVD risk. This

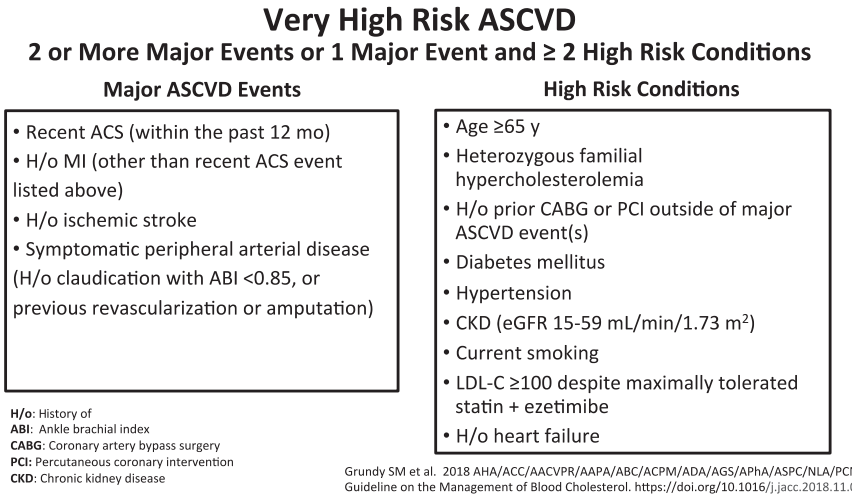

Figure 1 2018 American Heart Association/American College of Cardiology/Multisociety Guideline on Management of Cholesterol: Classification of very high risk atherosclerotic cardiovascular disease (ASCVD)*. *Note: the definitions of high and very high risk for atherosclerotic cardiovascular disease (ASCVD) outlined in the 2018 American Heart Association (AHA)/American College of Cardiology (ACC)/Multisociety Guideline differ from those used to qualify for entry into the Reduction of Cardiovascular Events with Icosapent Ethyl Intervention Trial (REDUCE-IT). However, a large majority of subjects in REDUCE-IT had 10-year ASCVD event risk ≥20%, as indicated by a 14.8% incidence of the key secondary end point (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) in the placebo group during median follow-up of 4.9 years, which projects to >30% 10-year risk.

heightened risk is associated with increased circulating concentrations of cholesterol carried by partially delipidated TG-rich lipoprotein particles,[22,23] and the often coexistent proinflammatory, prothrombotic, and oxidative milieu[23–25] associated with insulin resistance.[26] The 2018 AHA/ACC/Multisociety Guideline identifies moderate hypertriglyceridemia (TG ≥ 175 mg/dL) as a "risk-enhancing factor" to be considered in the clinician-patient risk discussion, the presence of which favors the initiation or intensification of statin therapy, but does not otherwise make specific recommendations about using TG-lowering drugs to improve cardiovascular outcomes.[16]

NLA's Recommendations for the Patient-Centered Management of Dyslipidemia, published in 2015, outlined the central role of elevated concentrations of cholesterol carried by atherogenic lipoprotein particles (ie, non–HDL-C) as a root cause of atherosclerosis and that reduction in the circulating levels of these lipoproteins would lower ASCVD risk in proportion to the extent that atherogenic cholesterol is reduced.[27,28] Non–HDL-C comprises cholesterol carried by all apolipoprotein B (apo B)–containing lipoproteins, including low-density lipoprotein (LDL), intermediate-density lipoprotein, lipoprotein (a), very-low-density lipoprotein (VLDL), chylomicrons, and chylomicron remnant particles. Throughout this article, the term VLDL-C will be used to denote cholesterol carried by all apo B–containing particles with density lower than LDL, which includes true VLDL-C, as well as chylomicrons and chylomicron remnant particles. Other terms have been used in the literature for this fraction, including remnant cholesterol and TG-rich lipoprotein cholesterol. Elevation in plasma TG is typically accompanied by an elevation in VLDL-C, although the relationship becomes nonlinear at higher levels of TG, particularly above 400 mg/dL, because severe TG elevation is associated with a higher molar ratio of TG to cholesterol in VLDL and other TG-rich lipoprotein particles.[29] Nevertheless, changes in plasma TG concentration induced by pharmaceutical agents such as omega-3 fatty acids, fibrates, niacin, and statins generally correlate strongly with changes in the VLDL-C concentration.[30]

Because of the central role in TG catabolism played by lipoprotein lipase (LPL), identification of mutations in apolipoproteins that alter the activity of this enzyme has been an important focus of studies on the impact of TG and VLDL-C levels on ASCVD risk. apo C3, which resides on the surface of TG-rich lipoproteins, inhibits LPL-mediated lipolysis of these lipoproteins and raises circulating TG levels. Exome sequencing studies of individuals of European or African American descent who have mutations in the gene encoding apo C3 demonstrated that heterozygous carriers of one of four loss-of-function mutations of *APOC3* had circulating TG concentrations that were 39% lower and coronary heart disease (CHD) risk that was 40% lower than noncarriers.[31] Mutations in the *APOA5*, *ANGPTL3*, and *ANGPTL4* genes, as well in the *LPL* gene itself, also result in the altered expression of proteins that affect LPL function, and add further support to the concept that elevated concentrations of TG and TG-rich lipoproteins contribute to ASCVD risk.[32–37]

A series of Mendelian randomization analyses has demonstrated that TG-lowering *LPL* variants and LDL-C-lowering LDL receptor (*LDLR*) variants were associated with similar reductions in risk of CHD per unit difference in LDL-C and VLDL-C, which is estimated with the Friedewald equation as the TG concentration in mg/dL divided

by five when the TG level is not markedly elevated.[38] LDL-C and VLDL-C (or TG) each lose statistical significance after adjustment for apo B concentration. Thus, genetically mediated differences in both components of non–HDL-C (LDL-C and VLDL-C) are independently associated with ASCVD risk to a similar degree per mg/dL difference. Furthermore, this relationship may be mediated through the concentration of circulating lipoprotein particles with atherogenic potential because each particle of LDL and VLDL contains a single molecule of apo B.

Several investigations have identified hypertriglyceridemia as a marker of increased residual ASCVD risk in statin-treated patients.[39–41] RCTs of TG-lowering treatments, including niacin[42,43] and some fibrates,[44] in which trial enrollment was not based on the presence of hypertriglyceridemia, did not achieve their primary end points of CHD or ASCVD risk reduction. However, among trials that included subgroup analyses for subjects with elevated baseline TG, particularly if accompanied by low HDL-C, pooled estimates suggest ASCVD risk reduction.[12–14,45] For example, in a meta-analysis of 10 RCTs of TG-lowering therapies, including fibrates, niacin and EPA ethyl esters, for which subgroup analyses were reported for subjects with TG elevation and/or TG elevation plus low HDL-C, the pooled estimate for relative risk reduction was 12% (95% CI: 5%–18%) overall, 18% (95% CI: 9%–27%) for subgroups with elevated TG, and 29% (95% CI: 19%–37%) for subgroups with elevated TG plus low HDL-C.[12]

Effects of long-chain omega-3 fatty acid interventions on ASCVD risk

A 2017 Science Advisory from the AHA stated that available evidence did not support the use of low-dose omega-3 fatty acid supplementation (approximately 850–1000 mg of EPA and DHA/d) to reduce ASCVD risk for individuals in the general population, including those with prediabetes or diabetes, who are not at high risk of ASCVD. However, it stated that low-dose omega-3 fatty acid supplementation was reasonable for secondary prevention of CHD in those with a recent CHD event and for heart failure patients with reduced ejection fraction.[46] This recommendation was based on a meta-analysis that showed modest risk reduction (RR) for CHD death (RR 0.91, 95% CI: 0.85–0.98) in secondary prevention[4] and a reduction in total mortality (RR: 0.91, 95% CI: 0.83–0.99) in heart failure patients with reduced ejection fraction.[47]

Results from a subsequent meta-analysis of 10 trials, using aggregated study-level data involving 77,917 individuals, 66% with a prior history of CHD, 28% with a prior stroke, and 37% with prior diabetes treated with daily dosages of EPA from 226 to 1800 mg and DHA from 0 to 1700 mg, suggested no significant effects on the risks of CHD, stroke, coronary, or noncoronary revascularization or major vascular events.[48] However, the results were consistent with a possible benefit for CHD death that was of marginal statistical significance (RR: 0.93, 95% CI: 0.85–1.00, $P = .05$) but similar in magnitude to previously reported findings.[4,49]

Since the publication of that meta-analysis, results from three large-scale RCTs of omega-3 fatty acid interventions have been published: A Study of Cardiovascular Events in Diabetes,[50] the Vitamin D and Omega-3 Trial,[51] and REDUCE-IT[15] When the results from the 2 trials (A Study of Cardiovascular Events in Diabetes and Vitamin D and Omega-3 Trial) using lower dosage interventions (840 mg/d EPA + DHA as ethyl esters) in primary prevention populations were added to those of the meta-analysis discussed previously,[48] a benefit of low-dosage omega-3 therapy for lowering risk of CHD death was further supported: 1405 events in 59,684 subjects for the omega-3 interventions compared with 1529 events in 59,560 subjects for the control conditions (RR: 0.92, 95% CI: 0.86–0.99, $P = .014$).[52] Significantly lower risks were also observed for myocardial infarction, total CHD, CVD death, and total CVD with pooled relative risk reduction estimates ranging from 5 to 8%.

REDUCE-IT: RCT of high-dose IPE on cardiovascular outcomes in statin-treated subjects with elevated TG

REDUCE-IT was a multicenter, randomized, double-blind, placebo-controlled trial of 8179 statin-treated subjects with established ASCVD, or with diabetes and at least one other risk factor. REDUCE-IT was undertaken to assess whether the addition of this highly purified and stable formulation of EPA ethyl esters (ie, IPE) could safely provide net ASCVD risk reduction benefit in patients already receiving evidence-based statin therapy who continued to have persistently elevated fasting TG.[15] Study subjects were men and women with established clinical ASCVD ≥45 years of age (secondary prevention cohort, 70.7% of those enrolled) or with type 2 diabetes mellitus ≥50 years of age requiring medication for their diabetes, with at least one additional risk factor (primary prevention cohort, 29.3% of those enrolled). All subjects were on a stable regimen of statin ± ezetimibe for at least 4 weeks before qualification, with fasting TG levels of 135 to 499 mg and a median baseline concentration of 216 mg/dL. They were required to have LDL-C 41 to 100 mg/dL and had a median baseline concentration of 75 mg/dL. Approximately 93% of subjects were receiving moderate- or high-intensity statin therapy, 6% were receiving ezetimibe, and none were receiving a PCSK9 inhibitor. The patients were randomized to receive 2 g of IPE twice daily with food, or a mineral oil placebo. The primary end point was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina, and the key secondary end point was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. The median follow-up was 4.9 years.

During the trial, there were one-year placebo-corrected reductions in TG of 19.7% ($P < .001$), non–HDL-C of 13.1% ($P < .0001$), LDL-C of 6.6% ($P < .001$), and HDL-C of 6.3% ($P < .001$) and at 2 years, an apo B reduction of 9.7% and a median reduction in high-sensitivity C-reactive protein (hs-CRP) of 39.9% (Table 1). Serum EPA levels increased from a baseline of 26.1 μg/mL to 144 μg/mL, a median increase of 358%.

A primary end-point event occurred in 17.2% of the patients in the IPE group, vs 22.0% of the patients in the placebo group (HR, 0.75; 95% CI, 0.68–0.83; $P < .001$), representing a relative risk reduction of 24.8%, an absolute risk reduction of 4.8%, and a number needed to treat to prevent one event of 21 (95% CI: 15–33), $P < .001$ (Fig. 2). A key secondary end point was reported in 11.2% of those taking IPE vs 14.8% of those in the placebo group (HR, 0.74; 95% CI, 0.65–0.83; $P < .001$), representing a relative risk reduction of 26.5%, an absolute risk reduction of 3.6%, and a number needed to treat of 28 (95% CI: 20–47; $P = .001$). All prespecified individual end points showed a lower hazard in the IPE group except for total mortality.

Treatment emergent adverse events occurred at similar rates in the IPE and placebo groups. There was a trend toward more bleeding-related disorders in the IPE group (2.7% vs 2.1%), but this did not reach statistical significance ($P = .06$). Notably, there was no significant excess of bleeding episodes in the central nervous system (0.3% vs 0.2%, $P = .42$) or gastrointestinal tract (1.5% vs 1.1%, $P = .15$), and there were no fatal bleeding episodes. Also of potential clinical importance, there was more peripheral edema (6.5% vs 5.0%, $P = .002$), constipation (5.4% vs 3.6%, $P < .001$), atrial fibrillation (5.3% vs 3.9%, $P = .003$), and atrial fibrillation requiring hospitalization (3.1% vs 2.1%, $P = .004$) with IPE than placebo.

A prespecified analysis of ASCVD outcomes in REDUCE-IT examined differences in the incidence of total primary end-point events, including second and third or higher events. IPE reduced total primary events (61 vs 89 per 1000 patient years for IPE vs placebo, respectively; rate ratio: 0.70, 95% CI: 0.62–0.78, $P < .001$). The totals for each of the components of the primary composite end point and the total key secondary end-point events were favorably affected (32 vs 44 per 1000 patient years for IPE vs placebo, respectively; rate ratio: 0.72, 95% CI: 0.63–0.82, $P < .001$).[53]

Effects of IPE were consistent across numerous prespecified and exploratory subgroups, with little indication of heterogeneity. Notably, the primary outcome did not differ significantly by baseline or on-treatment categories of TG concentration. There was significant heterogeneity by age category, with larger risk reduction in those aged <65 years compared with those aged ≥65 years (35% vs 13% relative risk reduction, P for heterogeneity = .004). There was also significantly larger relative risk reduction among subjects with high TG (≥200 mg/dL) and low HDL-C (≤35 mg/dL) compared with those who did not display this phenotype (38% vs 21%, P for heterogeneity = .04). Subgroup analyses should be interpreted with caution. However, it is of interest that this pattern has been observed previously in JELIS and studies of other agents that mainly lower TG-rich lipoprotein levels.[11–14]

Possible mechanisms to explain the ASCVD risk reduction in REDUCE-IT

A variety of lipid and nonlipid factors may contribute to the observed benefit of IPE on ASCVD event risk. It is likely that part of the benefit is attributable to a reduction in TG-rich lipoproteins and associated variables such as the circulating TG and VLDL-C concentrations. Multiple mechanisms may account for the effect of IPE to reduce the plasma concentrations of TG and TG-rich lipoproteins, including reduced hepatic secretion of VLDL and reduced TG-enrichment of those lipoproteins secreted; inhibition of diacylglycerol acyl transferase, the major TG-synthesizing enzyme in the liver; inhibition in the activity of phosphatidic acid phosphatase, an enzyme that controls the cellular

Table 1 REDUCE-IT: effects of icosapent ethyl and placebo on biomarkers[15]

	IPE, median (n = 4089)		PBO, median (n = 4090)			
Biomarker	Baseline	Year 1*	Baseline	Year 1*	PBO-corrected, median %Δ	%Δ *P*-value
TG (mg/dL)	216.5	175.0	216.0	221.0	−19.7	<.0001
Non-HDL-C (mg/dL)	118.0	113.0	118.5	130.0	−13.1	<.0001
LDL-C (mg/dL)	74.0	77.0	76.0	84.0	−6.6	<.0001
HDL-C (mg/dL)	40.0	39.0	40.0	42.0	−6.3	<.0001
apo B (mg/dL)	82.0	80.0	83.0	89.0	−9.7	<.0001
hs-CRP (mg/L)	2.2	1.8	2.1	2.8	−39.9	<.0001
EPA (μg/mL)	26.1	144.0	26.1	23.3	+358.8	<.0001

%Δ, percent change; apo, apolipoprotein; BL, baseline; EPA, eicosapentaenoic acid; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; PBO, placebo; TG, triglycerides; REDUCE-IT, Reduction of Cardiovascular Events with Icosapent Ethyl—Intervention Trial.

*apo B and hs-CRP were measured at year 2; all other biomarker measurements were at year 1.

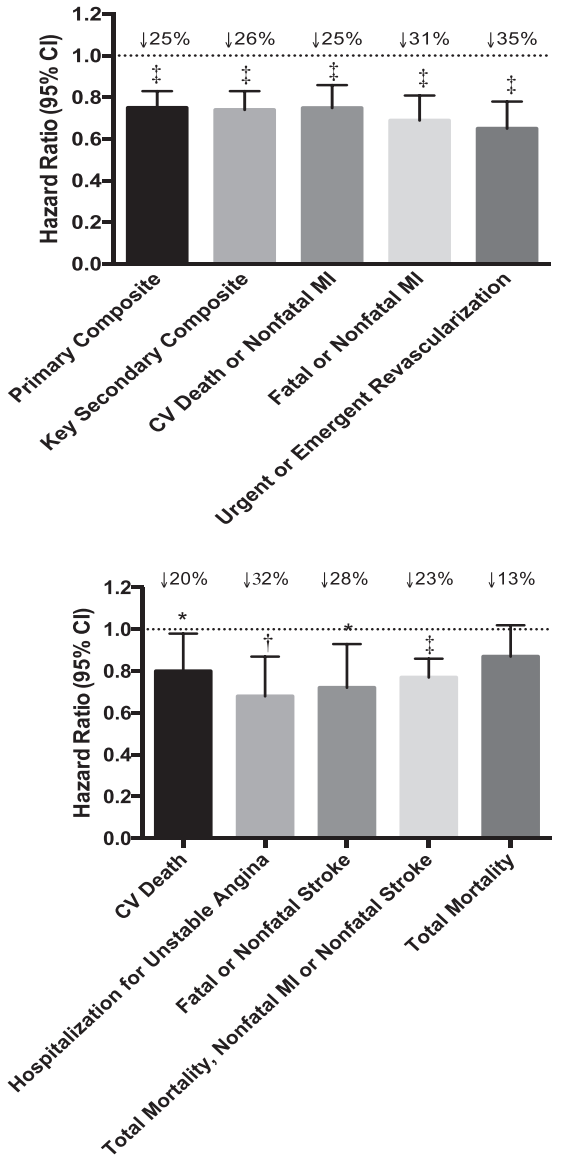

Figure 2 Hazard ratios and 95% confidence intervals for cardiovascular end points[1] from prespecified hierarchical testing of icosapent ethyl vs placebo in REDUCE-IT.[15] [1]Primary endpoint = CV death, MI, stroke, coronary revascularization and unstable angina; Key secondary end point = CV death, MI, and stroke. *$P < .05$; †$P < .01$; ‡$P < .001$. CI, confidence interval; CV, cardiovascular; MI, myocardial infarction; REDUCE-IT, Reduction of Cardiovascular Events with Icosapent Ethyl—Intervention Trial.

levels of diacylglycerol; reduced activity of the transcription of the gene for sterol element regulatory element binding protein 1c; and increased intracellular degradation of apo B.[10]

Changes in non–HDL-C reflect the net result of changes in both of its major components, LDL-C and VLDL-C.[27] In clinical trials of statin therapy, which predominantly lowers LDL-C, and fibrate therapy, which predominantly lowers VLDL-C (and TG) concentration, the difference between treatments in non–HDL-C is a strong predictor of cardiovascular outcome benefits. In a recent meta-regression analysis,[54] each 1 mmol/L (39 mg/dL) reduction in non–HDL-C concentration was associated with a relative risk reduction for major adverse cardiovascular events of 20% (95% CI: 18%–23%, n = 19 trials) for statin therapy and 21% (95% CI: 12%–29%, n = 8 trials) for fibrate therapy.

In REDUCE-IT, the placebo-corrected reduction in non–HDL-C level at year 1 was 15.5 mg/dL (0.37 mmol/L).[15] Based on the relationships observed in statin and fibrate trials, the expected relative risk reduction from non–HDL-C lowering would thus be ~8.8%, which is well below the 21.8% relative risk reduction observed. (Note that the relative risk reduction based on cumulative incidence in REDUCE-IT was slightly smaller than the HR risk reduction [based on incidence rates] of 24.8%.)

Therefore, it is reasonable to hypothesize that the risk reduction may be attributable, in part, to mechanisms other than effects on plasma lipids and lipoproteins. During REDUCE-IT, there was a 39.9% median placebo-corrected reduction (0.9 mg/L) in hs-CRP ($P < .001$), consistent with an anti-inflammatory effect.[15] Prior studies have also shown other potentially beneficial effects of long-chain omega-3 fatty acids, including reduced platelet activation, lower heart rate and blood pressure, antifibrotic and antioxidative effects, cardiac membrane stabilization, and increased red blood cell membrane fluidity.[55–58] Additional potential mechanisms for the favorable effects of long-chain omega-3 fatty acids, and EPA in particular, have been reviewed elsewhere in more detail.[55–58]

Plasma EPA may be a marker that correlates with other physiologic processes that contribute to risk reduction. This hypothesis is supported by analyses from the JELIS trial, in which differences between groups in TG (~5%) and non–HDL-C (~1%) levels were minimal, but EPA treatment was associated with a 19% relative risk reduction in the primary outcome of major adverse coronary events.[5] An analysis was completed of the event risk according to on-treatment level of EPA in all participants, which suggested a dose-response relationship. Those with plasma EPA ≥150 μg/mL (61% of those in the EPA group) had 20% (95% CI 1% to 36%) lower event risk than those in the reference group with EPA <87 μg/mL. Smaller and nonsignificantly lower risks (2%–5%) were observed for those in the intermediate EPA categories of 87 to 99 and 100 to 149 μg/mL.[59] Average consumption of fish rich in omega-3 fatty acids in Japan is higher than that in the United States[60,61] The mean baseline level of EPA of the Japanese subjects in JELIS, ~95 μg/mL, is markedly higher than the median value of 26 μg/mL among subjects in REDUCE-IT[15,59] The median on-treatment plasma EPA concentration at 1 year in REDUCE-IT was slightly less than the mean on-treatment level of 170 μg/mL observed in subjects receiving EPA ethyl esters in JELIS.[15,59] The median difference between groups for on-treatment level of EPA in REDUCE-IT (114.9 μg/mL) was larger than that for JELIS (mean difference ~67 μg/mL). Additional research will be needed to determine whether plasma EPA, the ratio of EPA to arachidonic acid, or other

biomarkers of omega-3 status such as plasma phospholipid or erythrocyte membrane levels will prove useful as treatment goals.

Recommendations from other organizations

Based on the results of REDUCE-IT, an update to the 2019 American Diabetes Association Standards of Medical Care was published by the American Diabetes Association's Professional Practice Committee in March 2019. Their recommendation is that the addition of IPE "be considered for patients with diabetes mellitus and atherosclerotic cardiovascular disease or other cardiac risk factors on a statin with controlled LDL-C, but with elevated triglycerides (135–499 mg/dL) to reduce cardiovascular risk."[62] Similar endorsement was provided in the 2019 European Society of Cardiology/European Atherosclerosis Society Guidelines for the Management of Dyslipidemia, which stated that the use of IPE in a dose of 2 g twice daily should be considered in combination with a statin in high-risk (or above) patients with TG levels 135 to 499 mg/dL, despite statin treatment.[63]

NLA recommendation on use of IPE for ASCVD risk reduction

Based on the considerations mentioned previously, for patients 45 years of age or older with clinical ASCVD, or 50 years or older with diabetes mellitus requiring medication and ≥1 additional risk factor (Additional risk factors include the following, based on the entry criteria in REDUCE-IT: age (men ≥55, women ≥65 years of age), cigarette smoker or stopped smoking within 3 months, hypertension (treated or untreated), HDL-C ≤40 mg/dL for men or ≤50 mg/dL for women, hs-CRP >3.0 mg/L, renal dysfunction with creatinine clearance >30 and < 60 mL/min, retinopathy, microalbuminuria or macroalbuminuria, ankle-brachial index <0.9 without symptoms of intermittent claudication.), with fasting TG 135 to 499 mg/dL on high-intensity or maximally tolerated statin, with or without ezetimibe, treatment with IPE is recommended for ASCVD risk reduction; evidence rating: class I, level B-R (Table 2).

Strength of recommendation and evidence grading for IPE therapy for ASCVD risk reduction

The Class (strength of recommendation) and level (quality) of evidence as described in the 2016 ACC/AHA Clinical Practice Guideline Recommendation Classification System is shown in Figure 3.[64,65] The conclusion, based primarily on the results of REDUCE-IT as a single large, high-quality, RCT, is that the use of 4 g/d of IPE for ASCVD risk reduction in hypertriglyceridemic adults with ASCVD and/or diabetes mellitus on high-intensity or maximally tolerated statin therapy, is considered a class I B-R recommendation. Although the results of JELIS also showed ASCVD risk reduction benefit with the use of 1.8 g/d of EPA ethyl esters, its lack of placebo control and use of exclusively low-intensity statins would not alone support a class 1A recommendation for the use of IPE. However, the results from JELIS were considered supportive of those from REDUCE-IT and did influence some elements of the recommendation.

Although the results of REDUCE-IT would appear to justify its classification as I B-R recommendation for use, there is not universal agreement that the presented evidence supports this viewpoint. Some have suggested that the favorable results of a single trial of a new drug, using a different mechanism of action than that which has already been established, might be driven by the play of chance, or unique elements of the study design or conduct. Concern has been raised in REDUCE-IT about the use of a mineral oil placebo, which has been associated with adverse effects on some cardiometabolic risk factors, possibly through partial interference with statin absorption.[15] An 8 mg/dL rise in LDL-C (5 mg/dL more than with IPE) over the course of the study was noted in the placebo arm from 76 mg/dL to

Table 2 NLA recommendation on use of icosapent ethyl for ASCVD risk reduction

NLA recommendation on use of icosapent ethyl for ASCVD risk reduction	COR	LOE
For patients aged 45 y or older with clinical ASCVD, or 50 y or older with diabetes mellitus requiring medication and ≥1 additional risk factor,* with fasting TG 135–499 mg/dL on high-intensity or maximally tolerated statin, with or without ezetimibe, treatment with icosapent ethyl is recommended for ASCVD risk reduction.	I	B-R

ASCVD, atherosclerotic cardiovascular disease; COR, class of the recommendation; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LOE, levels of the evidence; REDUCE-IT, Reduction of Cardiovascular Events with Icosapent Ethyl—Intervention Trial; TG, triglycerides.

The recommendation was graded by the class of the recommendation and by the levels of the evidence supporting the recommendation.

*Additional risk factors include the following, based on the entry criteria in REDUCE-IT: age (men ≥55 y, women ≥65 y of age), cigarette smoker or stopped smoking within 3 mo, hypertension (treated or untreated), HDL-C ≤40 mg/dL for men or ≤50 mg/dL for women, hs-CRP >3.0 mg/L, renal dysfunction with creatinine clearance >30 and < 60 mL/min, retinopathy, microalbuminuria or macroalbuminuria, ankle-brachial index <0.9 without symptoms of intermittent claudication.

CLASS (STRENGTH) OF RECOMMENDATION
CLASS I (STRONG) **Benefit >>> Risk**

Suggested phrases for writing recommendations:
• Is recommended
• Is indicated/useful/effective/beneficial
• Should be performed/administrated/other
• Comparative-Effectiveness Phrases:
  ○ Treatment / strategy A is recommended / indicated in preference to treatment B
  ○ Treatment A should be chosen over treatment B

CLASS IIa (MODERATE) **Benefit >> Risk**

Suggested phrases for writing recommendations:
• Is reasonable
• Can be useful/effective/beneficial
• Comparative-Effectiveness Phrases:
  ○ Treatment/strategy A is probably recommended/indicted in preference to treatment B
  ○ It is reasonable to choose treatment A over treatment B

CLASS IIb (WEAK) **Benefit ≥ Risk**
Suggested phrases for writing recommendations: • May/might be reasonable • May/might be considered Usefulness/effectiveness is unknown/unclear/uncertain or not well established
CLASS III: No Benefit (MODERATE) **Benefit = Risk**
Suggested phrases for writing recommendations: • Is not recommended • Is not indicated/useful/effective/beneficial • Should not be performed/administered/other
CLASS III: Harm (STRONG) **Risk > Benefit**
Suggested phrases for writing recommendations: • Potentially harmful • Causes harm • Associated with excess morbidity/mortality • Should not be performed/administered/other

* As described in the 2015 ACC/AHA Clinical Practice Guideline Recommendation Classification System

LEVEL (QUALITY) OF EVIDENCE
LEVEL A
• High-quality evidence from more than 1 RCT • Meta-analyses of high-quality RCTs • One or more RCTs corroborated by high-quality registry studies
LEVEL B-R (Randomized)
• Moderate-quality evidence from 1 or more RCTs • Meta-analysis of moderate-quality RCTS
LEVEL B-NR (Nonrandomized)
• Moderate-quality evidence from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies • Meta-analyses of such studies
LEVEL C-LD (Limited Data)
• Randomized or nonrandomized observational or registry studies with limitations of design or execution • Meta-analyses of such studies • Physiological or mechanistic studies in human subjects
LEVEL C-EO (Expert Opinion)
• Consensus of expert opinion based on clinical experience

* As described in the 2015 ACC/AHA Clinical Practice Guideline Recommendation Classification System

Figure 3 2016 American College of Cardiology/American Heart Association Clinical Practice Guideline Classification System: Strength of Recommendation and Evidence Grading System.[64,65] ACC, American College of Cardiology; AHA, American Heart Association; RCT, randomized controlled trial.

84 mg/dL, and an increase in hs-CRP from 2.1 to 2.8 mg/L was also noted. These considerations impact the question of whether the observed benefit was entirely due to the study drug, or may have been partially contributed to by harm from the mineral oil control.[66] These remain important questions. However, as described in an editorial that accompanied the REDUCE-IT paper, based on the modest changes from baseline with the mineral oil placebo in lipids and other risk markers, such as hs-CRP, it appears unlikely that adverse effects of the placebo control can explain more than a small fraction of the observed benefit.[67] Furthermore, it is important to note that the 19% relative risk reduction in major adverse coronary events in JELIS was with a lower dosage (1.8 g/d EPA) in a trial without a placebo control. For comparison, in REDUCE-IT, relative risk reductions of 31% to 35% were observed in fatal or nonfatal myocardial infarction, hospitalization for unstable angina, and urgent or emergency revascularization.

When considering approval for a new indication, the U.S. FDA may waive the requirement for a second confirmatory study when the effectiveness can be extrapolated from other types of data (eg, use in a new population or different dose or regimen) or when a single, well-done multicenter trial is completed with a substantial improvement in a patient-centered outcome. Whether the highly favorable results of REDUCE-IT meet those criteria to win an FDA approval for the indication of ASCVD risk reduction remains to be seen at the time of this writing. However, based on the strength of the findings, the study design, the favorable directionality of JELIS as a confirmatory study, and the safety and favorable side effect profile of IPE, the NLA supports the use of this agent in statin-treated patients with ASCVD and/or diabetes mellitus and TG elevation (135–499 mg/dL). IPE is, therefore, a third class of evidence-based therapy, joining ezetimibe and PCSK9 inhibitors, for use as an adjunct to statins for ASCVD risk reduction (Fig. 4).

It should be noted that the subjects randomized to IPE or placebo in REDUCE-IT all had LDL-C in the range of 41 to 100 mg/dL while on stable-dose, moderate- or high-intensity statin therapy. The NLA recommendation is that high- and very-high-risk patients receive high-intensity statin therapy or maximally tolerated statin therapy for management of LDL-C. IPE should be considered for those with TG elevation despite statin therapy, with or without ezetimibe. The review panel did not feel that it was necessary to restrict IPE to those with LDL-C in the range of 41 to 100 mg/dL because the subjects in JELIS showed 19% major adverse coronary event risk reduction in the EPA arm while taking low-intensity statin therapy with a mean on-trial level of LDL-C >130 mg/dL. Ezetimibe and/or PCSK9 inhibitor therapy may be considered for patients in need of additional LDL-C lowering. Limited evidence is available regarding the use of IPE in conjunction with these therapies because only ~6% of REDUCE-IT patients were taking ezetimibe and none were treated with a concomitant PCSK9 inhibitor.

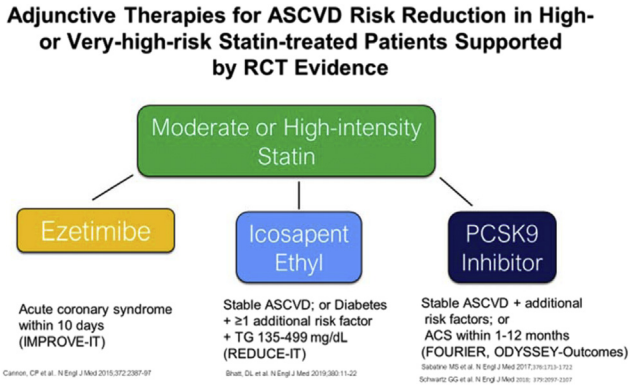

Figure 4 NLA recommendations on adjunctive therapies for ASCVD risk reduction in high- or very-high-risk statin-treated patients. ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (with Evolocumab); IMPROVE-IT, Improved Reductions of Outcomes: Vytorin Efficacy International Trial; NLA, National Lipid Association; ODYSSEY-Outcomes, Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab; PCSK9, proprotein convertase subtilisin kexin type 9; RCT, randomized controlled trial; REDUCE-IT, Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial; TG, triglyceride.

Key future studies

As the roles of various mechanisms by which IPE reduces ASCVD risk are not fully understood, results of pending mechanistic investigations from the REDUCE-IT data set and other ASCVD outcomes trials will help further clarify important questions. At present, it is unknown whether high dosage (3–4 g/d) EPA and DHA combination therapy will produce similar results to those of high dosage (3–4 g/d) IPE. An additional important issue is whether the use of the selective peroxisome proliferator activated receptor alpha modulator, pemafibrate,[68] a drug in development, which significantly lowers TG and VLDL-C, inhibits apo C3 activity, and attenuates postprandial hyperlipidemia, will also produce ASCVD risk reduction benefits in hypertriglyceridemic subjects on statin therapy. Ongoing trials in progress for agents that mainly alter plasma TG and TG-rich lipoproteins that might shed light on the mechanisms of IPE and other therapies include the Outcomes Study to Assess Statin Residual Risk Reduction with Epanova in High CV Risk Patients with Hypertriglyceridemia (STRENGTH; NCT02104817), Effect of Vascepa on Improving Coronary Atherosclerosis in People with High Triglycerides Taking Statin Therapy (EVAPORATE; NCT02926027), Efficacy Study Regarding the Beneficial Effects of Omega-3 Fatty Acids on Cardiometabolic Health (RESPECT-EPA; NCT02042272), Omega-3 Fatty Acids in Elderly Patients with Acute Myocardial Infarction (OMEMI; NCT01841944), and Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes (PROMINENT; NCT03071692). Key aspects of the study designs of STRENGTH[69] and PROMINENT[70] are summarized in Table 3.

Table 3 Key ASCVD outcome trials in progress in patients with hypertriglyceridemia[69,70]

Study and drug	Objective	Study design and duration	Patient characteristics	Primary end point(s)	Secondary end points	Secondary end points	Estimated study completion date
STRENGTH Omega-3 carboxylic acids (NCT02104817)	To determine whether omega-3 carboxylic acids 4 g/d vs corn oil placebo reduces the incidence of CV events in high-risk statin-treated patients with hypertriglyceridemia and low HDL-C	Randomized, double-blind, placebo-controlled, 5-y follow-up	N = 13,086, multinational. Men and women aged ≥18 y at high-risk for CVD. Statin treated for >4 wk and have LDL-C <100 or LDL-C ≥100 mg/dL on maximally tolerated statin. Baseline TG ≥ 180 to <500 mg/dL. HDL-C <42 mg/dL men or <47 women. ≥50% secondary prevention	Time to first occurrence of CV death, nonfatal MI, nonfatal stroke, emergent/elective coronary revascularization, or hospitalization for unstable angina.	1. The composite measure of CV events that include the first occurrence of CV death, nonfatal MI and nonfatal stroke 2. The composite measure of coronary events that include the first occurrence of cardiac death. (cont.)	3. The first occurrence of individual components of MACE 4. Time to CV death	October 2020
PROMINENT Pemafibrate (NCT03071692)	To determine whether pemafibrate 0.2 mg twice daily vs placebo reduces the incidence of CV events in patients with type 2 diabetes	Randomized, double-blind, placebo-controlled 4-y follow-up	N = 10,000, multinational. Men and women with type 2 diabetes, age ≥50 y if male or ≥ 55 y if female (primary prevention cohort) or age ≥18 y and established ASCVD (secondary prevention cohort). TG 200–499 mg/dL and HDL-C ≤40 mg/dL. On moderate- or high-intensity statin with LDL-C ≤70 mg/dL, or ≤100 mg/dL if statin intolerant.	Number of patients with first occurrence of nonfatal MI, nonfatal ischemic stroke, hospitalization for unstable angina requiring unplanned coronary revascularization, or CV death.	1. Time to first occurrence of any component of the 3-component composite end point of nonfatal MI, nonfatal stroke, or CV death 2. Time to first occurrence of any component of the primary end point or hospitalization for HF 3. Time to first occurrence of any component of the primary end point or all-cause mortality	5. Time to first occurrence of any new or worsening PAD 6. Lipid end points, visit 1 to 4 mo visit, total cholesterol, TG, HDL-C, non–HDL-C (calculated), VLDL-C (calculated), apoA1, apoC3, and apoE 7. Nonfasting remnant cholesterol end point (week 0 to month 6)	May 2022

(*continued on next page*)

Table 3 (*continued*)

Study and drug	Objective	Study design and duration	Patient characteristics	Primary end point(s)	Secondary end points	Secondary end points	Estimated study completion date
			One-third primary prevention and two-thirds secondary prevention		4. Time to first occurrence of any component of the primary end point, any coronary revascularization or hospitalization for HF (cont.)		

apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiac event; MI, myocardial infarction; NCT, National Clinical Trial; PAD, peripheral artery disease; PROMINENT, Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes; STRENGTH, Outcomes Study to Assess Statin Residual Risk Reduction with Epanova in High CV Risk Patients with Hypertriglyceridemia; TG, triglycerides; VLDL-C, very-low-density lipoprotein cholesterol.

Conclusions

The results of REDUCE-IT provide evidence to support ASCVD risk reduction with use of IPE as an adjunct to statin therapy in patients with high or very-high ASCVD risk who have TG elevation. IPE has now joined ezetimibe and PCSK9 inhibitors as evidence-based therapies that can be recommended as adjuncts to statin therapy. The results of pending studies examining the mechanisms to explain the observed benefits of IPE and to elucidate the roles of other therapeutic options for patients with TG elevation are expected to provide important additional insights into the management of ASCVD risk in these patients.

Acknowledgments

The authors gratefully acknowledge the critical review of the manuscript by Eliot A. Brinton, MD, of the Utah Lipid Center and capable assistance with editing and formatting by Mary R. Dicklin, PhD, of Midwest Biomedical Research.

Financial disclosures

C.E.O. and T.A.J. disclose that in the past 12 months, they have nothing to disclose. K.C.M. discloses that in the past 12 months he has received consulting fees and/or research grant support from Acasti, Akcea, Amgen, Corvidia, Matinas BioPharma, Pharmavite, and Regeneron.

References

1. Del Gobbo LC, Imamura F, Aslibekyan S, et al. Omega-3 polyunsaturated fatty acid biomarkers and coronary heart disease: pooling project of 19 cohort studies. *JAMA Intern Med*. 2016;176:1155–1166.
2. de Goede J, Geleijnse JM, Boer JM, Kromhout D, Verschuren WM. Marine (n-3) fatty acids, fish consumption, and the 10-year risk of fatal and nonfatal coronary heart disease in a large population of Dutch adults with low fish intake. *J Nutr*. 2010;140:1023–1028.
3. Alexander DD, Miller PE, Van Elswyk ME, Kuratko CN, Bylsma LC. A meta-analysis of randomized controlled trials and prospective cohort studies of eicosapentaenoic and docosahexaenoic long-chain omega-3 fatty acids and coronary heart disease risk. *Mayo Clin Proc*. 2017;92:15–29.
4. Rizos EC, Ntzani EE, Bika E, Kostapanos MS, Elisaf MS. Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: a systematic review and meta-analysis. *JAMA*. 2012;308:1024–1033.
5. Yokoyama M, Origasa H, Matsuzaki M, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet*. 2007;369:1090–1098.
6. 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;354:447–455.
7. Origin Trial Investigators, Bosch J, Gerstein HC, et al. n-3 Fatty acids and cardiovascular outcomes in patients with dysglycemia. *N Engl J Med*. 2012;367:309–318.
8. Risk and Prevention Study Collaborative Group, Roncaglioni MC, Tombesi M, Avanzini F, et al. n-3 Fatty acids in patients with multiple cardiovascular risk factors. *N Engl J Med*. 2013;368:1800–1808.

9. Maki KC, Dicklin MR. Omega-3 fatty acid supplementation and cardiovascular disease risk: glass half full or time to nail the coffin shut? *Nutrients*. 2018;10.
10. Skulas-Ray AC, Wilson PWF, Harris WS, et al. Omega-3 fatty acids for the management of hypertriglyceridemia: a science advisory from the American Heart Association. *Circulation*. 2019;140:e673–e691.
11. Saito Y, Yokoyama M, Origasa H, 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;200:135–140.
12. Maki KC, Guyton JR, Orringer CE, Hamilton-Craig I, Alexander DD, Davidson MH. Triglyceride-lowering therapies reduce cardiovascular disease event risk in subjects with hypertriglyceridemia. *J Clin Lipidol*. 2016;10:905–914.
13. 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;217:492–498.
14. Sacks FM, Carey VJ, Fruchart JC. Combination lipid therapy in type 2 diabetes. *N Engl J Med*. 2010;363:692–694author reply 4–5.
15. Bhatt DL, Steg PG, Miller M, et al. cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med*. 2019;380:11–22.
16. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *J Am Coll Cardiol*. 2019;73:e285–e350.
17. Robinson JG, Huijgen R, Ray K, Persons J, Kastelein JJ, Pencina MJ. Determining when to add nonstatin therapy: a quantitative approach. *J Am Coll Cardiol*. 2016;68:2412–2421.
18. Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. *J Cardiovasc Risk*. 1996;3:213–219.
19. Nordestgaard BG, Benn M, Schnohr P, Tybjaerg-Hansen A. Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women. *JAMA*. 2007;298:299–308.
20. Freiberg JJ, Tybjaerg-Hansen A, Jensen JS, Nordestgaard BG. Nonfasting triglycerides and risk of ischemic stroke in the general population. *JAMA*. 2008;300:2142–2152.
21. Jorgensen AB, Frikke-Schmidt R, Nordestgaard BG, Tybjaerg-Hansen A. Loss-of-function mutations in APOC3 and risk of ischemic vascular disease. *N Engl J Med*. 2014;371:32–41.
22. Varbo A, Benn M, Tybjaerg-Hansen A, Jorgensen AB, Frikke-Schmidt R, Nordestgaard BG. Remnant cholesterol as a causal risk factor for ischemic heart disease. *J Am Coll Cardiol*. 2013;61:427–436.
23. Nordestgaard BG. Triglyceride-rich lipoproteins and atherosclerotic cardiovascular disease: new insights from epidemiology, genetics, and biology. *Circ Res*. 2016;118:547–563.
24. Antonios N, Angiolillo DJ, Silliman S. Hypertriglyceridemia and ischemic stroke. *Eur Neurol*. 2008;60:269–278.
25. Rochlani Y, Pothineni NV, Kovelamudi S, Mehta JL. Metabolic syndrome: pathophysiology, management, and modulation by natural compounds. *Ther Adv Cardiovasc Dis*. 2017;11:215–225.
26. Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; national heart, lung, and blood institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*. 2009;120:1640–1645.
27. Jacobson TA, Ito MK, Maki KC, et al. National lipid association recommendations for patient-centered management of dyslipidemia: part 1–full report. *J Clin Lipidol*. 2015;9:129–169.
28. Jacobson TA, Maki KC, Orringer CE, et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: part 2. *J Clin Lipidol*. 2015;9:S1–S122.e1.
29. Berglund L, Brunzell JD, Goldberg AC, Goldberg IJ, Stalenhoef A. Treatment options for hypertriglyceridemia: from risk reduction to pancreatitis. *Best Pract Res Clin Endocrinol Metab*. 2014;28:423–437.
30. Maki KC, Bays HE, Dicklin MR. Treatment options for the management of hypertriglyceridemia: strategies based on the best-available evidence. *J Clin Lipidol*. 2012;6:413–426.
31. TG and HDL Working Group of the Exome Sequencing Project, National Heart, Lung, and Blood Institute, Crosby J, Peloso GM, Auer PL, et al. Loss-of-function mutations in APOC3, triglycerides, and coronary disease. *N Engl J Med*. 2014;371:22–31.
32. Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease. *Lancet*. 2014;384:626–635.
33. Rosenson RS, Davidson MH, Hirsh BJ, Kathiresan S, Gaudet D. Genetics and causality of triglyceride-rich lipoproteins in atherosclerotic cardiovascular disease. *J Am Coll Cardiol*. 2014;64:2525–2540.
34. Jorgensen AB, Frikke-Schmidt R, West AS, Grande P, Nordestgaard BG, Tybjaerg-Hansen A. Genetically elevated nonfasting triglycerides and calculated remnant cholesterol as causal risk factors for myocardial infarction. *Eur Heart J*. 2013;34:1826–1833.
35. Myocardial Infarction Genetics and CARDIoGRAM Exome Consortia Investigators, Stitziel NO, Stirrups KE, Masca NG, et al. Coding variation in ANGPTL4, LPL, and SVEP1 and the risk of coronary disease. *N Engl J Med*. 2016;374:1134–1144.
36. Dewey FE, Gusarova V, Dunbar RL, et al. Genetic and pharmacologic inactivation of ANGPTL3 and cardiovascular disease. *N Engl J Med*. 2017;377:211–221.
37. Triglyceride Coronary Disease Genetics Consortium and Emerging Risk Factors Collaboration, Sarwar N, Sandhu MS, Ricketts SL, et al. Triglyceride-mediated pathways and coronary disease: collaborative analysis of 101 studies. *Lancet*. 2010;375:1634–1639.
38. Ference BA, Kastelein JJP, Ray KK, et al. Association of triglyceride-lowering LPL variants and LDL-C-lowering LDLR variants with risk of coronary heart disease. *JAMA*. 2019;321:364–373.
39. Miller M, Cannon CP, Murphy SA, et al. Impact of triglyceride levels beyond low-density lipoprotein cholesterol after acute coronary syndrome in the PROVE IT-TIMI 22 trial. *J Am Coll Cardiol*. 2008;51:724–730.
40. Kastelein JJ, van der Steeg WA, Holme I, et al. Lipids, apolipoproteins, and their ratios in relation to cardiovascular events with statin treatment. *Circulation*. 2008;117:3002–3009.
41. Faergeman O, Holme I, Fayyad R, et al. Plasma triglycerides and cardiovascular events in the treating to new targets and incremental decrease in end-points through aggressive lipid lowering trials of statins in patients with coronary artery disease. *Am J Cardiol*. 2009;104:459–463.
42. AIM-HIGH Investigators, Boden WE, Probstfield JL, Anderson T, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med*. 2011;365:2255–2267.
43. Landray MJ, Haynes R, Hopewell JC, et al, Group HPS2-THRIVE Collaborative Group. Effects of extended-release niacin with laropiprant in high-risk patients. *N Engl J Med*. 2014;371:203–212.
44. ACCORD Study Group, Ginsberg HN, Elam MB, Lovato LC, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med*. 2010;362:1563–1574.
45. Jun M, Foote C, Lv J, et al. Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis. *Lancet*. 2010;375:1875–1884.
46. Siscovick DS, Barringer TA, Fretts AM, et al. Omega-3 polyunsaturated fatty acid (fish oil) supplementation and the prevention of clinical cardiovascular disease: a science advisory from the American Heart Association. *Circulation*. 2017;135:e867–e884.
47. Tavazzi L, Maggioni AP, Marchioli R, et al. 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;372:1223–1230.
48. Aung T, Halsey J, Kromhout D, et al. Associations of omega-3 fatty acid supplement use with cardiovascular disease risks: meta-analysis

of 10 trials involving 77917 individuals. *JAMA Cardiol*. 2018;3:225–234.
49. Maki KC, Palacios OM, Bell M, Toth PP. Use of supplemental long-chain omega-3 fatty acids and risk for cardiac death: an updated meta-analysis and review of research gaps. *J Clin Lipidol*. 2017;11:1152–11560 e2.
50. ASCEND Study Collaborative Group, Bowman L, Mafham M, Wallendszus K, et al. Effects of n-3 fatty acid supplements in diabetes mellitus. *N Engl J Med*. 2018;379:1540–1550.
51. Manson JE, Cook NR, Lee IM, et al. Marine n-3 fatty acids and prevention of cardiovascular disease and cancer. *N Engl J Med*. 2019;380:23–32.
52. Hu Y, Hu FB, Manson JE. Marine omega-3 supplementation and cardiovascular disease: an updated meta-analysis of 13 randomized controlled trials involving 127 477 participants. *J Am Heart Assoc*. 2019;8:e013543.
53. Bhatt DL, Steg PG, Miller M, et al. Effects of icosapent ethyl on total ischemic events: from REDUCE-IT. *J Am Coll Cardiol*. 2019;73:2791–2802.
54. Marston NA, Giugliano RP, Im K, et al. Association between triglyceride lowering and reduction of cardiovascular risk across multiple lipid-lowering therapeutic classes: a systematic review and meta-egression analysis of randomized controlled trials. *Circulation*. 2019;140:1308–1317.
55. Ganda OP, Bhatt DL, Mason RP, Miller M, Boden WE. Unmet need for adjunctive dyslipidemia therapy in hypertriglyceridemia management. *J Am Coll Cardiol*. 2018;72:330–343.
56. Preston Mason R. New insights into mechanisms of action for omega-3 fatty acids in atherothrombotic cardiovascular disease. *Curr Atheroscler Rep*. 2019;21:2.
57. Mozaffarian D, Prineas RJ, Stein PK, Siscovick DS. Dietary fish and n-3 fatty acid intake and cardiac electrocardiographic parameters in humans. *J Am Coll Cardiol*. 2006;48:478–484.
58. Mozaffarian D, Wu JH. Omega-3 fatty acids and cardiovascular disease: effects on risk factors, molecular pathways, and clinical events. *J Am Coll Cardiol*. 2011;58:2047–2067.
59. Itakura H, Yokoyama M, Matsuzaki M, et al. Relationships between plasma fatty acid composition and coronary artery disease. *J Atheroscler Thromb*. 2011;18:99–107.
60. Otsuka R, Tange C, Nishita Y, et al. Fish and meat intake, serum eicosapentaenoic acid and docosahexaenoic acid levels, and mortality in community-dwelling japanese older persons. *Int J Environ Res Public Health*. 2019;16.
61. Papanikolaou Y, Brooks J, Reider C, Fulgoni VL 3rd. U.S. adults are not meeting recommended levels for fish and omega-3 fatty acid intake: results of an analysis using observational data from NHANES 2003-2008. *Nutr J*. 2014;13:31.
62. American Diabetes Association; 2019. https://www.diabetes.org/newsroom/press-releases/2019/ada-issues-critical-updates-to-2019-standards-of-care. Accessed September 19, 2019.
63. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2019;ehz455. https://doi.org/10.1093/eurheartj/ehz455.
64. Wilson DP, Jacobson TA, Jones PH, et al. Use of lipoprotein(a) in clinical practice: a biomarker whose time has come. a scientific statement from the National Lipid Association. *J Clin Lipidol*. 2019;13:374–392.
65. Halperin JL, Levine GN, Al-Khatib SM, et al. Further evolution of the ACC/AHA clinical practice guideline recommendation classification system: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Circulation*. 2016;133:1426–1428.
66. Haslam A, Prasad V. Confirmatory trials for drugs approved on a single trial. *Circ Cardiovasc Qual Outcomes*. 2019;12:e005494.
67. Kastelein JJP, Stroes ESG. FISHing for the miracle of eicosapentaenoic acid. *N Engl J Med*. 2019;380:89–90.
68. Fruchart JC. Pemafibrate (K-877), a novel selective peroxisome proliferator-activated receptor alpha modulator for management of atherogenic dyslipidaemia. *Cardiovasc Diabetol*. 2017;16:124.
69. Nicholls SJ, Lincoff AM, Bash D, et al. Assessment of omega-3 carboxylic acids in statin-treated patients with high levels of triglycerides and low levels of high-density lipoprotein cholesterol: rationale and design of the STRENGTH trial. *Clin Cardiol*. 2018;41:1281–1288.
70. Pradhan AD, Paynter NP, Everett BM, et al. Rationale and design of the pemafibrate to reduce cardiovascular outcomes by reducing triglycerides in patients with diabetes (PROMINENT) study. *Am Heart J*. 2018;206:80–93.