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The case for adding eicosapentaenoic acid (icosapent ethyl) to the ABCs of cardiovascular disease prevention

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ABSTRACT

The high-purity eicosapentaenoic acid (EPA) prescription fish oil-derived omega-3 fatty acid (omega-3), icosapent ethyl (IPE), was recently approved by the United States Food and Drug Administration (FDA) for cardiovascular disease (CVD) prevention in high-risk patients. This approval is based on the 25% CVD event risk reduction observed with IPE in the pre-specified primary composite endpoint (cardiovascular [CV] death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina) in the landmark Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT). Notably, this reduction in CVD event risk with IPE was an incremental benefit to well-controlled low-density lipoprotein cholesterol; patients in REDUCE-IT had elevated triglyceride (TG) levels (135–499 mg/dL) and either had a history of atherosclerotic CVD or diabetes with additional CV risk factors. Given the CVD event risk reduction in REDUCE-IT, within a year following trial results, several global medical societies added IPE to their clinical guidelines. IPE is a stable, highly purified, FDA-approved prescription EPA ethyl ester. In contrast, mixed omega-3 products (docosahexaenoic acid + EPA combinations) have limited or no evidence for CVD event risk reduction, and nonprescription fish oil dietary supplements are not regulated as medicine by the FDA. We offer our perspective and rationale for why this evidence-based EPA-only formulation, IPE, should be added to the 'E' in the ABCDEF methodology for CV prevention. We provide multiple lines of evidence regarding an unmet need for CVD prevention beyond statin therapy, IPE clinical trials, IPE cost-effectiveness analyses, and proposed pleiotropic (non-lipid) mechanisms of action of EPA, as well as other relevant clinical considerations. See Figure 1 for the graphical abstract.

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ABCDEF → E for EPA

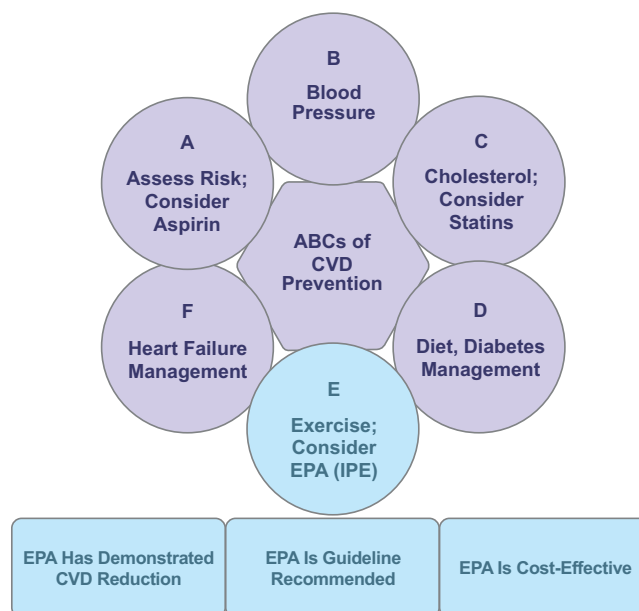


Figure 1. Graphical abstract.

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Introduction

The current 'ABCDE' strategy for cardiovascular disease (CVD) prevention includes the following approach: A for assessment of risk, antiplatelet therapy such as aspirin, and atrial fibrillation management; B for blood pressure management; C for cholesterol management and cessation of cigarette smoking; D for diet/lifestyle modification and diabetes management; E for exercise; and F for heart failure management [1–3]. While statins are a mainstay for CVD prevention, there remains an approximate 65% residual risk of cardiovascular (CV) events that still may be present even in individuals who have well-controlled low-density lipoprotein cholesterol (LDL-C) [4–7]. This residual risk for CV events represents a large unmet clinical need [8].

Recently, the prescription fish oil-derived omega-3 fatty acid (omega-3), a highly purified, stable ethyl ester preparation of eicosapentaenoic acid (EPA), named icosapent ethyl (IPE; Vascepa®, Amarin Pharma, Inc., Bedminster, NJ) as an add-on to statins demonstrated a 25% reduction in atherosclerotic CVD events in the landmark Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT) [9]. The strength of evidence of IPE in REDUCE-IT prompted several major medical societies to update their guidelines, practice standards, and scientific advisories within a year of announcement of the trial's results [10–13].

Here we offer evidence supporting the concept that prescription EPA (IPE) could be considered under 'E' in the traditional ABCDEF strategy for CVD prevention. We build our rationale for the inclusion of EPA by providing evidence of 1) unmet needs for CVD prevention beyond statin therapy with associated clinical and economic costs; 2) strong and consistent trial results in REDUCE-IT; 3) possible pleiotropic mechanisms of action of EPA; 4) cost-effectiveness analyses; 5)

adoption of IPE by medical society guidelines, practice standards, and scientific statements; and 6) other relevant clinical considerations.

Unmet clinical needs in CVD prevention: a focus on hypertriglyceridemia

CVD is the leading cause of death in the United States (US), responsible for 1 in every 3 deaths [14]. This translates to over 800,000 deaths annually, or 1 death every 38 seconds. Overall, 92.1 million American adults are living with some form of CVD or the after-effects of stroke. In 2017, the total (direct and indirect) costs of CVD were estimated to be 330 USD billion, and are forecasted to reach 749 USD billion by 2035 [15].

An analysis from the National Health and Nutrition Examination Survey (NHANES) 2007–2014 estimates that over 56 million US adults have triglyceride (TG) levels >150 mg/dL [16] and over 70 million US adults have TG levels >135 mg/dL [17]. Of statin-treated adults, 15 million have TG levels >135 mg/dL. The threshold at which TG-associated CVD risk begins to increase has been reported to range from TG levels >135 mg/dL to TG levels as low as >50 mg/dL [18–20]. Genetic data (mutational analyses, genome-wide association analyses, and Mendelian randomization studies), epidemiological data from general population studies, an analysis from a prospective clinical trial, and administrative claims data have suggested that TG levels and/or TG-rich lipoproteins may increase the risk for CV events [21–24]. A recent article on real-world risk of CV outcomes showed that approximately 25% of patients with atherosclerotic CVD with well-controlled LDL-C (41–100 mg/dL) have elevated TG levels (135–499 mg/dL) (Figure 2(a)), and the rate of adverse CV events increases when elevated TG levels remain untreated (Figure 2(b)) [20].

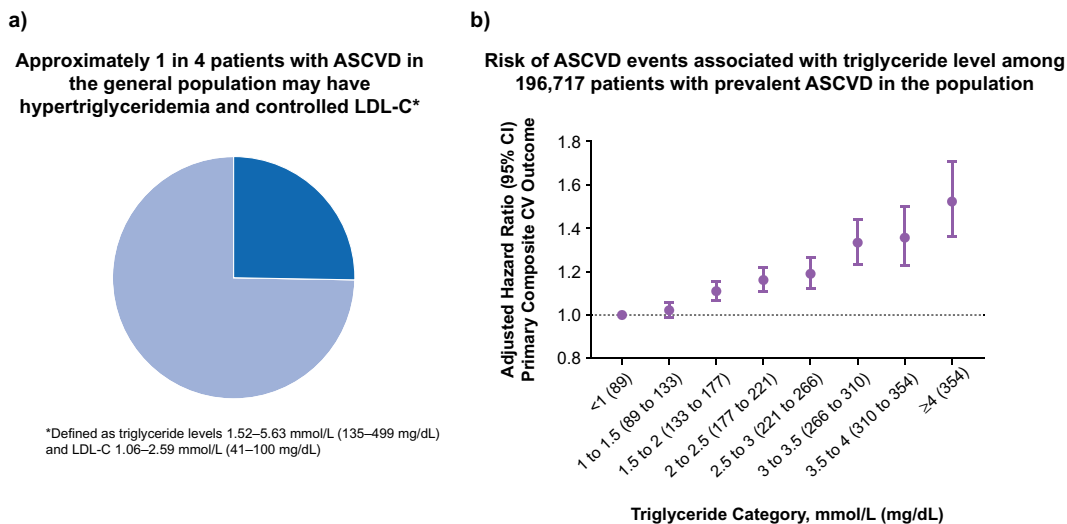


Figure 2. (a) Proportion of patients with atherosclerotic cardiovascular disease (ASCVD) in the Ontario, Canada population with hypertriglyceridemia and controlled low-density lipoprotein cholesterol (LDL-C). (b) The adjusted association between triglyceride level and cardiovascular events among individuals with ASCVD in the Ontario, Canada population. Adapted with permission from Lawler PR, Kotrri G, Koh M, et al. Real-world risk of cardiovascular outcomes associated with hypertriglyceridaemia among individuals with atherosclerotic cardiovascular disease and potential eligibility for emerging therapies. *Eur Heart J.* 2020;41(1):86–94, by permission of Oxford University Press [20].

Residual risk for CV events persists in cholesterol-treated patients even with very low LDL-C, indicating additional factors beyond LDL-C are critically important to address [8]. Indeed, the results from a clinical trial of LDL-C-lowering therapy, evolocumab, evaluated as add-on therapy to statins, demonstrated that in spite of achieved median LDL-C as low as 30 mg/dL, significant residual risk still remained [25].

Omega-3s: IPE, a stable, highly purified EPA ethyl ester

EPA is a long-chain polyunsaturated fatty acid found in fish oil [26]. IPE consists of >96% pure EPA as an ethyl ester. The FDA originally approved IPE 4 g/day as an adjunct to diet to reduce TG levels in adult patients with severe hypertriglyceridemia (TG \geq 500 mg/dL) based on the results of the Multi-center, placebo-controlled, Randomized, double-blind, 12-week study with an open-label Extension (MARINE) [27]. In the MARINE study, 229 diet-stable patients with very high TG levels were randomized to IPE 4 g/day, IPE 2 g/day, or placebo. IPE 4 g/day, compared with placebo, decreased TG levels by 33.1% ($P = 0.0001$). MARINE was followed by the ANCHOR study, a placebo-controlled, randomized, double-blind, 12-week clinical trial which compared IPE 4 g/day, IPE 2 g/day, and placebo in high-risk statin-treated patients with residually elevated TG levels (\geq 200–499 mg/dL) [28]. Compared with placebo, IPE 4 g/day reduced TG levels by 21.5% ($P < 0.0001$) [27,28]. In both of these studies, LDL-C levels were not increased. Subsequently, based on the results of REDUCE-IT, the FDA approved an indication for IPE as an adjunct to maximally tolerated statin therapy to reduce the risk of myocardial infarction (MI), stroke, coronary revascularization, and unstable angina requiring hospitalization in adult patients with elevated TG levels (\geq 150 mg/dL) and established CVD or diabetes mellitus and 2 or more additional risk factors for CVD [29].

CV outcomes trials (CVOTs) of EPA

JELIS

Prior to REDUCE-IT, the open-label Japan EPA Lipid Intervention Study (JELIS [NCT00231738]; $N = 18,645$), using 1.8 g/day of a purified EPA ethyl ester formulation available only in Japan and nearly identical to IPE reported that EPA + statin significantly lowered major coronary events by 19% compared with the statin-only control (hazard ratio [HR], 0.81; 95% CI, 0.69–0.95; $P = 0.011$) [30]. In JELIS, men aged 45 to 75 years and postmenopausal women aged up to 75 years with or without coronary artery disease and with a total cholesterol level \geq 251.35 mg/dL on statin therapy were randomized to either 1.8 g/day of EPA versus statin-only control. Following then-current Japanese treatment guidelines, patients were treated with 10 mg of pravastatin or 5 mg of simvastatin once daily as first-line treatment (the pravastatin and simvastatin doses could be increased to 20 mg and 10 mg, respectively, if hypercholesterolemia was considered ‘uncontrolled’). Baseline total cholesterol, LDL-C, high-density lipoprotein cholesterol (HDL-C), and TG levels were 275 mg/dL, 181 mg/dL, 59 mg/dL, and 153 mg/dL, respectively, in the EPA group. There were no significant differences in the

change in HDL-C or LDL-C between the EPA and statin-only groups. However, there was a small but statistically significant difference noted in TG level reductions between both groups; TG levels were lowered by 9% in the EPA group versus 4% in the statin-only group ($P < 0.001$). Therefore, the benefits of EPA in JELIS were not attributable to TG lowering alone; rather, other ‘pleiotropic,’ or non-lipid EPA mechanisms of action likely contributed to the benefits, some of which are summarized in Table 1 [9,31–41]. A subanalysis of primary prevention cases ($n = 14,981$) in JELIS found that, among patients with high TG levels (>150 mg/dL) and low HDL-C levels (<40 mg/dL), EPA + statin significantly reduced the risk of major coronary events versus statin alone by 53% (HR, 0.47; 95% CI, 0.23–0.98; $P = 0.043$) [42]. In JELIS, EPA was generally well tolerated, with most drug-related adverse events (AEs) characterized as mild [30]. AEs were slightly higher in the EPA + statin group (25.3% vs 21.7%; $P < 0.0001$), including low rates of gastrointestinal disorders (3.8% vs 1.7%) and low rates of bleeding (1.1% vs 0.6%).

REDUCE-IT

The results of REDUCE-IT, a randomized, double-blind, placebo-controlled, multi-center, international trial, were published online in November 2018 in the *New England Journal of Medicine* [9] and simultaneously presented at the American Heart Association (AHA) annual scientific sessions. REDUCE-IT investigated the FDA-approved prescription, high-purity, stable EPA, IPE, at 4 g/day (given as 2 g twice daily) versus placebo as an add-on to statin therapy in 8179 patients with TG levels above 135 mg/dL. The trial initially had a TG entry criterion of 150 mg/dL, which included a 10% lower TG level (135 mg/dL) due to intra-individual variability. However, the first protocol amendment in May 2013 changed the lower limit of TG entry criterion to 200 mg/dL. The trial enrolled adults \geq 45 years of age with established CVD or \geq 50 years of age with diabetes and at least one additional CV risk factor. In addition, patients were required to have baseline LDL-C levels of 41 to 100 mg/dL and be on stable statin treatment for at least 4 weeks. These patients were well treated, with 93% receiving moderate- to high-intensity statin therapy. This was reflected in their baseline median LDL-C levels of 74.0 mg and 76.0 mg in the IPE and control groups, respectively.

After a median follow-up of 4.9 years, patients randomized to IPE experienced a statistically significant 25% relative risk reduction (HR, 0.75; 95% CI, 0.68–0.83; $P < 0.001$) and an absolute risk reduction of 4.8% (95% CI, 3.1–6.5) in the primary 5-point composite endpoint of time to first event for CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina (17.2% of patients in the IPE group vs 22% in the placebo group; $P < 0.001$; Figure 3) [9,72]. The number needed to treat (NNT) to prevent one primary endpoint was 21 (95% CI, 15–33) over 4.9 years. The relative risk of MI was reduced by 31%, stroke by 28%, CV death by 20%, urgent or emergent revascularization by 35%, and hospitalization for unstable angina by 32%. In addition, the key 3-point composite secondary endpoint, which consisted of CV death, nonfatal MI, or nonfatal stroke, was reduced by 26% (11.2% of patients in the IPE group vs 14.8% of patients in the placebo group; HR, 0.74; 95% CI,

Table 1. Select Pleiotropic Effects of EPA.**Antithrombotic and antiplatelet**

- Decreased platelet aggregation: EPA decreased platelet aggregation and inhibited AA-induced thromboxane A2 formation [43]
- Decreased platelet adhesion:
 - EPA reduced platelet adhesion to collagen type I by 60%–65%
 - Fish oil equivalent to 6 g EPA/day reduced platelet pseudopodia [44]
- Decreased thromboxane A2/increased thromboxane A3 levels:
 - EPA added to human thrombocytes incubated with AA decreased thromboxane A2 and increased thromboxane A3 [45]
 - In human platelet-rich plasma, EPA did not induce platelet aggregation [46]

Anti-inflammatory

- Decreased hsCRP:
 - In ANCHOR, IPE 4 g/day decreased hsCRP vs placebo by 21.5% ($P < 0.01$) [31]
 - In REDUCE-IT, IPE decreased hsCRP vs placebo at year 2 by 39.9% (last visit, 37.6%); $P < 0.001$ [9]
- Decreased pentraxin-3: In patients with CAD treated with PCI, EPA added to statin therapy after 9 months reduced pentraxin 3 levels vs statin alone [47]
- Decreased Lp-PLA₂: In ANCHOR, IPE 4 g/day decreased Lp-PLA₂ by 19.6% in patients with hsCRP >2.0 vs placebo [48]
- Decreased NLRP3 inflammasome activation:
 - EPA blocked NLRP3 inflammasome activation in an animal model of ischemic stroke [49]
 - EPA decreased NLRP3 gene expression in adipose tissue and in classically activated THP-macrophages [50]
- Decreased toll-like receptor 4: EPA reduced gene expression of toll-like receptor 4 by $>50\%$ in mice fed a high-fat diet vs control [51]
- Decreased NFκB: EPA reduced the genetic expression of NFκB in a cell culture with THP-1 macrophages [52]
- Decreased inflammatory cytokines:
 - EPA reduced gene expression of IL-1b, TNF-α, and MCP-1 in cell culture with THP-1 macrophages [52]
 - EPA downregulated expression of IL-6 mRNA in IL-1b-stimulated C6 glioma cells [53]
- Increased anti-inflammatory cytokine IL-10:
 - EPA significantly increased the production of IL-10 in lipopolysaccharide-activated monocytes ($P < 0.05$) [54]
 - EPA increased IL-10 expression in peripheral blood monocytes in obese patients with dyslipidemia [55]
- Decreased endothelial adhesion molecules:
 - EPA inhibits monocyte adhesion to endothelial cells [56]
 - EPA decreases plasma concentrations of soluble ICAM and VCAM [56]

Increased 'resolution of inflammation': specialized pro-resolving mediators

- RvE1 was found to bind to the LTB4 receptor, BLT1, on human PMNs and attenuated LTB4-induced proinflammatory signals and PMN migration in an in-vitro study [57]
- RvE2 was found to enhance phagocytosis of human macrophages and anti-inflammatory cytokine (IL-10) production [58]
- RvE3 was found to have potent inhibitory action on neutrophil chemotaxis both in-vitro and in-vivo [59]

Anti-oxidant

- Increased paraoxonase in patients with type 2 DM:
 - EPA 2 g increased PON1 activity and levels over 8 weeks vs placebo [60]
 - EPA over 8 weeks significantly increased gene expression of PON2 vs placebo [61]
- Inhibition of lipid/lipoprotein oxidation:
 - EPA inhibited the oxidation of apoB lipoproteins (LDL-C, sdLDL, VLDL-C) in an in-vitro study [115]
 - EPA inhibited the oxidation of HDL isolated from the plasma of healthy volunteers; the sustained antioxidant effects of EPA on HDL oxidation were not replicated by DHA [114]
 - EPA inhibited oxidation of sdLDL, model membranes, and cholesterol crystal domain formation [62]

Improved endothelial function

- EPA significantly increased NO production and reduced glucose inhibition of NO in cultured human endothelial cells [63]
- EPA significantly improved FMD by 51% in patients with elevated TG ($P < 0.0001$); EPA/AA ratio was found to be significantly associated with the change in FMD ($P = 0.010$) [64]
- EPA improved PFBF during reactive hyperemia to the level in normolipidemic controls; recovery of PFBF correlated positively with EPA levels ($P < 0.05$) and the EPA/AA ratio ($P < 0.01$) [65]
- EPA improved vascular function as measured by strain gauge plethysmography in patients with type 2 DM on statin therapy [66]
- EPA improved endothelial function in patients with CAD, LDL-C < 100 mg/dL on statin therapy, and impaired FMD [67]
- EPA with an atorvastatin metabolite improved endothelial function through increased NO in an in-vitro study [41]

Increased cholesterol efflux

- Increasing EPA phosphatidylcholine content of reconstituted HDL-C was demonstrated to increase cholesterol efflux [68]
- EPA inhibited glucose-induced membrane cholesterol crystalline domain formation in an in-vitro study using multilamellar vesicles [41]
- EPA and DPA inhibited oxidation of membrane cholesterol domains in an in-vitro study utilizing multilamellar vesicles [62]

Increased adiponectin

- EPA after 3 months significantly increased adiponectin vs placebo among obese patients with dyslipidemia ($P < 0.01$) [69]
- Change in pulse wave velocity, a measure of arterial stiffness, was negatively correlated with change in adiponectin ($P < 0.01$) and in IL-10 expression of monocytes ($P < 0.05$) [55]

Anti-arrhythmic

- EPA may reduce the risk of ventricular arrhythmia by inhibiting the fast sodium current (I_{Na}), L-type calcium inward current (I_{Ca}) and enhancing the slowly activating delayed rectifying outward potassium current (I_{Ks}), thus shortening cardiac action potential [70,71,92,93]
- EPA reduces cytosolic Ca^{2+} overload, thus reducing the risk of triggered induced arrhythmia [70,71,92,93]

AA, arachidonic acid; apo, apolipoprotein; BLT1, leukotriene B4 receptor BLT1; Ca^{2+} , calcium; CAD, coronary artery disease; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; DM, diabetes mellitus; EPA, eicosapentaenoic acid; FMD, flow-mediated dilation; hsCRP, high-sensitivity C-reactive protein; HDL-C, high-density lipoprotein cholesterol; ICAM, intercellular adhesion molecule; IL, interleukin; IPE, icosapent ethyl; LTB4, leukotriene B4 receptor 1; LDL-C, low-density lipoprotein cholesterol; Lp-PLA₂, lipoprotein-associated phospholipase A₂; MCP, monocyte chemoattractant protein; mRNA, messenger ribonucleic acid; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, NLR family pyrin domain containing 3; NO, nitric oxide; PCI, percutaneous coronary intervention; PFBF, peak forearm blood flow; PON, paraoxonase; PMNs, polymorphonuclear leukocytes; REDUCE-IT, Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial; Rv, resolvin; sdLDL, small dense LDL; THP-1, monocyte/macrophage; TNF-α, tumor necrosis factor alpha; VLDL-C, very-low-density lipoprotein cholesterol; VCAM, vascular cell adhesion molecule.

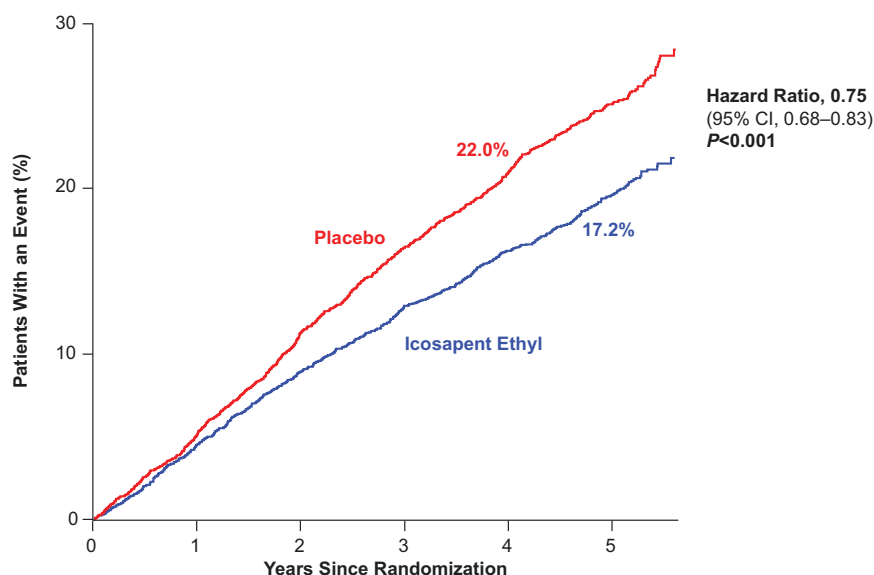


Figure 3. REDUCE-IT primary endpoint: cardiovascular death, myocardial infarction, stroke, coronary revascularization, and unstable angina. The relative risk reduction was 24.8%, the absolute risk reduction was 4.8%, and the number-needed-to-treat was 21. CI, confidence interval; REDUCE-IT, Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial. From N Engl J Med, Bhatt DL, Steg G, Miller M, et al, Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia, 380(1):11–22, ©2019 Massachusetts Medical Society. Adapted with permission from Massachusetts Medical Society [9,72].

0.65–0.83; $P < 0.001$). This translated to an NNT of 28 (95% CI, 20–47) over 4.9 years [9].

As noted above, IPE as add-on therapy to statins achieved a 25% risk reduction in the primary composite CVD endpoint incremental to that provided by statins, resulting in an NNT of 21 over 4.9 years (Figure 3) [72]. In a subgroup of patients with TG levels ≥ 200 mg/dL and HDL-C levels ≤ 35 mg/dL, IPE reduced the primary composite endpoint by 38% compared with placebo (P value for interaction, 0.04; NNT 11).

Another clinically relevant analysis from REDUCE-IT demonstrated that first and subsequent CVD events, in a total events analysis, were reduced by 30% (95% CI, 0.62–0.78; $P < 0.0001$) [73]. Reductions of 25% occurred for the first CVD event, and

reductions of 32%, 31%, and 48% occurred for successive second, third, and fourth CV events, respectively (Figure 4) [73]. This is especially important given that patients who experience a first CVD event are at higher risk of subsequent events. The impact of total CVD event reduction in REDUCE-IT is substantial: for every 1000 patients treated with IPE for 5 years, approximately 159 total primary endpoints could be prevented, including 12 CV deaths, 42 MIs, 14 strokes, 76 coronary revascularizations, and 16 episodes of hospitalization for unstable angina [74].

Results from a pre-specified analysis of the 3146 REDUCE-IT patients from the USA subgroup who received IPE as add-on to statins demonstrated a 31% relative risk reduction (HR, 0.69;

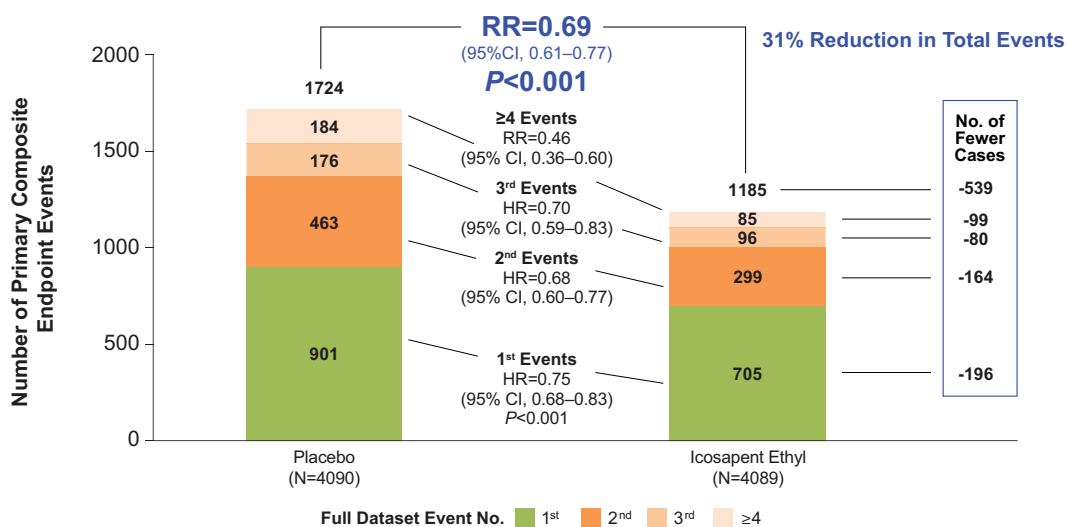


Figure 4. REDUCE-IT: reduction in first and subsequent ischemic events. The Wei-Lin-Weissfeld (WLW) method was used for 1st events, 2nd events, and 3rd events categories; a negative binomial model was used for ≥ 4 events and overall treatment comparison. CI, confidence interval; HR, hazard ratio; REDUCE-IT, Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial; RR, relative risk. Adapted with permission from Bhatt et al [73].

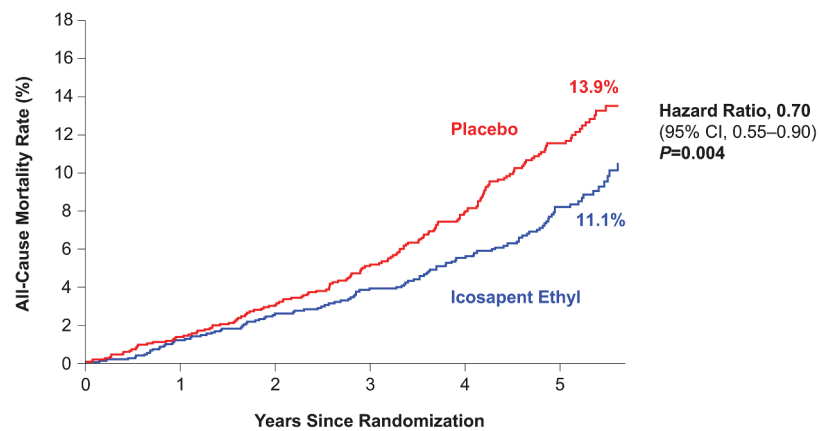


Figure 5. REDUCE-IT USA: all-cause mortality from 3146 patients randomized in the United States, Kaplan-Meier time-course. Importantly, all-cause mortality was not significantly reduced in the total REDUCE-IT study population; however, a statistically significant 30% reduction in all-cause mortality was observed in the USA subgroup. The relative risk reduction was 30%, the absolute risk reduction was 2.6%, and the number-needed-to-treat was 39. *P* for interaction = 0.02. CI, confidence interval; REDUCE-IT, Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial; Reproduced with permission from Bhatt DL, Miller M, Brinton EA, et al. REDUCE-IT USA: results from the 3,146 patients randomized in the United States. *Circulation*. 2020;141(5):367–375 [17,72].

95% CI, 0.59–0.80; *P* = 0.000001) in CVD events (NNT, 15) [17]. Here again, consistency of results was evident with reduction in CV death of 34% (HR, 0.66; 95% CI, 0.49–0.90; *P* = 0.007), MI by 28% (HR, 0.72; 95% CI, 0.56–0.93; *P* = 0.01), and stroke by 37% (HR, 0.63; 95% CI, 0.43–0.93; *P* = 0.02). Unlike in the full study cohort, there was statistically significant 30% reduction in all-cause mortality in the USA subgroup (HR, 0.70; 95% CI, 0.55–0.90; *P* = 0.004) (NNT, 39; Figure 5). A limitation of this study is that REDUCE-IT was not powered to evaluate individual subgroups, including the pre-specified REDUCE-IT USA subgroup. Safety and tolerability findings from the USA subgroup were consistent with the full study cohort.

REDUCE-IT was not a TG-lowering study; like JELIS, it was designed as a CVOT, although baseline TG level was an inclusion criterion. In the IPE and control groups, baseline TG levels were 216.5 mg/dL and 216.0 mg/dL, respectively, and baseline LDL-C levels were 85.8 mg/dL and 86.7 mg/dL (Hopkins), respectively. There was a significant reduction from baseline to last visit in TG levels in both groups (21.6% in the IPE group, *P* < 0.001; 6.5% in the control group, *P* < 0.001); compared with the control group, IPE lowered TG levels by 14.1% (*P* < 0.001). There was a small, non-significant decrease in LDL-C levels in the IPE group (–1.2%, *P* = 0.14) and a significant increase in LDL-C levels in the control group (6.5%, *P* < 0.001). Compared with the control group, IPE lowered LDL-C levels by 7.4% (*P* < 0.001). Non-HDL-C levels decreased by 8.6% in the EPA group compared with the control group (*P* < 0.001). These IPE-induced reductions in TG, LDL-C, and non-HDL-C levels were modest and do not appear to account for any substantial portion of the CV risk reduction seen in REDUCE-IT, as shown in REDUCE-IT EPA [75]. The 14 mg/dL median decrease in non-HDL-C levels from baseline would be expected to generate only a 6% to 8% reduction in CV events [76]. In regards to TG lowering, primary and key secondary CVD event endpoint reductions were similar for IPE irrespective of baseline TG levels (≥ 150 vs < 150 mg/dL or ≥ 200 vs < 200 mg/dL) or achieved TG levels at 1 year (≥ 150 vs < 150 mg/dL) [9].

A greater percentage of patients in the IPE group than in the control group were hospitalized for atrial fibrillation or flutter, although the rates were low (3.1% vs 2.1%, respectively; *P* = 0.004) and the incidence was greater in patients with a previous history of atrial fibrillation or flutter [77]. Adverse cardiac events typically associated with atrial fibrillation (such as heart attack, stroke, cardiac arrest, and sudden death) were each reduced by >25% in the IPE group [9]. The overall rates of serious adverse bleeding events were 2.7% in the IPE group and 2.1% in the control group (*P* = 0.06), and there were no fatal bleeding events in either group. There were no significant differences between the IPE and control groups in rates of adjudicated hemorrhagic stroke, serious central nervous system bleeding, or gastrointestinal bleeding. As with any therapy, IPE's noted AEs should be weighed against its efficacy in reducing CV events as part of a shared decision-making model with patients. This includes consideration of IPE's atrial fibrillation/flutter and bleeding profile. Higher rates of peripheral edema and constipation were reported with IPE versus control (6.5% vs 5.0%, *P* = 0.002; 5.4% vs 3.6%, *P* < 0.001, respectively); however, there was no significant difference in heart failure between groups. Interestingly, there was a lower rate of anemia with IPE versus control (4.7% vs 5.8%; *P* = 0.03). The rates of AEs and serious AEs leading to discontinuation were similar in the two groups. There were no significant differences in total treatment-emergent AEs between the two groups.

Proposed non-lipid mechanisms of EPA

As mentioned previously, the IPE-induced reductions in TG, non-HDL-C, and LDL-C levels in REDUCE-IT cannot fully explain the magnitude of the CVD risk reduction. Thus, the non-lipid pleiotropic mechanisms of EPA may have contributed to the CVD reduction [78].

Inflammation is one of the key components of atherosclerosis, and high-sensitivity C-reactive protein (hsCRP) is a

nonspecific marker of inflammatory disease that has been shown to be predictive of CVD events independent of cholesterol level [79,80]. In a meta-analysis of population-based prospective cohort studies, hsCRP was shown to be predictive of CVD in both primary and secondary prevention [81–83]. Notably, in REDUCE-IT, IPE lowered hsCRP levels by 39.9% at year 2 ($P < 0.001$) [9]. The inflammatory hypothesis of atherothrombosis targeting a cytokine upstream to hsCRP was tested in the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS), which evaluated whether the fully human monoclonal antibody targeting interleukin-1b (canakinumab) could prevent recurrent vascular events [84]. The primary endpoint of the first occurrence of nonfatal MI, nonfatal stroke, or CV death in patients taking 150 mg was reduced by 15% (HR, 0.85; 95% CI 0.74–0.98; $P = 0.021$) compared with placebo. Furthermore, hsCRP levels were significantly reduced by 37% in the 150 mg group compared with placebo ($P < 0.001$). In a secondary analysis of CANTOS, patients receiving canakinumab who achieved hsCRP levels of <2.0 mg/L had a 25% decrease in the trial's primary endpoint compared with placebo (multivariable-adjusted HR [HR^{adj}], 0.75; 95% CI, 0.66–0.85; $P < 0.0001$), whereas there was no significant between-group difference among those with on-treatment hsCRP levels ≥ 2.0 mg/L (HR^{adj}, 0.90; 95% CI, 0.79–1.02; $P = 0.11$) [85]. Likewise, in REDUCE-IT, anti-inflammatory effects of EPA, suggested by favorable changes in hsCRP, may have contributed to CVD event risk reduction.

Sudden cardiac death is frequently preceded by ventricular fibrillation (VF) or ventricular tachycardia (VT). Epidemiologic studies show lower levels of omega-3s are associated with increased risk of primary cardiac arrest [86] and sudden death [87]. Low EPA serum levels have been associated with increased risk of ventricular arrhythmias (VT and VF); in a study of 200 patients undergoing percutaneous coronary intervention (PCI) within 12 hours of MI and followed for 30 days, low EPA levels ($<2.94\%$ of total fatty acids), compared with high EPA levels ($\geq 2.94\%$) were associated with a significantly higher incidence of ventricular arrhythmias (19.5% vs 6.2%; $P = 0.009$) [88]. In a retrospective study in patients with Brugada syndrome, an autosomal-dominant disorder associated with characteristic ECG changes and sudden cardiac death secondary to VF, low levels of EPA independently predicted risk of cardiogenic syncope [89]. The effect of EPA on arrhythmia was evaluated in 115 patients with an acute MI who underwent PCI and were randomized within 24 hours to 1.8 g/day of EPA versus control and followed for 30 days [90]. EPA significantly reduced the composite endpoint of death, re-infarction, stroke, VF/flutter/paroxysmal atrial fibrillation compared with control (10.5% vs 29.3%; $P = 0.01$) [90]. In a time-course analysis of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI) Prevenzione trial, a supplement of EPA + DHA (1 g/day) significantly lowered total mortality after only 3 months of treatment by 41% ($P = 0.037$), with 42% of total mortality at 3 months comprising sudden cardiac death [91]. In JELIS, no conclusions regarding EPA's effect on sudden cardiac death could be made, as there were only 35 total cases, 17 (0.2%) in the control group and 18 (0.2%) in the EPA group [30]. In REDUCE-IT, adjudicated

sudden cardiac death, a pre-specified tertiary endpoint, was reduced by 31% in the EPA group compared with the placebo group (1.5% vs 2.1%; HR, 0.69; 95% CI 0.50–0.96) [9]. However, it is appreciated that sudden cardiac death, as a pre-specified tertiary endpoint, was not adjusted for multiple comparisons and, compared with the primary and key secondary endpoints, represents a much smaller number of events.

Additional, multifaceted pleiotropic effects have been reported with EPA and are summarized in Table 1 [9,31–41]. Some of these proposed mechanisms include anti-inflammatory, anti-oxidation, anti-arrhythmic, anti-thrombotic, anti-platelet, and cell membrane stability/signaling effects; improvement of endothelial function; reduction of cholesterol crystal domains; and plaque stabilization and/or regression [9,31–41,92,93].

Relationship between EPA levels and CVD events

JELIS

JELIS was the first CVOT to evaluate whether pure EPA (1.8 g/day) would reduce the risk of coronary artery disease; as noted previously, at a mean follow-up of 4.6 years, EPA reduced the risk of major coronary events by 19% compared with statin-only control ($P < 0.011$) [30]. The EPA level increased from 97 mg/L to 169 mg/L in the EPA group, while it was unchanged at 93 mg/L in the control group [30]. In further evaluation of JELIS, a higher plasma EPA level was inversely associated with the risk of major coronary events (HR, 0.71; $P = 0.018$ in the EPA intervention group) [94]. Patients with on-treatment plasma EPA levels ≥ 150 mg/L had a 20% reduction in major coronary events versus those with plasma EPA levels <87 mg/L (adjusted HR, 0.80; $P = 0.042$). There was a 22% reduction in major coronary events in patients with on-treatment serum EPA levels ≥ 200 mg/L versus those with EPA levels <200 mg/L (HR, 0.78; 95% CI, 0.62–0.99; $P = 0.043$).

REDUCE-IT

The REDUCE-IT study investigators recently reported the evaluation of EPA levels and CV outcomes [75]. Baseline median serum EPA level was 26.1 mg/L in both the IPE and the control group. At 5 years, the median serum EPA level and median % change from baseline in the IPE group were 158 mg/L and 463.6%, respectively; as expected, the serum EPA level and median % change from baseline in the control group was only 25.3 mg/L and -2% , respectively. The between-group difference for the median % change from baseline was 448.1% ($P < 0.0001$). The EPA levels achieved with IPE treatment correlated strongly ($P < 0.001$) with the primary endpoint and the key secondary endpoints, including CV death, MI, stroke, coronary revascularization, unstable angina, sudden cardiac death, cardiac arrest, new heart failure, and all-cause mortality. Serum EPA levels appeared to be associated with most of the relative risk reduction achieved by IPE in REDUCE-IT, with only minimal contribution by TG, LDL-C, HDL-C, non-HDL-C, apolipoprotein B, hsCRP, and remnant lipoprotein cholesterol [75]. EPA's myriad non-lipid beneficial pleiotropic effects likely contribute to its impact on reducing residual CVD event risk [95]. Further investigation is warranted to

elucidate these mechanisms of EPA and their possible relationship to CV event risk reduction.

Cost-effectiveness of IPE

Multiple analyses of IPE have demonstrated favorable cost-effectiveness. In a cost-effectiveness model, the ethyl ester preparation of pure EPA used in JELIS (same active moiety as IPE) led to cost savings and improved utility [96]. In October 2019, the Institute for Clinical and Economic Review (ICER) published its cost-effectiveness review of IPE based on REDUCE-IT [97]. The ICER report found that IPE 4 g/day as studied in REDUCE-IT resulted in 18,000 USD per quality-adjusted life-year (QALY) gained, and 16,000 USD per QALY when revascularization and unstable angina were included. For background, the AHA's 'high value' standard is <\$50,000 per QALY gained [98]. Therefore, ICER deemed IPE 'high long-term value for money.' A preliminary analysis presented at the 2019 AHA annual scientific sessions

found that use of IPE was projected to not only be cost-effective but also to reduce long-term healthcare costs; this analysis demonstrated that IPE led to exceptional benefit in terms of CVD event reduction as well as cost-savings in-trial and over patients' lifetime in the majority of simulations undertaken [99]. This analysis offers the rare finding of better outcomes at lower healthcare costs (dominant strategy).

Impact of REDUCE-IT findings on clinical practice recommendations

REDUCE-IT results have important implications for the role of IPE in the treatment paradigm for CVD. Indeed, after the trial results were published, several global medical societies adopted IPE into their guidelines, practice standards, or advisories. Table 2 provides a summary of the recommendations from the American Diabetes Association (ADA), the AHA, the European Society of Cardiology (ESC), the European

Table 2. Statements From Medical Societies and the US FDA Regarding IPE (pure EPA) Post-REDUCE-IT.

Medical Society	Date	Guidelines/Standards/Advisory Statements
American Diabetes Association – ADA [10,100,102]	March 2019	<ul style="list-style-type: none"> • ADA's Standards of Medical Care updated Section 10, Treatment of Other Lipoprotein Fractions or Targets, states: <ul style="list-style-type: none"> – In patients with ASCVD or other cardiac risk factors on a statin with controlled LDL-C but elevated TG (135–499 mg/dL), the addition of icosapent ethyl should be considered to reduce CV risk – Level A – It should be noted that data are lacking with other omega-3 fatty acids, and results of REDUCE-IT should not be extrapolated to other products – Combination therapy (statin/fibrate) has not been shown to improve atherosclerotic CV disease and is generally not recommended – Level A – Combination therapy (statin/niacin) has not been shown to provide additional CV benefit above statin therapy alone, may increase the risk of stroke with additional side effects, and is generally not recommended – Level A
American Heart Association – AHA Science Advisory [11]	August 2019	<ul style="list-style-type: none"> • The AHA issued a Scientific Advisory that dietary supplements are not recommended and that positive outcomes results were demonstrated in REDUCE-IT: <ul style="list-style-type: none"> – The use of omega-3 fatty acids (4 g/day) for improving ASCVD risk in patients with hypertriglyceridemia is supported by a 25% reduction in MACE in REDUCE-IT – The potency, quality, and efficacy of dietary supplement are not initially reviewed or approved, nor are they subsequently monitored or assured by the FDA; thus, they are not indicated for the treatment of disease – In the treatment of patients with very high TG levels with 4 g/day, EPA + DHA agents reduce TG by ≥30% with concurrent increases in LDL-C, whereas EPA-only does not raise LDL-C in patients with very high TG levels
European Atherosclerosis Society/European Society of Cardiology – EAS/ESC [13]	August 2019	<ul style="list-style-type: none"> • The EAS and ESC jointly updated patient treatment guidelines to state: In high-risk (or above) patients with TG between 1.5 and 1.6 mmol/L (135–499 mg/dL) despite statin treatment, n-3 PUFAs (icosapent ethyl 2 × 2 g/day) should be considered in combination with statins – Class IIa, Level B
National Lipid Association – NLA [12]	September 2019	<ul style="list-style-type: none"> • NLA Position on the Use of Icosapent Ethyl in High- and Very High-Risk Patients states: <ul style="list-style-type: none"> – For patients, ≥45 years with clinical ASCVD, or ≥50 years with type 2 diabetes requiring medication and ≥1 additional risk factor, and fasting TGs 135–499 mg/dL on a maximally tolerated statin, with or without ezetimibe, treatment with icosapent ethyl is recommended for ASCVD reduction – Class 1, Level B-R
American Heart Association Scientific Statement [101]	April 2020	<ul style="list-style-type: none"> • The AHA recommends consideration of icosapent ethyl in patients with type 2 diabetes for further CV risk reduction when TGs remain elevated despite maximally tolerated statin for management of coronary artery disease
New FDA-approved indication: FDA-approved label expansion beyond TG lowering	December 2019	<ul style="list-style-type: none"> • Icosapent ethyl is indicated as an adjunct to maximally tolerated statin therapy to reduce the risk of MI, stroke, coronary revascularization, and unstable angina requiring hospitalization in adult patients with elevated TG levels (≥150 mg/dL) and established CV disease or diabetes mellitus and 2 or more additional risk factors for CV disease^a

^aBold text highlights aspects of expanded label indication that notably differ from language in updated guidelines and REDUCE-IT entry criteria.

ADA, American Diabetes Association; AHA, American Heart Association; CV, cardiovascular; EAS, European Atherosclerosis Society; EPA, eicosapentaenoic acid; ESC, European Society of Cardiology; FDA, Food and Drug Administration; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NLA, National Lipid Association; REDUCE-IT, Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial; TG, triglyceride.

Atherosclerosis Society (EAS), and the National Lipid Association (NLA) [10–13,100,101,102].

The guideline recommendations regarding patients for whom IPE treatment would be appropriate are closely based on REDUCE-IT entry criteria and most predate the label expansion. The wording of the new FDA-approved indication (Table 2) has several notable aspects that are distinct from the REDUCE-IT entry criteria and warrant further discussion. Among these is that, in contrast to REDUCE-IT entry criteria, which required TG levels to be ≥ 135 to < 500 mg/dL during screening, the new FDA-approved indication does not specify a maximal TG level and the minimal level was set at 150 mg/dL. Another notable difference is that the new FDA indication states that patients should be on ‘maximally tolerated statin therapy,’ which was not an element of the REDUCE-IT design or any of the REDUCE-IT–related guideline updates. Maximally tolerated statin therapy is a component of the 2018 Multi-Society Blood Cholesterol Guidelines [103]. Statin doses, however, were not maximized for REDUCE-IT. Instead, LDL-C was controlled, generally on moderate- to high-intensity statin therapy. The degree of LDL-C control, rather than the statin dosage, is the primary focus of cholesterol guidelines from the American Association of Clinical Endocrinologists [104], EAS, and ESC [13]. In contrast, maximally tolerated statin therapy is defined as the highest tolerated intensity and frequency of a statin, which can be zero in patients who are statin-intolerant [105]. Statin intolerance has been defined as experiencing unacceptable AEs/significant biomarker abnormalities while on statin treatment that resolve with statin discontinuation and recur with re-challenge with ≥ 2 different statins (including 1 at the lowest approved dose) [105–107]. Also, the FDA removed age from the indication; in REDUCE-IT, all patients had to be 45 years of age or older. Finally, the qualifying number of CV risk factors in patients with diabetes differs between the approved label and the REDUCE-IT criteria: while the study included patients 50 years of age or older with diabetes and ‘at least one additional risk factor,’ the FDA-approved indication includes patients with diabetes and ‘2 or more additional risk factors.’

Additional considerations

We explore a few additional considerations by answering some common questions.

What is the historic evidence for the use of mixed Omega-3s (EPA + DHA combinations) in CVD prevention?

Recently, two large CVOTs of mixed omega-3 fatty acids (EPA + DHA combinations) – the Vitamin D and Omega-3 Trial (VITAL) and A Study of Cardiovascular Events in Diabetes (ASCEND) – reported results. The mixed omega-3 fatty acid (EPA + DHA) combinations failed to lower primary endpoints in these CV outcome trials [108,109]. In addition, a recent systematic review and meta-analysis of these trials found that each 1-g/day increase in EPA intake was associated with a significant 7% relative risk reduction in major vascular events ($P < 0.0001$) while each 1-g/day increase in DHA intake was not ($P = 0.27$) [110]. A limitation of this meta-analysis is that

studies included were quite heterogeneous, which may have resulted in skewed data.

What is the evidence for the use of fish oil dietary supplements in CVD Prevention?

A recent review concluded that dietary fish oil supplements should not be considered as an effective substitute for prescription omega-3 fatty acids [111]. Considering the totality of evidence supporting this claim, practice guidelines have advised as follows: the ADA standards of care states that other, non-prescription formulations of omega-3 lack compelling evidence for CVD event risk reduction and should not be used for prevention [10]. The AHA noted in a science advisory that fish oil dietary supplements are neither reviewed nor approved by the FDA and that fish oil dietary supplements are not indicated for TG level lowering for patients with any degree of TG level elevation [11]. The AHA science advisory also noted that products containing DHA may increase LDL-C levels in patients with very high TG levels [11]. Preclinical and clinical studies have demonstrated that EPA and DHA have distinct tissue distributions, as well as disparate effects on membrane structure and lipid dynamics, rates of lipid oxidation, and cholesterol domains [32,40,112,113]. In laboratory studies, EPA inhibited oxidation of HDL and apoB–containing lipoproteins over a greater period of time than DHA [114,115]. In a membrane laboratory model, DHA, unlike EPA, altered the membrane by increasing cholesterol domain formation and membrane fluidity [116]. How these membrane-stabilizing and anti-oxidant effects of EPA possibly translate to CVD risk reduction is unknown [112,113]. Unless and until mixed omega-3s (EPA + DHA combinations) show compelling evidence of CV benefit, REDUCE-IT findings should not be extrapolated to other omega-3 fatty acid products, including other prescription products.

What are some considerations regarding the use of fibrates or niacin in CVD prevention?

Niacin and fibrates in large outcome studies, as add-on therapy to statins, failed to meet their primary CV endpoints. In the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) study, the addition of niacin to a statin did not show CV benefit compared with statin alone. In the Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE), the niacin group not only failed to achieve its primary CV endpoint, but had an increased risk of serious AEs [117,118]. Similarly, studies of fibrates, including the Action to Control Cardiovascular Risk in Diabetes (ACCORD Lipid) and Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) failed to achieve their primary CV endpoints, although fibrates may potentially benefit patients with high TG and low HDL levels [119–121]. Given the lack of positive CVOT data associated with the combined use of statin with fibrates or niacin to date, the 2019 ADA Standards of Care states that combinations of statins with either fibrates or with niacin are generally not recommended for CV event prevention (Level A evidence; Table 2) [100]. The FDA also removed the indications for the use of fibrates and

niacin with statins in 2016 due to a lack of benefit in CVOTs with these combinations. An ongoing CVOT utilizing a newer fibrate (pema-fibrate) in patients with type 2 diabetes, elevated TG levels, and on statin therapy (PROMINENT; NCT03071692) may be informative.

What CVOTs of other EPA or mixed omega-3 combinations are ongoing or recently terminated?

A few CV outcomes trials of other omega-3s of particular interest are ongoing* or recently terminated** [32]:

- RESPECT-EPA* (UMIN000012069) [122]: The Randomized Trial for Evaluation in Secondary Prevention Efficacy of Combination Therapy—Statin and Eicosapentaenoic Acid is currently following approximately 3900 patients with established atherosclerotic CVD, on a statin, randomized to 1.8 g/day EPA versus no EPA to explore benefit on CV outcomes.
- STRENGTH** (NCT02104817) [123]: The Statin Residual Risk Reduction With Epanova in High CV Risk Patients With Hypertriglyceridemia trial was aimed at evaluating the impact of prescription mixed EPA + DHA omega-3 carboxylic acids on CV outcomes. However, following the recommendation from an independent Data Monitoring Committee, the trial was closed due to its low likelihood of demonstrating CV benefit.
- OMEMI* (NCT01841944) [124]: The Omega-3 Fatty Acids in Elderly Patients With Acute Myocardial Infarction trial includes 1400 participants aged 70 to 82 years with acute MI who were discharged from the hospital. Patients are randomized to 1.8 g/day EPA + DHA to assess whether supplementation in addition to modern therapy versus corn oil placebo would reduce the combined CV endpoint of death, nonfatal MI, stroke, and revascularization by at least 30% over a planned 2-year follow-up period. The mixed omega 3 dietary supplement used in this study is Pikasol (3 capsules [3 g concentrated fish oil] needed to provide the 1.8 g of omega-3s [~930 mg EPA and ~660 mg DHA]).

If, in the future, a mixed omega-3 product shows a compelling CV outcome benefit, the 'E' in the ABCDEF CV prevention strategy may be revisited and expanded to also include such an EPA + DHA combination product. Until then, high-purity EPA as IPE holds the evidence.

Conclusions

Despite the use of statins and other cholesterol-lowering therapies, substantial residual CVD event risk poses a major healthcare and economic challenge, even with well-controlled LDL-C levels. The cost of CVD is substantial. In the landmark CV outcomes trial REDUCE-IT, IPE, a stable, highly purified prescription EPA at 4 g/day, decreased CVD events by 25% when added to statins. This represents the largest CVD event risk reduction of any therapy studied in addition to statins and led to the FDA expanding the approval of IPE to include CVD event prevention. The benefits in

CVD event risk reduction with IPE are likely due to multifactorial pleiotropic mechanisms beyond TG level lowering. IPE has been deemed very cost-effective in multiple analyses and has been added to several global practice guidelines. IPE, a highly purified and stable ethyl ester preparation of EPA, holds evidence of CV benefit whereas mixed omega-3s (combinations of EPA + DHA) have failed to impress in recent CV outcome trials. Fish oil dietary supplements are not regulated as medicine by the FDA. Therefore, due to all of the evidence presented, we believe that evidence-based EPA as IPE should be considered as a new entry under 'E' in the ABCDEFs for CVD prevention as a new standard of care.

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Declaration of interest

Kamini Trivedi is a former stock shareholder of Amarin Pharma, Inc.

Viet Le reports no conflicts of interest.

John R. Nelson is a former stock shareholder of and currently serves as a speaker's bureau member, consultant, and advisor to Amarin Pharma Inc., from which he has received honorarium.

Declaration of interest

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