American Journal of Cardiovascular Drugs
https://doi.org/10.1007/s40256-023-00583-8

REVIEW ARTICLE

A Critical Review of Icosapent Ethyl in Cardiovascular Risk Reduction

Jessica Huston[1] · Hannah Schaffner[2] · Alyssa Cox[1] · Alexander Sperry[2] · Shelby Mcgee[3] · Payeng Lor[4] · Logan Langley[1] · Blake Skrable[5] · Majdi Ashchi[6] · Mohannad Bisharat[6] · Ashwini Gore[7] · Thomas Jones[7] · David Sutton[8] · Mae Sheikh-Ali[8] · Jason Berner[9] · Rebecca Goldfaden[2]

Accepted: 5 April 2023

Abstract

Icosapent ethyl (IPE) was the first fish oil product the US Food and Drug Administration (FDA) approved to reduce the risk of atherosclerotic cardiovascular disease (ASCVD) in adults. IPE is an esterified version of eicosapentaenoic acid (EPA) and acts as a prodrug in the body to exert its effects. IPE affects the body primarily through triglyceride (TG) reduction and was initially indicated for hypertriglyceridemia in addition to statin therapy or for patients with statin intolerances. Various studies have investigated this agent, and multiple subanalyses have been conducted since the FDA approval. These subanalyses have assessed factors such as sex, statin therapy, high-sensitivity C-reactive protein levels (hs-CRP), and various inflammatory biomarkers in groups of patients taking IPE. This article aims to provide a critical review of the clinical data available regarding cardiovascular benefits of IPE in patients with ASCVD and its value as a treatment option for patients with elevated TG levels.

Key Points

Icosapent ethyl was the first fish oil product approved by the US FDA to reduce the risk of atherosclerotic cardiovascular disease in adults.

Icosapent ethyl is an esterified version of eicosapentaenoic acid (EPA) and acts as a prodrug in the body to exert its effects.

1 Background

Cardiovascular diseases (CVDs) are the leading causes of death each year, resulting in approximately 659,000 deaths in the USA [1, 2]. Treatment and prevention of cardiovascular (CV) outcomes is essential for reducing the risk of major adverse events including stroke, atherosclerotic cardiovascular disease (ASCVD), myocardial infarction (MI), heart failure (HF), recurrent angina pain, transient ischemic attack, and all-cause death and mortality [2]. ASCVD includes major risk factors such as age, family history, smoking, blood pressure, diabetes mellitus (DM), and low levels of high-density lipoprotein cholesterol (HDL-C). Elevations in triglycerides (TGs) and low-density lipoprotein cholesterol (LDL-C) levels are also important markers used to identify CV risk in patients and are residual ASCVD risk factors in patients receiving statin treatment [3, 4]. The use of HMG-CoA reductase inhibitors, otherwise known as statins, as monotherapy has modest effects on hypertriglyceridemia, indicating a need for additional therapy for patients to achieve their health goals and prevent disease progression [4]. Other

✉ Rebecca Goldfaden
rg@eastcoastresearch.net

1 College of Pharmacy, University of Florida, Jacksonville, USA

2 East Coast Institute for Research, Jacksonville, USA

3 Philadelphia College of Osteopathic Medicine, Philadelphia, USA

4 School of Pharmacy, Medical College of Wisconsin, Milwaukee, USA

5 University of California San Diego, San Diego, USA

6 Ashchi Heart and Vascular Center, Jacksonville, USA

7 The Jones Center, Macon, USA

8 Northeast Florida Endocrine and Diabetes Associates, Jacksonville, USA

9 Georgia Mountain Endocrinology, Canton, USA

Published online: 15 May 2023

medications introduced to the market for this purpose include bempedoic acid, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, omega-3 fatty acids, ezetimibe, fibrates, bile acid sequestrants, and niacin [5]. Of these classes of medications available, omega-3 fatty acids are proven to be efficacious in lowering TGs, and their potential use as a therapeutic option for reduction in CV risk is of clinical interest. The currently available preparations of omega-3 fatty acids otherwise known as fish oil, include icosapent ethyl, omega-3-acid ethyl ester, and omega-3-carboxylic acids. However, omega-3-carboxylic acid was discontinued during the phase III STRENGTH study due to a low likelihood of benefit to patients with mixed dyslipidemia (MDL) who are at risk of CVD [6]. While omega-3-acid ethyl ester and omega-3-carboxylic acid are combination products that include both eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), icosapent ethyl is a 99.99% pure composition of EPA. The function of EPA includes reduction in platelet aggregation, vasodilation, antiproliferation, plaque stabilization, and reduction in lipid action [7]. IPE is absorbed into the membrane phospholipid and coronary plaques and is thought to have beneficial effects on the pathway from plaque formation to plaque rupture [8]. IPE is currently indicated as adjunct therapy to maximally tolerated statin therapy to aid in reduction in risk of MI, stroke, coronary revascularization, and unstable angina requiring hospitalization in adult patients with TG levels $\geq$ 150 mg/dL and established CVD or DM with two or more additional CVD risk factors. It is also used as adjunctive therapy to diet to reduce hypertriglyceridemia ($\geq$ 500 mg/dL) and is the first fish oil product to be FDA approved to reduce ASCVD in adults [9]. The efficacy of using highly purified IPE for CV risk reduction has been reviewed in various studies including REDUCE-IT, JELIS, and ANCHOR and shows promising results. Moreover, the Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention study (REDUCE-IT) compared the efficacy of IPE in reducing CV events in high-risk patient populations who have hypertriglyceridemia despite being on statin therapy and DM with one or more CV risk factors. The overall value of the benefits of IPE for CV risk was reviewed to determine if it is a cost-effective treatment option [10]. Furthermore, an analysis of the REDUCE-IT study suggests that treatment with IPE may be cost-effective in this high-risk patient population [10]. This review serves to evaluate the various clinical studies related to IPE and the results associated with them as it relates to CV risk reduction.

2 Mechanism of Action

Commonly known as fish oil, the dietary supplement containing multiple polyunsaturated fatty acids is said to have cardioprotective effects [11]. While some of the fatty acids present in fish oil have benefits, others such as arachidonic acid (AA) and docosahexaenoic acid (DHA) do not provide the same beneficial effects. IPE is unique to the class of omega-3 fatty acids in that it exclusively contains the omega-3 fatty acid EPA, which is thought to provide CV benefit in the form of risk reduction. EPA has a unique chemical structure that allows it to change the properties of cellular membranes [12]. The 20-carbon fatty acid contains EPA where the omega-6 fatty acid AA would otherwise be present [12]. While AA tends to produce pro-inflammatory and pro-thrombotic forms, EPA has the opposite effect. It is proposed that increasing the EPA:AA ratio increases CV benefits, while lower EPA:AA ratios results in increased CVD risks [11]. This is explained by the mediators associated with EPA and AA. Prostaglandin E2 (PGE2), leukotriene B4 (LTB4), and thromboxane A2 (TXA2) result from AA as the metabolic precursor. Each of these mediators plays a role in increasing vascular permeability and vasodilation, enhancing local blood flow, inducing release of lysosomal enzymes, and promoting activation and aggregation of platelets [11]. EPA, on the other hand, is a precursor for resolvins and competes with AA for inclusion into membrane phospholipids, resulting in decreased inflammatory effects [11].

Additionally, other available omega-3 products contain EPA; however, they also contain DHA, which has been shown to elevate LDL-C levels [12]. While it is not yet completely understood, the difference between EPA and DHA effects may be partly due to the lipoprotein subfractions they affect [13]. DHA has also been thought to promote core lipid transfer, downregulate LDL receptor expression and, thus, LDL receptor-mediated LDL-C clearance, and increase conversion of very-low-density lipoprotein (VLDL) to LDL, all leading to an increase in LDL-C [12]. IPE stands apart in the group of omega-3 fatty acids due to its purity of EPA and exclusion of DHA.

Further, EPA is thought to reduce steps in the atherogenesis pathway, lower TG and non-high density lipoprotein cholesterol (non-HDL-C) levels, increase anti-inflammatory and anti-thrombotic mediators through its metabolism, and improve endothelial function [11, 12]. Since increases in CV risk have been correlated with loss of endothelial-derived nitric oxide (NO) and NO-mediated vasodilation, it is relevant to explain that EPA has shown to increase endothelial NO synthase (eNOS) coupling efficiency and the NO/$ONOO^-$ (nitric oxide/peroxynitrite) release ratio, while DHA has no effect on $ONOO^-$. Additionally, the metabolites of omega-3 fatty acids have shown to have multifactorial roles during endothelial inflammation and atherosclerosis [14]. Since IPE is composed of 99.99% EPA, it is distinguished in the benefits it can provide in terms of CV risk reduction compared with the other available preparations that include a mixture of EPA and DHA [15].

3 Clinical Studies

3.1 MARINE

To define the efficacy of IPE in treatment of dyslipidemia, MARINE, a 12-week, prospective study including a 40-week open-label extension period, assessed the efficacy and safety of IPE in 224 participants with TG levels exceeding 500 mg/dL despite previous treatment with TG-lowering therapies [16]. A total of 229 participants were randomized 1:1:1 to IPE 2 g, IPE 4 g, or placebo daily following a 4–6-week lead-in period of diet, lifestyle, and medication stabilization and, when applicable, a washout of select lipid-altering medications. Baseline participant characteristics were balanced among assigned treatment arms and largely accounted for white, nondiabetic males under the age of 65 years without statin treatment at randomization. The primary endpoint was the median absolute change from baseline in TGs at week 12. Median TG reductions of −26.6% and −7.0% were observed in the 4 g and 2 g groups, respectively, yielding −33.1% ($p < 0.0001$) and −19.7% ($p = 0.0051$) absolute reductions versus placebo (+9.7%). Subgroup analyses conducted per baseline TG levels and statin use revealed substantial primary outcome changes among participants taking both 2 g and 4 g IPE doses. Participants in the IPE group with baseline TG values > 500 mg/dL ($N = 191$), ≤ 750 mg/dL ($N = 136$), and > 750 mg/dL ($N = 88$) demonstrated respective placebo-adjusted reductions of −35.7% ($p < 0.0001$), −25.1% ($p = 0.0006$), and −45.4% ($p = 0.0001$) at the 4 g dose and lesser −24.9% ($p = 0.0007$), −9.1% ($p = 0.282$), and −32.9% ($p = 0.0016$) at the 2 g dose. In the statin use subgroups, greatest absolute benefit was observed in statin-treated participants versus those not treated at baseline (−40.7%, $p = 0.0276$ versus −16.4, $p = 0.0360$); however, unadjusted change from baseline in the 2 g group, specifically, was negative in participants not taking a statin (−10.2%) yet positive in those statin-treated (+11.1%). Median placebo-adjusted changes were substantial in VLDL-C (−28.6%, $p = 0.0002$), Lp-PLA2 (−13.6%, $p = 0.0003$), ApoB (−8.5%, $p = 0.0019$), TC (−16.3%, $p < 0.0001$), non-HDL-C (−17.7%, $p < 0.0001$), and VLDL-TG (−25.8%, $p = 0.0023$) levels of participants in the 4 g arm and in VLDL-C (−15.3%, $p = 0.038$), TC (−6.8%, $p = 0.0148$), and non-HDL-C (−8.1%, $p = 0.0182$) levels of participants in the 2 g arm. Throughout the study, IPE demonstrated a reserved safety profile, as approximately 35% of participants in each of the 2 g IPE, 4 g IPE, and placebo groups experienced at least one treatment-emergent adverse event (TEAE), and most TEAEs were considered mild to moderate in severity and unrelated to IPE. Gastrointestinal TEAEs were most frequent, with greatest respective incidences of diarrhea, nausea, and eructation observed in the placebo (7%, 5%, 3%) and 2 g IPE (5%, 7%, 1%) groups and minimal incidence in the 4 g IPE group (1%, 1%, 0%) [16]. Overall, treatment with IPE at 2 g and 4 g doses proved safe and effective at lowering TG levels in participants with elevated TG levels despite current treatment. Notably, the effect on VLDL should be examined further as this may directly correlate with the effect on CV risk reduction. As hypothesized with DHA promoting core lipid transfer and, thus, increasing conversion of VLDL to LDL, the reduction of VLDL and subsequently LDL with EPA treatment may stimulate the effect on reducing CV risk factors.

3.2 ANCHOR

To assess the effects of IPE in high-risk, statin-treated patients exclusively, ANCHOR, a 12-week, prospective study of IPE, evaluated participants with residually high TG levels despite LDL-C levels within normal limits [17]. All 702 participants were randomized 1:1:1 to IPE 2 g, IPE 4 g, or placebo daily following a 4–6-week lead-in period of lifestyle stabilization and washout of prohibited statin-lowering agents, if necessary. To be included in the study, participants were required to be at high risk of CVD per National Cholesterol Education Program Adult Treatment Panel III guidelines and have a minimum 4-week treatment history with stable dosing of atorvastatin, simvastatin, or rosuvastatin with or without ezetimibe, a mean fasting TG level of 200–500 mg/dL following two samples, and LDL-C level of 40–115 mg/dL. Baseline participant characteristics were balanced among assigned treatment arms and largely accounted for white, male, diabetic adults under 65 years of age with mean HbA1c < 7% and median TG and LDL-C values of 259.0 mg/dL and 83.0 mg/dL, respectively. The primary outcome measured the median absolute change from baseline in TGs at week 12. Final assessments of change in TG levels revealed unadjusted differences from baseline of −17.5%, −5.6%, and +5.9% in participants taking IPE 4 g, IPE 2 g, and placebo, respectively, yielding significant placebo-adjusted reductions of −21.5% ($p < 0.0001$) in the 4 g arm and −10.1% ($p = 0.0005$) in the 2 g arm. Subgroup analyses were conducted per statin type and efficacy regimen, diabetes status, and baseline TG level tertiles. Among statin subgroups within the 4 g arm, atorvastatin demonstrated the greatest placebo-adjusted change (−28.4%, $p < 0.0001$), while notable reductions were also seen with rosuvastatin (−23.4%, $p < 0.0001$) and simvastatin (− 18.8%, $p < 0.0001$). Within the 2 g IPE arm, participants taking atorvastatin, rosuvastatin, and simvastatin exhibited respective placebo-adjusted TG reductions from baseline of −2.4% ($p = 0.6642$), −5.7% ($p = 0.2512$), and −14.3% ($p = 0.0004$). Benefit was also observed across statin efficacy subgroups, as participants taking low-, medium-,

and high-efficacy statins demonstrated respective −13.1% ($p = 0.5467$), −20.1% (< 0.0001), and −26.0% (< 0.0001) placebo-adjusted TG reductions in the 4 g IPE arm and −13.8 ($p = 0.6784$), −8.7% ($p = 0.0139$), and −11.7% ($p = 0.0200$) in the 2 g IPE arm. In assessment of absolute TG reductions from baseline per diabetes status, both diabetic and nondiabetic participants within the 2 g and 4 g IPE groups exhibited benefit in comparison with placebo, as −23.2% ($p < 0.0001$) and −16.8% ($p = 0.0005$) reductions were reported for diabetics and nondiabetics, respectively, in the 4 g IPE group, while −9.8% ($p = 0.0074$) and −10.8% ($p = 0.0261$) reductions were seen in the 2 g IPE group. Baseline TG levels appeared to directly correlate with the TG-lowering efficacy of IPE following subgroup analyses per baseline tertiles of TG levels < 230.5 mg/dL, 230.5 to < 289.5 mg/dL, and ≥ 289.5 mg/dL. Respective placebo-adjusted reductions from baseline within the first, second, and third tertiles were −14.4% ($p = 0.0020$), −17.9% ($p < 0.0001$), and −31.1% ($p < 0.0001$) in the 4 g IPE group and −4.1% ($p = 0.3694$), −9.9% ($p = 0.0324$), and −16.9% ($p = 0.0043$) in the 2 g IPE group. Respective median placebo-adjusted reductions reported for the 4 g and 2 g IPE groups were greatest in VLDL-TG (−26.5%, $p < 0.0001$; −11.3, $p = 0.0049$), VLDL-C (−24.4%, $p < 0.0001$; −10.5%, $p = 0.0093$), Lp-PLA2 (−19.0%, $p < 0.0001$; −8.0%, $p < 0.0001$), and hs-CRP (−22.0%, $p = 0.0005$; −6.8%, $p = 0.2889$). Subgroup analyses of median absolute change in non-HDL-C were conducted per statin efficacy regimens, revealing substantial placebo-corrected reductions from baseline of −13.9% ($p < 0.0001$) and −15.8% ($p < 0.0001$) in participants of the 4 g IPE group taking medium- and high-efficacy statins, respectively. Among the study population, approximately 45% of participants experienced at least one TEAE; most TEAEs were considered mild to moderate in severity and unrelated to IPE. TEAEs related to infections and infestations occurred in highest incidences of 13.3%, 12.7%, and 16.3% in the 4 g IPE, 2 g IPE, and placebo groups, respectively. Gastrointestinal disorders also occurred in relatively high incidences of approximately 11.5% in each of the IPE groups and 17.2% in the placebo group. Occurrences of musculoskeletal and connective tissue disorders were, conversely, higher in the IPE treatment arms, as total incidences of 7.7% and 7.6% were observed within the IPE 4 g and 2 g groups, respectively, while only 4.3% total incidence was reported for placebo [17]. Treatment with IPE showed favorable results in reducing the lipid levels studied. The efficacy in reductions in TG levels correlating with baseline TG levels with greatest reduction in the group with baseline TG levels ≥ 289.5 mg/dL administered both 2 g IPE and 4 g IPE should be considered when evaluating potential CV risk reduction for patients with increased TG levels.

3.3 JELIS

Early recognition of evidence suggesting a potential correlation between long-term omega-3 fatty acid intake and CV mortality reduction prompted investigation of related effects specific to EPA use in patients with hypercholesterolemia through the Japan EPA Lipid International Study (JELIS) [7]. In the prospective, open-label, blinded endpoint investigation, major coronary event rates were monitored in 18,645 participants randomized 1:1 to receive 300 mg EPA three times daily plus statin therapy or statin therapy alone over an approximate 5-year follow-up period. Exclusive to Japanese individuals, the study design aimed to examine effects of supplemental EPA in a population known to have regular omega-3 fatty acid intake through dietary fish consumption. Eighty percent of participants were classified as primary prevention, and CV risk factors most prevalent among the study population included current smoking (19%) as well as diagnosis of diabetes (16%) or hypertension (36%). Primary outcome analyses compared rates of any major coronary event, including sudden cardiac death, fatal and nonfatal MI, and other nonfatal events including unstable angina pectoris, angioplasty, stenting, or coronary artery bypass grafting between the two study arms and CV prevention class subgroups. The EPA group demonstrated a 2.8% incidence of cumulative coronary events, effecting a statistically significant 19% risk reduction [hazard ratio (HR) 0.81, 95% confidence interval (CI) 0.69–0.95, $p = 0.011$] relative to the 3.5% incidence observed in those receiving statin therapy alone. Cumulative coronary event rates favoring the EPA group were also indicated in both primary and secondary prevention subgroup data. Similar, nonsignificant relative reductions of 18% (HR 0.82, 95% CI 0.63–1.06, $p = 0.132$) in primary prevention participants and 19% (HR 0.81, 95% CI 0.66–1.00, $p = 0.048$) in secondary prevention patients were reported. Additionally, primary outcome analyses per CV prevention stratum revealed a higher risk of fatal MI with treatment in primary prevention participants (HR 1.00, 95% CI 0.32–3.11, $p = 0.995$) compared with secondary prevention participants (HR 0.64, 95% CI 0.21–1.94, $p = 0.421$), as well as a higher risk of sudden cardiac death in primary versus secondary prevention participants (HR 1.25, 95% CI 0.34–4.67, $p = 0.736$ versus HR 1.02, 95% CI 0.47–2.19, $p = 0.967$). Combined coronary event analyses were also conducted with data of time to coronary death or MI, fatal MI or nonfatal MI, coronary death alone, and nonfatal coronary events. All results favored EPA plus statin over statin therapy alone, yet a significant between-group difference was reported only in occurrences of nonfatal coronary events (HR 0.81, 95% CI 0.68–0.96, $p = 0.015$). Combined endpoint analyses per prevention stratum revealed a higher risk of coronary death in primary (HR 1.10, 95% CI

0.47–2.60, $p = 0.822$) versus secondary (HR 0.87, 95% CI 0.46–1.64, $p = 0.667$) prevention participants. Reductions in TC (−19%) and LDL-C (−25%) from baseline were similar between both treatment groups, with slightly greater reduction of LDL-C seen in those receiving a statin alone. Reduction in TGs from baseline in those receiving EPA (−9%) was significantly greater than that in the statin alone group (−4%) ($p < 0.0001$), with particularly robust reductions of approximately −20% and −25% demonstrated by a subgroup of participants in the statin and IPE groups, respectively, with baseline TGs ≥ 150 mg/dL. Safety analyses indicated a higher cumulative incidence of adverse events in the EPA group (25.3%) than the control group (21.7%) ($p < 0.0001$). Substantial differences between EPA and control groups were also found in reports of pain (1.6%, 2.0%, $p = 0.04$) gastrointestinal disturbances (3.8%, 1.7%, $p < 0.0001$), skin abnormalities (1.7%, 0.7%, $p < 0.0001$), and hemorrhages (1.1%, 0.6%, $p = 0.0006$), respectively. Additionally, incidence of newly diagnosed stomach cancer in the EPA group (0.6%) was notably higher than that in the control group (0.4%) ($p = 0.09$). Investigators suggested a potential influence of consistently high fish intake on coronary outcomes in the study population. Specifically, the proposed effect of high intake on nonfatal coronary events was supported by a significantly greater relative difference observed in nonfatal coronary events versus other coronary outcomes, as such differences were not reported in similar study populations without high fish intake [7]. While a statistically significant risk reduction was present for the patients treated with EPA versus statin therapy alone for cumulative coronary events, further studies should account for high fish intake and sample size stratification between subgroups.

3.4 REDUCE-IT

With availability of evidence supporting an association between EPA intake and risk of coronary events in statin-treated patients alongside efficacy and safety data of IPE in treatment of hypertriglyceridemia, investigators sought to further examine effects of IPE intake on CV risk in a large sample of participants with elevated TGs despite statin therapy. The REDUCE-IT study was then designed to compare 5-year ischemic event rates between high-risk participants given IPE 2 g twice daily or matching placebo [18]. Participants included statin-treated, hypertriglyceridemic adults age ≥ 45 years with established CVD or age ≥ 50 years with DM and at least one additional CV risk factor. Male participants categorized as secondary prevention accounted for approximately 70% of the total study population, while 58% of participants were diagnosed with type 2 DM, and 93% were taking a moderate- to high-intensity statin at baseline. Among participants in both the IPE and placebo groups, 17.2% and 22.0%, respectively, met the primary endpoint composite of CV death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina, yielding a statistically significant 25% relative risk reduction (HR 0.75, 95% CI 0.68–0.83, $p < 0.001$) and number needed to treat (NNT) of 21 with IPE administration. All IPE subgroups demonstrated reduced occurrence of the primary endpoint when compared with placebo, apart from increased incidence observed in participants taking a low-efficacy statin at baseline (HR 1.12, 95% CI 0.74–1.69). Of note, difference in benefit demonstrated between diabetic (HR 0.77, 95% CI 0.68–0.87) and nondiabetic (HR 0.73, 95% CI 0.62–0.85) subgroups was not substantial (Int. $p = 0.56$), nor was difference between subgroups with baseline TGs ≥ 150 mg/dL (HR 0.75, 95% CI 0.68–0.83) and < 150 mg/dL (HR 0.79, 95% CI 0.57–1.09) (Int. $p = 0.83$). Overall, greatest relative risk reductions in the primary composite endpoint were demonstrated by subgroups representing non-white race, age < 65 years, baseline TGs ≥ 200 mg/dL alongside HDL-C ≤ 35 mg/dL, and baseline hsCRP ≤ 2 mg/L. Risk reductions reported in remaining subgroups were consistent with that of the cumulative primary composite outcome, as they ranged from 20% to 30%. Initial analysis of the key composite secondary endpoint revealed a significant 26% relative risk reduction in the IPE group when compared with placebo (HR 0.74, 95% CI 0.65–0.83, $p < 0.001$). Substantial risk reductions versus placebo were also observed in the IPE of each subsequent stratum except death from any cause (HR 0.87, 95% CI 0.74–1.02). Assessment of most individual and combined secondary outcome components yielded similar, approximate 25–30% reductions in risk with IPE treatment relative to placebo. However, greater treatment benefit was reported per occurrence of urgent or emergent revascularization (HR 0.65, 95% CI 0.55–0.78, $p < 0.001$) and hospitalization for unstable angina (HR 0.68, 95% CI 0.53–0.87, $p = 0.002$) within the IPE group, while comparatively less reduction in risk of CV death relative to placebo was observed (HR 0.80, 95% CI 0.66–0.98, $p = 0.03$). As in the primary composite subgroup analysis results, all IPE subgroups demonstrated reduced occurrence of the secondary composite endpoint when compared with placebo, apart from increased incidence observed in participants taking a low-efficacy statin at baseline (HR 1.20, 95% CI 0.74–1.93). Within the reported subgroup outcome results, notable differences were seen between low, medium (HR 0.74, 95% CI 0.63–0.87), and high (HR 0.66, 95% CI 0.54–0.82) statin efficacy groups (Int. $p = 0.10$), non-white (HR 0.55, 95% CI 0.38–0.82) and white (HR 0.76, 95% CI 0.67–0.86) races (Int. $p = 0.13$), and age groups < 65 years (HR 0.65, 95% CI 0.54–0.78) and ≥ 65 years (HR 0.82, 95% CI 0.70–0.97) (Int. $p = 0.06$). Greatest relative reductions in risk of the secondary composite endpoint were

demonstrated by subgroups representing non-white race, participants from the USA (HR 0.69, 95% CI 0.57–0.83), ages < 65 years, baseline TGs < 150 mg/dL (HR 0.66, 95% CI 0.44–0.99), baseline TGs ≥ 200 mg/dL alongside HDL-C ≤ 35 mg/dL (HR 0.68, 95% CI 0.53–0.88), and high-efficacy statin use, while risk reductions in remaining subgroups were consistent with the cumulative secondary composite outcome results and ranged from approximately 20% to 30%. Risk reductions were also observed in occurrence of cardiac arrest (HR 0.52, 95% CI 0.31–0.86), sudden cardiac death (HR 0.69, 95% CI 0.50–0.96), and ischemic stroke (HR 0.64, 95% CI 0.49–0.85) [18]. Within the study, 3693 patients had a history of prior MI, and the primary endpoint was reduced from 26.2% to 20.2% in those treated with IPE compared with placebo. There was a 35% relative risk reduction in total ischemic events, 34% decrease in MI, 30% reduction in CV death, and 20% lower rate of all-cause mortality, but a slightly higher rate of atrial fibrillation within the IPE treatment group for this subgroup [19]. Alternatively, participants in the IPE group demonstrated greater risk of new-onset diabetes relative to placebo (HR 1.04, 95% CI 0.73–1.47). Increased risk of carotid revascularization (HR 1.18, 95% CI 0.70–1.98) and hemorrhagic stroke (HR 1.28, 95% CI 0.56–2.93) were also observed with IPE treatment, though a relatively smaller number of participants were represented by data in these outcomes. Approximately 81% of participants in both the IPE and placebo groups experienced at least one TEAE. Approximately 30% of participants in each group experienced a serious TEAE, though most events did not lead to death or withdrawal of treatment. Similarly, mild to moderate TEAEs were unrelated to the study drug. Safety outcomes were comparable between both study groups; however, the IPE group demonstrated a notably higher incidence of atrial fibrillation (5.3%) than that of the placebo group (3.9%), while rates substantially lower in the IPE group were reported for anemia (4.7% versus 5.8%, $p = 0.03$), diarrhea (9.0% versus 11.1%, $p = 0.002$), and constipation (5.4% versus 3.6%, $p < 0.001$) [19]. This study demonstrated that the use of 2 g of IPE twice daily has significant effects in reducing clinically important events studied in the primary endpoint. Further studies have strengthened the results of the REDUCE-IT study by extending the findings to patients with high cardiovascular risk, which includes prior MI, prior coronary revascularization with PCI or CABG, diabetes, and severe renal dysfunction [20].

3.5 REDUCE-IT Subanalyses

In response to robust outcomes data presented in REDUCE-IT, supportive analyses in subgroup populations were executed to further assess and refine the role of IPE in CV risk reduction.

3.5.1 REDUCE-IT USA

Due to prior evidence suggesting a generalized difference in derived treatment benefits between clinical study participants from the USA versus other areas, investigators sought to determine the potential CV benefit of IPE versus placebo in US patients. The subanalysis, REDUCE-IT USA, assessed data specific to REDUCE-IT participants from the USA, including data from 38.5% ($N = 3146$) of individuals originally randomized to study treatment. Analysis of the primary endpoint assessed data from 18.2% of participants treated with IPE and 24.7% of participants administered placebo [21]. Results revealed a significant 31% relative risk reduction (HR 0.69, 95% CI 0.59–0.80, $p < 0.0001$) and 6.5% absolute risk reduction in the IPE group when compared with placebo, yielding an NNT of 15. Alternatively, a 20% relative risk reduction favoring IPE versus placebo (HR 0.80, 95% CI 0.71–0.91, $p < 0.0001$) was identified in participants from areas outside of the USA, and a notable difference in the primary composite outcome between US and non-US subgroups was reported (Int. $p = 0.14$). In analysis of the primary composite endpoint per baseline characteristics of US subgroup participants, minimal variation was found within most categories. However, assessment of the outcome per baseline statin efficacy revealed substantially less potential benefit from IPE treatment in participants taking a low-efficacy statin (HR 1.08, 95% CI 0.59–1.96) versus a medium- (HR 0.65, 95% CI 0.52–0.80) or high-efficacy statin (HR 0.67, 95% CI 0.53–0.86) (Int $p = 0.28$). Additionally, outcome data per baseline LDL-C tertile demonstrated a notable difference in derived benefit from IPE treatment between participants with LDL-C of > 65 to ≤ 80 mg/dL (HR 0.87, 95% CI 0.67–1.13) and participants with LDL-C of ≥ 12 to ≤ 65 mg/dL (HR 0.59, 95% CI 0.45–0.77) or > 80 to ≤ 222 mg/dL (HR 0.63, 95% CI 0.48–0.83) (Int. $p = 0.09$). From a total of 1272 adjudicated ischemic events within the US subgroup, investigators defined proportion of first (53%) and subsequent (47%) events individually defined within the primary composite endpoint. Overall treatment comparison per event recurrence revealed substantial benefit with IPE treatment relative to placebo (RR 0.68, 95% CI 0.57–0.82, $p < 0.0001$), while distributional between-group comparisons demonstrated relatively less recurrence not only in first events, but also in second (HR 0.65, 95% CI 0.53–0.79), third (HR 0.63, 95% CI 0.49–0.81), and fourth or more (RR 0.67, 95% CI 0.44–1.02) [22]. A 31% relative risk reduction in the key secondary composite outcome was also reported in the IPE group versus placebo (HR 0.69, 95% CI 0.57–0.83, $p < 0.0001$) along with an absolute risk reduction

of 4.6% and NNT of 22. In participants outside of the USA, a 23% relative reduction in risk of the secondary composite outcome (HR 0.77, 95% CI 0.66–0.91) was reported. Among the individual and combined secondary endpoints, notable differences between US and non-US subgroups were seen in first occurrences of CV death (Int. $p = 0.09$), hospitalization for unstable angina (Int. $p = 0.12$), total mortality or nonfatal MI or nonfatal stroke (Int. $p = 0.15$), and total mortality (Int. $p = 0.02$), each of whose results was comparatively favorable for US participants. Safety results for the US subgroup were comparable to those of the original study, including results for arrhythmias [18, 20, 21].

3.5.2 REDUCE-IT CABG

The REDUCE-IT CABG subanalysis aimed to quantify residual CV benefit derived from treatment with IPE versus placebo in patients with a history of coronary artery bypass grafting (CABG). Hierarchal analyses of REDUCE-IT primary and secondary endpoint data specific to participants with a confirmed history of CABG were conducted per the prespecified sequence applied in the original study. Outcomes in the IPE ($N = 897$) and placebo ($N = 940$) groups of CABG patients were then compared with those in study participants with a history of ASCVD lacking prior CABG. The primary endpoint analysis included data from 22.0% and 28.2% of participants initially randomized to IPE and placebo, respectively. Results demonstrated a relative risk reduction of 24% in prior CABG participants of the IPE group compared with placebo (HR 0.76, 95% CI 0.63–0.92, $p = 0.004$), yielding an absolute risk reduction of 6.2% (95% CI 2.3–10.2%) and number needed to treat of 16. In patients with a history of ASCVD without prior CABG, an insignificantly greater risk reduction of 29% was observed with IPE (HR 0.71, 95% CI 0.62–0.82, $p < 0.0001$) (Int. $p = 0.55$). A comparison of cumulative primary endpoint event rates among all participants revealed substantially lower occurrences within the IPE group (RR 0.64, 95% CI 0.50–0.81, $p = 0.0002$). Rate of event recurrences were also assessed as 375 and 570 adjudicated events in the IPE and placebo groups, respectively, and were stratified per first, second, and third or greater occurrence. Within all three strata, significant reductions favoring IPE over placebo were observed. Analysis of the key secondary endpoint included data from 14.7% and 20.7% of participants initially randomized to IPE and placebo, respectively. A 31% reduction in risk relative to placebo was observed in the IPE group of participants with prior CABG (HR 0.69, 95% CI 0.56–0.87, $p = 0.001$), effecting an absolute risk reduction of 6.0% (95% CI 2.5–9.5%) with a NNT of 17. In participants with a history of ASCVD without prior CABG, the IPE group demonstrated a lesser, 26% reduction relative to placebo (HR 0.74, 95% CI 0.62–0.88, $p = 0.0005$) (Int. $p = 0.69$). In hierarchal analyses of individual and combined secondary endpoint events, risk reductions relative to placebo were reported for all outcomes in prior CABG participants taking IPE, with greatest reductions in time to CV death or nonfatal MI (HR 0.68, 95% CI 0.53–0.86, $p = 0.001$), fatal or nonfatal MI (HR 0.60, 95% CI 0.45–0.81, $p = 0.0005$), and urgent or emergent revascularization (HR 0.62, 95% CI 0.44–0.86, $p = 0.004$). Participants in the IPE group with ASCVD but lacking a history of CABG also demonstrated reductions in risk of all secondary endpoints assessed, with outcomes similar to those in prior CABG participants. However, a substantially greater yet expected reduction in risk of hospitalization for unstable angina was reported for non-CABG participants (HR 0.53, 95% CI 0.38–0.73, $p < 0.0001$) compared with CABG participants (HR 0.91, 95% CI 0.59–1.41, $p = 0.67$) taking IPE [23].

3.5.3 REDUCE-IT RENAL

The REDUCE-IT RENAL subanalysis examined the efficacy of IPE for CV prevention in individuals with reduced kidney function. Data from all REDUCE-IT participants were included in both prespecified and post hoc analyses. Prespecified data categories per baseline eGFR of < 60 mL/min/1.73 m^2, 60 to < 90 mL/min/1.73 m^2, and ≥ 90 mL/min/1.73 m^2 were further stratified in the post hoc analysis to reflect chronic kidney disease (CKD) stages, creating categories per baseline eGFR; > 15 to < 30 mL/min/1.73 m^2, ≥ 30 to < 45 mL/min/1.73 m^2, ≥ 45 to < 60 mL/min/1.73 m^2, and ≥ 60 mL/min/1.73 m^2. Significant relative reductions in risk of the primary composite endpoint were reported for IPE in all eGFR categories, with changes of −29% (HR 0.71, 95% CI 0.59–0.85, $p = 0.0002$) in participants with eGFR < 60 mL/min/1.73 m^2, −20% (HR 0.80, 95% CI 0.70–0.92, $p = 0.001$) in participants with eGFR 60 to < 90 mL/min/1.73 m^2, and −30% (HR 0.70, 95% CI 0.56–0.89, $p = 0.003$) in participants with eGFR ≥ 90 mL/min/1.73 m^2. In post hoc analysis of the primary composite endpoint, relative risk reductions of −41%, −17%, −34%, and −23% were reported in redefined eGFR groups of > 15 to < 30 mL/min/1.73 m^2 (HR 0.59, 95% CI 0.21–1.68), ≥ 30 to < 45 mL/min/1.73 m^2 (HR 0.83, 95% CI 0.59–1.16), ≥ 45 to < 60 mL/min/1.73 m^2 (HR 0.66, 95% CI 0.53–0.84), and ≥ 60 mL/min/1.73 m^2 (HR 0.77, 95% CI 0.69–0.87), respectively. However, the cumulative between group difference was found to be unsubstantial (Int. $p = 0.52$). Notable relative reductions in risk of the key secondary composite endpoint were also seen with IPE in all eGFR categories, with changes of −29% (HR 0.71, 95% CI 0.57–0.88, $p = 0.001$) in participants with eGFR < 60 mL/min/1.73 m^2, −23% (HR 0.77, 95% CI 0.64–0.91, $p = 0.002$) in participants with eGFR 60 to < 90 mL/min/1.73 m^2, and −30% (HR 0.70, 95% CI 0.52–0.94, $p = 0.02$) in participants with eGFR

≥ 90 mL/min/1.73 m^2. Notably, increased occurrences of CV death (HR 1.01, 95% CI 0.57–1.79) and total mortality (HR 1.04, 95% CI 0.63–1.71) relative to placebo were reported in participants with eGFR ≥ 90 mL/min/1.73 m^2. Additionally, treatment benefit was comparatively similar among eGFR groups in most outcome results excluding fatal or nonfatal stroke, in which participants with eGFR ≥ 90 mL/min/1.73 m^2 demonstrated a substantial 59% risk reduction (HR 0.41, 95% CI 0.20–0.86) much greater than those seen in participants with reduced renal function (Int. $p = 0.20$). In post hoc analysis of the secondary composite endpoint, relative risk reductions of −33%, −28%, −29%, and −25% were reported in redefined eGFR groups of > 15 to < 30 mL/min/1.73 m^2 (HR 0.67, 95% CI 0.23–1.95), ≥ 30 to < 45 mL/min/1.73 m^2 (HR 0.72, 95% CI 0.49-1.05), ≥ 45 to < 60 mL/min/1.73 m^2 (HR 0.71, 95% CI 0.55–0.92), and ≥ 60 mL/min/1.73 m^2 (HR 0.75, 95% CI 0.64–0.87), respectively. However, the cumulative between-group difference was found to be unsubstantial (Int. $p = 0.97$). Safety analyses revealed a direct relationship between renal function and TEAE rates with IPE and placebo, as approximately 86%, 81%, and 76% of participants in both treatment groups with eGFR < 60 mL/min/1.73 m^2, 60 to < 90 mL/min/1.73 m^2, and ≥ 90 mL/min/1.73 m^2 groups, respectively, reported at least one TEAE. Approximately 12–13% of participants with eGFR < 90 mL/min/1.73 m^2 and 10% of participants with normal renal function experienced a drug-related TEAE. Renal status also influenced bleeding-related adverse event rates, which were comparatively higher in the IPE versus placebo arms and increased with descending eGFR. Bleeding-related adverse events reported with IPE versus placebo treatment, respectively, occurred in 9.1% versus 8.0% ($p = 0.41$) of participants with eGFR ≥ 90 mL/min/1.73 m^2 group, 11.0% versus 9.7% ($p = 0.15$) of participants with eGFR 60 to < 90 mL/min/1.73 m^2 group, and 18.0% versus 13.3% ($p = 0.007$) of participants with eGFR < 60 mL/min/1.73 m^2. Serious bleeding-related adverse event rates were similar between the IPE and placebo groups of participants with eGFR > 60 mL/min/1.73 m^2, as 1.2% versus 1.7% ($p = 0.44$) and 2.6% versus 2.3% ($p = 0.50$) rates were reported for the IPE versus placebo arms of the eGFR ≥ 90 mL/min/1.73 m^2 and eGFR 60 to < 90 mL/min/1.73 m^2 groups, respectively. Rates of treatment-emergent atrial fibrillation or flutter did not appear to strongly correlate with changes in renal status, though events did occur more frequently with IPE treatment than placebo. Atrial fibrillation or flutter TEAEs reported with IPE versus placebo, respectively, occurred in 4.5% versus 2.9% ($p = 0.07$) of participants with eGFR ≥ 90 mL/min/1.73 m^2 group, 7.4% versus 5.9% ($p = 0.22$) of participants with eGFR 60 to < 90 mL/min/1.73 m^2 group, and 5.7% versus 4.6% ($p = 0.09$) of participants with eGFR < 60 mL/min/1.73 m^2. Positively adjudicated atrial fibrillation or flutter events requiring at least 24 h of hospitalization were comparatively more frequent in participants administered IPE but did not correspond to renal status, as 2.8% versus 1.7% ($p = 0.13$), 4.2% versus 3.0% ($p = 0.17$), and 2.8% versus 1.8% ($p = 0.03$) rates were reported for the IPE versus placebo arms of the eGFR ≥ 90 mL/min/1.73 m^2, eGFR 60 to < 90 mL/min/1.73 m^2, and eGFR of < 60 mL/min/1.73 m^2 groups, respectively. Rates of serious atrial fibrillation or flutter events ranged from 0.2% to 1.1%; however, no substantial differences in occurrence between IPE and placebo groups were indicated [24].

3.5.4 Consistency of Benefit of IPE by Background Statin Type in REDUCE-IT

The relevance of statin type in REDUCE-IT was examined through subanalysis of the study primary composite and key secondary composite outcomes data per baseline statin agent and lipophilicity. Statin agents assessed in the analysis included atorvastatin, simvastatin, rosuvastatin, and pravastatin. Significant relative reductions in risk of the primary composite endpoint were observed in participants of the IPE groups taking atorvastatin (HR 0.79, 95% CI 0.67–0.93, $p = 0.006$), simvastatin (HR 0.79, 95% CI 0.65–0.96, $p = 0.02$), and rosuvastatin (HR 0.73, 95% CI 0.57–0.94, $p = 0.01$), while nonsignificant reduction was seen in IPE group participants taking pravastatin (HR 0.79, 95% CI 0.54–1.16, $p = 0.24$). However, differences between outcomes per statin agent were ultimately negligible (Int. $p = 0.95$). Similarly, with primary endpoint assessments according to lipophilicity, significant benefit relative to placebo was demonstrated by both lipophilic statins (HR 0.78, 95% CI 0.69–0.88, $p < 0.0001$) and lipophobic statins (HR 0.75, 95% CI 0.61–0.93, $p = 0.007$) administered with IPE, though the between-group difference in treatment effect was determined to be nonsignificant (Int. $p = 0.67$). Relative reductions in risk of the key secondary composite endpoint were observed in all statins with IPE. Treatment benefit was most notable in participants taking atorvastatin (HR 0.73, 95% CI 0.59–0.89, $p = 0.002$) and rosuvastatin (HR 0.71, 95% CI 0.52–0.97, $p = 0.03$); however, risk reductions were demonstrated by IPE participants taking simvastatin (HR 0.86, 95% CI 0.68–1.10, $p = 0.24$) and pravastatin (HR 0.78, 95% CI 0.50–1.23, $p = 0.29$), as well. However, minimal difference between outcomes per statin agent was found (Int. $p = 0.68$). Substantial reductions in risk of the secondary endpoint were reported in both the lipophilic statin (HR 0.76, 95% CI 0.66–0.88, $p = 0.0003$) and lipophobic statin (HR 0.73, 95% CI 0.57–0.95, $p = 0.02$) groups; however, the difference in treatment effect between these groups was negligible (Int. $p = 0.74$) [25].

3.5.5 A REDUCE-IT Biomarker Substudy

The mechanism of CV risk reduction regarding the effects of IPE compared with mineral oil in the REDUCE-IT study remain ambiguous. The biomarker substudy aimed to evaluate measured levels of interleukin-1β, interleukin-6, hsCRP, OxLDL, homocysteine, lipoprotein(a), and Lp-PLA2 from archived serum samples of the REDUCE-IT study participants. The analysis of these samples examined the possible correlation between treatment allocation and the potential effects on a series of biomarkers in pathways known to associate with atherosclerosis risk. The changes seen at the 12-month checkpoint and the 24-month checkpoint were similar and showed median percent increases in the mineral oil comparator group from baseline. The increases found at 12 months were 1.5% for homocysteine, 2.2% for lipoprotein(a), 10.9% for oxidized LDL-C, 16.2% for interleukin-6, 18.5% for lipoprotein-associated phospholipase A2, 21.9% for hsCRP, and 28.9% for interleukin-1β (all p values < 0.001). Though these increases stayed similar through the end of the study for the mineral oil group, interestingly, there were very modest effects in the IPE group on these biomarkers. The differences from baseline in this group at the end of study were found to be +6.17% for homocysteine, +4.41% for lipoprotein(a), +0.15% for oxidized LDL-C, +3.01% for interleukin-6, −1.30% for lipoprotein-associated phospholipase A2, and no statistical difference for hs-CRP or for interleukin-1β (all significant results p values < 0.001). Overall, it is seen that the IPE group showed minimal effects on the biomarkers, whereas it seemed that across the board an increase in these biomarkers was found in the mineral oil control group. The validity of mineral oil as a comparator/placebo is discussed thoroughly as it is used in many prior studies such as the JUPITER, CIRT, CANTOS, and SPIRE studies without these findings. However, the design of the REDUCE-IT study does not make it possible to determine if any adverse events associated with the mineral oil placebo affected clinical outcomes. Further analysis will be needed to determine if these biomarkers may have played a role in the mechanism for CV risk reduction or provide insight on the pathways that may be involved [26]. Additionally, further studies are needed to determine the cause of this effect by adding in a true neutral comparator.

3.5.6 A REDUCE-IT Heart Failure Substudy

The REDUCE-IT study showed a reduced risk for ASCVD among a broad group of statin-treated patients, but the specific benefit for those with heart failure (HF) is unknown. The study included 1446 patients with HF, and changes in TGs and hs-CRP were compared with baseline in both the placebo and IPE treatment group. IPE reduced TGs 15.4%, and hs-CRP 35.1% compared with placebo. When comparing the patients with HF versus those without, there were similar improvements in both TGs and hs-CRP levels, and CV risk reduction among both groups treated with IPE [27].

3.5.7 REDUCE-IT PCI

This post hoc analysis reviewed the group of patients in the REDUCE-IT study that had a prior percutaneous coronary intervention (PCI), due to their increased risk of CV events. A total of 3408 patients in the study had a prior PCI; in the IPE treatment group, 34% had a reduction in the primary end point as well as 34% reduction in secondary endpoint compared with placebo. There was also a large reduction in total coronary revascularizations and revascularization subtypes, with a 39% reduction in total events. The use of IPE in patients with a prior PCI showed significant results for reducing the 5-year risk of recurrent events [28].

3.5.8 REDUCE-IT Smoking

Miller et al. evaluated the results of the REDUCE-IT study and performed a post hoc subgroup analysis in participants with presence of smoking history. Compared with placebo, IPE use in combined current and former smokers ($n = 4913$) was associated with significant reductions in time to the primary composite endpoint (HR 0.77, 95% CI 0.68–0.87, $p < 0.0001$) and in total events (RR 0.71, 95% CI 0.61–0.82, $p < 0.0001$). These results suggest that IPE could be a useful clinical tool in reducing overall CV risk associated with a history of cigarette smoking [29].

3.6 RESPECT-EPA

The Randomized trial for Evaluation in Secondary Prevention Efficacy of Combination Therapy-Statin and EPA (RESPECT-EPA) is a combination of two studies, the first being a multicenter open-label randomized controlled trial and the second being a prospective cohort biomarker study. Patients began enrollment from November 2013 to October 2017, and the study is still underway. The purpose of this study was to evaluate the utilization of EPA as a combination therapy with high-intensity statins, thus addressing a data gap left by the JELIS study, which did not study EPA in addition to current secondary CVD prevention practices. A total of 2460 patients aged 20–79 years with a history of CAD, on statin therapy and with a low endogenous plasma EPA-to-AA ratio were identified and randomized to treatment group and a control group with median EPA:AA ratios of 0.243 and 0.245, respectively. The results of the randomized controlled portion of the study show that the primary outcome (cardiovascular death, MI, stroke, unstable angina

requiring hospitalization, and revascularization) occurred in 10.9% of the IPE group versus 14.9% of the control group ($p = 0.055$). The secondary outcome (sudden cardiac death, MI, unstable angina, or coronary revascularization) occurred in 8.0% of the IPE group versus 11.3% of the control group ($p = 0.031$). Additionally, gastrointestinal disorders occurred in 3.4% of the IPE group versus 1.2% of the control group ($p < 0.001$). Findings of increased risk of atrial fibrillation in the EPA group were reported, which remains consistent with findings in the REDUCE-IT study. Of note, the RESPECT-EPA study did not meet the expected number of events used for calculation of statistical power; therefore, the study may be underpowered.

3.6.1 CHERRY

The CHERRY study was a randomized, nonblinded, parallel group, multicenter study designed to investigate whether coronary plaque regression and stabilization are further aided by the additional administration of EPA to pitavastatin therapy. The study enrolled 192 Japanese subjects from September 2009 to July 2014 and were randomized into receiving either 4 mg pitavastatin daily or 4 mg pitavastatin with 1800 mg EPA daily. The pitavastatin/EPA group showed a greater prevalence of reduction in total atheroma volume compared with the pitavastatin group (81% versus 61% $p = 0.002$). IB-IVUS analyses revealed that lipid volume was significantly decreased during the follow-up period in the pitavastatin/EPA group. However, the incidence of MACE events was not significantly different between the groups during this time period.

3.6.2 EVAPORATE

To examine the effect of IPE on coronary plaque progression, EVAPORATE, a prospective, 18-month study, was conducted in statin-treated, hypertriglyceridemic individuals with coronary atherosclerosis confirmed through multidetector computed tomography (MDCT) angiography [33]. Participants were randomized 1:1 to IPE 4 g daily or matching placebo then evaluated at baseline, 9 months, and 18 months for plaque volume progression rates. Participants had a mean age of approximately 57 years and mean body mass index (BMI) of approximately 33 kg/m^2. Of plaque types identified in the study, fibrous plaque was most prevalent, seen in 74.7% and 57.9% of participants in the IPE and placebo groups, respectively, while low-attenuation plaque (LAP) was least prevalent among study groups (5.1% and 6.5%). The study primary endpoint was change from baseline in LAP volume at month 18, measured with MDCT angiography. A significant −17% reduction in LAP was observed in the IPE group, while a +109% increase was seen with placebo ($p = 0.0061$). Secondary endpoints were sequentially measured and included change from baseline in total plaque, total noncalcified plaque, fibrofatty plaque, fibrous plaque, and calcified plaque. Notable reductions in each plaque type were observed with IPE treatment, apart from calcified plaque, which demonstrated a small −1% overall change with treatment and +15% change with placebo ($p = 0.0531$). In participants of the placebo group, plaque progression was indicated by median increases from baseline in all plaque types at month 18, while notable median changes of −34% ($p = 0.0002$), −20% ($p = 0.0028$), −19% ($p = 0.0005$), and −9% ($p = 0.0019$) in fibrofatty plaque, fibrous plaque, total noncalcified plaque, and total plaque, respectively, were seen in the IPE group. Assessments of lipid parameters revealed little change from baseline at month 18. Median TG reductions of −89.3 mg/dL and −92.1 mg/dL ($p = 0.91$) and LDL-C reductions of −2.4 mg/dL and –12.8 mg/dL ($p = 0.23$) were seen in the IPE and placebo groups, respectively, while both groups demonstrated similar median +0.7 mg/dL increases in HDL-C ($p = 0.53$) [33]. The results regarding IPE decreasing plaque progression aid in substantiating the claim of CV risk reduction as the link between CV events and plaque progression is widely understood. A study that evaluates both plaque progression and CV events in patients receiving IPE would further confirm these outcomes.

4 Discussion

Omega-3 fatty acids have gained the attention of experts, specifically IPE for its favorable effects on lipid lowering, TG lowering, modulation of anti-inflammatory markers, and effects on CV risk reduction that were observed in clinical studies. As a result, a final draft guidance was recently released recommending IPE for reducing the risk of CV events such as heart attacks and strokes in patients with elevated TG levels [34]. This draft guidance from the UK's National Institute for Health and Care Excellence (NICE) is expected to be published in its final form this summer and would bring a benefit to approximately 425,000 people [34].

In relation to possible adverse effects (AEs) of IPE, it was well tolerated in patients with established CV disease or patients with diabetes at increased risk of CV events and did not demonstrate significant differences between comparator groups with clinical relevance. Interestingly, the REDUCE-IT study showed an increased incidence of atrial fibrillation. However, since there was no increased incidence of stroke in the study, it is believed that there is no clinical relevance to this AE [18]. The REDUCE-IT study also presented safety results that showed an increase in minor bleeding, specifically gastrointestinal bleeding. Despite the presence of either AE (increased incidence of atrial fibrillation or gastrointestinal bleeding), it was not considered to be a reason to avoid

Table 1 Baseline characteristics and results from landmark trials

Data	Study endpoint	Intervention	Baseline characteristics	Results
MARINE	Change in TG levels from baseline to week 12	1:1:1 ratio. 4 g daily IPE 2 g daily IPE Placebo	Age—53 years T2DM—88% TG—39% with > 750 mg/dL LDL—92 mg/dL Statin use—25%	TGs decreased by 26.6% and 7.0 for 4 g/day and 2 g/day groups Increased by 7.0% in placebo
ANCHOR	Change in TG levels from baseline to week 12	1:1:1 ratio. 4 g daily IPE 2 g daily IPE Placebo	Age—61 years TG—259.0 mg/dL LDL—83 mg/dL 83.2% taking moderate-to-high-intensity statin	20.1%, and 26% decrease in TG for 2 g/day and 4 g/day of IPE
JELIS	Composite occurrence of ASCVD events	1:1 ratio 300 mg EPA PO TID + statin Statin only	Age—61 years CAD—19.7% LDL—182 mg/dL TG—154 mg/dL	RRR fatal MI—21% nonfatal MI 25% UA 24% CABG/PCI 14%
REDUCE-IT	Composite occurrence of ASCVD events	1:1 ratio 2 g IPE PO BID Placebo	Age—64 years T2DM—57.8% TG—216 mg/dL 39% with > 750 mg/dL LDL—75 mg/dL 93% taking moderate-to-high-intensity statin	HR 0.75 (0.68–0.83) ($p < 0.001$) Rate of occurrence was 17.2% in intervention group 22% in placebo group

ASCVD atherosclerotic cardiovascular disease, *BID* twice daily, *CABG* coronary artery bypass grafting, *CAD* coronary artery disease, *CRP* C-reactive protein, *DHA* docosahexaenoic acid, *EPA* eicosapentaenoic acid, *IL* interleukin, *IPE* icosapent ethyl, *LDL* low-density lipoprotein, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *PO* by mouth (per oral), *RRR* relative risk reduction, *T2DM* type 2 diabetes mellitus, *TG* triglycerides, *UA* unstable angina

treatment with IPE in this population. Recently presented data from the RESPECT-EPA study, which evaluated EPA in combination with statin therapy on secondary prevention, reported increased incidence of atrial fibrillation in the IPE group along with gastrointestinal disorders in 3.4% of the IPE group compared with 1.2% in the control group ($p < 0.001$) [39]. The study did conclude that IPE may be associated with a reduction in CV outcomes in Japanese patients with CAD. Future studies on the long-term use of IPE in a real-world setting would provide more insight on AEs.

The conversation surrounding IPE and CV risk reduction has certainly been debated as far as efficacy is concerned. The promising results of preliminary studies have shown the efficacy of TG reduction and safety of IPE, and the REDUCE-IT study continued with favorable outcomes data leading to the FDA approval of IPE for adjunctive therapy in reducing the risk of CV events in adults with elevated TG levels. However, the ambiguous anti-inflammatory effects of IPE and mechanism for CV risk reduction is still not completely understood, leaving many to question the role IPE plays on CV risk reduction in patients with high-risk ASCVD.

Landmark studies evaluating IPE (Table 1) have demonstrated TG reduction and reduction of CV risk compared with placebo or standard of care. Expert opinions have weighed in on the CV risk reduction results with IPE and are mixed in their conclusions. One opinion from Patel et al. demonstrated that the patients receiving the greatest clinical benefit with IPE were those with the highest TG levels at baseline [35]. This point further argued that the mechanism for CV risk reduction was outside the effect of TG lowering, and IPE was reducing residual risk for CV events. We saw in the REDUCE-IT study that the participants with highest TG levels demonstrated a 25% relative risk reduction and a 30% relative risk reduction in total ischemic events when treated with IPE ($p < 0.05$) [35]. Another study evaluating participants without clinical CVD measured coronary artery calcium (CAC) scores compared with omega-3 fatty acid levels and found that long-term CVD events were fewer in those who attained higher plasma omega-3 fatty acid levels and were more apparent at higher CAC scores, which is a strong predictor of CV events and precise marker of coronary atherosclerosis [36]. With very few safe and effective therapies available to reduce the rates of ischemic stroke in patients with vascular disease, it is important to note that rates of first ischemic stroke were reduced by 36% with IPE compared with placebo. It is possible that the mechanisms or underlying pathophysiology may be contributing to the risk reduction; nonetheless, CV risk reduction is evident.

Additional opinions have surfaced calling the placebo used in the REDUCE-IT study into question. Nissen et al.

claims that the results of the REDUCE-IT study may be misleading due to the use of mineral oil as a comparator. The opinion further claimed that mineral oil may cause increased LDL-C levels and is therefore not "neutral," which may have impacted the results seen in the control arm as it relates to the incidence of clinical outcomes. It was noted that the study results showed increased LDL-C levels for those participants in the placebo group [37]. Alternatively, Olshansky et al. reported that the use of mineral oil as a comparator would not affect biomarkers on the basis of their study of the safety and use of mineral oil in clinical studies. This study concluded that pharmaceutical grade mineral oil is a neutral comparator since it is made of saturated straight-chain *n*-alkanes and is therefore a purified version of the mineral oil that is considered food grade. Various studies using mineral oil were evaluated, and it was determined that there was no meaningful effect on biomarkers such as TGs, LDL, HDL, hs-CRP, and others, and the adverse effects noted from mineral oil use resulted from its laxative-like properties [38]. Ultimately, a reduction in CV death was observed with IPE, which is a critical outcome for clinical studies evaluating medications in the cardiovascular space. It should be noted that, while the differences among background therapies and comparator therapies are being questioned, the benefits observed with IPE were detected regardless of baseline LDL-C or TGs.

The CV risk reduction from IPE may be due to the reduction in plaque formation, reduction in VLDL and subsequent LDL levels and LDL-C formation, or reduction in inflammatory markers. The study to evaluate IPE for adults at high risk of CV, MITIGATE, will include approximately 39,600 participants with established ASCVD [39]. The study is a prospective, open-label, parallel group study that will randomize participants to receive IPE 2 g twice daily compared with usual care in a 1:10 ratio for a minimum of 6 months [40]. This real-world efficacy study will help establish the role of IPE in CV risk reduction for patients at high risk with the additional examination of the role of IPE on inflammation regarding upper respiratory infections and coronavirus disease 2019 (COVID-19). Further studies to uncover the underlying mechanisms and additional effects of IPE are underway.

Determining the beneficial effectiveness of IPE versus its comparators has an important impact on cost in addition to patient health. An analysis was performed to determine the impact that IPE would have on the US adult population regarding prevention of ASCVD events and healthcare costs based on the results of the REDUCE-IT study. Using the National Health and Nutrition Examination Surveys (NHANES) and Optum Research Database (ORD), 3.6 million REDUCE-IT eligible cohorts were derived. The 5-year first-event rate without treatment with IPE was observed to be 19%. Using the regimen from the REDUCE-IT study there is potential for the event rate to be lowered to 13.1%, preventing 212,000 events. Annual treatment costs for all eligible patients were estimated to be $6 billion, but with a total of $1.8 billion saved due to prevention of first events. The total 5-year rate, including first and recurrent events, has potential to be reduced from 42.5% to 28.9%, preventing 490,000 events when treated with IPE for 5 years. Overall, treating all REDUCE-IT-eligible US adults is costly, but could help prevent a substantial amount of ASCVD events and associated direct and indirect costs [41].

5 Conclusions

While the mechanism is not thoroughly understood, evidence shows that IPE is efficacious in reducing risk of CV events in those with elevated TG levels, and many global medical societies recognize IPE as an important therapy in CV prevention and treatment. IPE with its 99.99% pure composition of EPA, is the first fish oil or omega-3 ethyl ester to show these results. With each new analysis, new hypotheses are made as to the reasons for its efficacy. Major clinical studies are ongoing and will hopefully provide more insight and data to further support the possibility of IPE serving as an alternative option for patients who cannot tolerate statins or who require additional therapy for CV risk reduction or reduction of TG levels.

Declarations

Funding No external funding was used in the preparation of this manuscript.

Conflict of Interest: Jessica Huston, Hannah Schaffner, Alyssa Cox, Alexander Sperry, Shelby Mcgee, Payeng Lor, Logan Langley, Blake Skrable, Majdi Ashchi, Mohannad Bisharat, Ashwini Gore, Thomas Jones, David Sutton, Mae Sheikh-Ali, Jason Berner, and Rebecca Goldfaden declare that they have no conflict of interest.

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Availability of Data and Material Not applicable.

Code Availability Not applicable.

Authors' Contributions JH was involved in supervision, data curation, analysis, reviewing, editing, and writing. Hannah Schaffer was involved in data curation, analysis, and writing. Alyssa Cox was involved in data curation, writing, and analysis. SM was involved in data curation, analysis, and writing. PL was involved in data curation, analysis, and writing. LL was involved in data curation, analysis, and writing. BS

was involved in data curation, analysis, and writing. MA was involved in reviewing and editing. MB was involved in reviewing and editing. AG was involved in reviewing and editing. TJ was involved in reviewing and editing. DS was involved in reviewing and editing. MS-A was involved in reviewing and editing. JB was involved in reviewing and editing. AS was involved in reviewing and editing. RG was involved in the conceptualization, project administration, reviewing and editing. Please describe each task performed by each author (e.g., conceptualization, data curation, analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing, reviewing and editing, etc.).

References

1. World Health Organization. (n.d.). The top 10 causes of death. World Health Organization. Retrieved June 30, 2022, from https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death.Accessed 30 Jun 2022.
2. Centers for Disease Control and Prevention. Heart disease facts. Centers for Disease Control and Prevention. 2022. Retrieved June 30, 2022, from https://www.cdc.gov/heartdisease/facts.htm. Accessed 30 Jun 2022.
3. 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(3):330–43. https://doi.org/10.1016/j.jacc.2018.04.061.
4. Wong ND, Zhao Y, Quek R, Blumenthal RS, Budoff MJ, Cushman M, Garg P, Sandfort V, Tsai M, Lopez J. Residual atherosclerotic cardiovascular disease risk in statin-treated adults: The Multi-Ethnic Study of Atherosclerosis. J Clin Lipidol. 2017;11(5):1223–33. https://doi.org/10.1016/j.jacl.2017.06.015.
5. Daniels SR. Guidelines for Screening, Prevention, Diagnosis and Treatment of Dyslipidemia in Children and Adolescents. [Updated 2020 Jan 18]. In: Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK395579/?report. Accessed 30 Jun 2022.
6. Update on phase III strength trial for epanova in mixed ... - astrazeneca. (n.d.). Retrieved June 30, 2022, from https://www.astrazeneca.com/media-centre/press-releases/2020/update-on-phase-iii-strength-trial-for-epanova-in-mixed-dyslipidaemia-13012020.html. Accessed 30 Jun 2022.
7. Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, Oikawa S, Sasaki J, Hishida H, Itakura H, Kita T, Kitabatake A, Nakaya N, Sakata T, Shimada K, Shirato K, Japan EPA lipid intervention study (JELIS) Investigators. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet (London, England). 2007;369(9567):1090–8. https://doi.org/10.1016/S0140-6736(07)60527-3.
8. Budoff MJ, Muhlestein JB, Bhatt DL, Le Pa VT, May HT, Shaikh K, Shekar C, Kinninger A, Lakshmanan S, Roy SK, Tayek J, Nelson JR. Effect of icosapent ethyl on progression of coronary atherosclerosis in patients with elevated triglycerides on statin therapy: a prospective, placebo-controlled randomized trial (EVAPORATE): interim results. Cardiovasc Res. 2021;117(4):1070–7. https://doi.org/10.1093/cvr/cvaa184.
9. About VASCEPA® (icosapent Ethyl). (n.d.). Official Patient Site | VASCEPA® (icosapent ethyl). https://www.vascepa.com/about-vascepa/(n.d.). Amarin Corporation. https://amarincorp.com/docs/Vascepa-PI.pdf. Accessed 30 Jun 2022.
10. Weintraub WS, Bhatt DL, Zhang Z, et al. Cost-effectiveness of icosapent ethyl for high-risk patients with hypertriglyceridemia despite statin treatment. JAMA Netw Open. 2022;5(2):e2148172. https://doi.org/10.1001/jamanetworkopen.2021.48172.
11. Nelson JR, Raskin S. The eicosapentaenoic acid:arachidonic acid ratio and its clinical utility in cardiovascular disease. Postgrad Med. 2019;131(4):268–77. https://doi.org/10.1080/00325481.2019.1607414.
12. Brinton EA, Mason RP. Prescription omega-3 fatty acid products containing highly purified eicosapentaenoic acid (EPA). Lipids Health Dis. 2017;16:23. https://doi.org/10.1186/s12944-017-0415-8.
13. Yang ZH, Amar M, Sampson M, et al. Comparison of omega-3 eicosapentaenoic acid versus docosahexaenoic acid-rich fish oil supplementation on plasma lipids and lipoproteins in normolipidemic adults. Nutrients. 2020;12(3):749. https://doi.org/10.3390/nu12030749.
14. Sherratt SCR, Libby P, Bhatt DL, et al. A biological rationale for the disparate effects of omega-3 fatty acids on cardiovascular disease outcomes. Prostaglandins Leukot Essent Fatty Acids. 2022;182:102450. https://doi.org/10.1016/j.plefa.2022.102450.
15. Weintraub HS. Overview of prescription omega-3 fatty acid products for hypertriglyceridemia. Postgrad Med. 2014;126(7):7–18. https://doi.org/10.3810/pgm.2014.11.2828.
16. Bays HE, Ballantyne CM, Kastelein JJ, Isaacsohn JL, Braeckman RA, Soni PN. Eicosapentaenoic acid ethyl ester (AMR101) therapy in patients with very high triglyceride levels (from the Multi-center, plAcebo-controlled, Randomized, double-blINd, 12-week study with an open-label Extension [MARINE] Trial). Am J Cardiol. 2011;108(5):682–90. https://doi.org/10.1016/j.amjcard.2011.04.015.
17. Ballantyne CM, Bays HE, Kastelein JJ, et al. Efficacy and safety of eicosapentaenoic acid ethyl ester (AMR101) therapy in statin-treated patients with persistent high triglycerides (from the ANCHOR Study). Am J Cardiol. 2012;110(7):984–92. https://doi.org/10.1016/j.amjcard.2012.05.031.
18. Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, Juliano RA, Jiao L, Doyle RT Jr, REDUCE-IT Investigators, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. Circulation. 2019;380(1):11–22. https://doi.org/10.1056/NEJMoa1812792.
19. Gaba P, Bhatt DL, Steg PG, REDUCE-IT Investigators, et al. Prevention of cardiovascular events and mortality with icosapent ethyl in patients with prior myocardial infarction. J Am Coll Cardiol. 2022;79(17):1660–71. https://doi.org/10.1016/j.jacc.2022.02.035.
20. Gaba P, Bhatt DL, Mason RP, REDUCE-IT Investigators, et al. Benefits of icosapent ethyl for enhancing residual cardiovascular risk reduction: a review of key findings from REDUCE-IT. J Clin Lipidol. 2022. https://doi.org/10.1016/j.jacl.2022.05.067.
21. Bhatt DL, Miller M, Brinton EA, et al. REDUCE-IT USA. Circulation. 2020;141(5):367–75. https://doi.org/10.1161/CIRCULATIONAHA.119.044440.
22. Gaba P, Bhatt DL, Giugliano RP, et al. Comparative reductions in investigator-reported and adjudicated ischemic events in REDUCE-IT. J Am Coll Cardiol. 2021;78(15):1525–37. https://doi.org/10.1016/j.jacc.2021.08.009.
23. Verma S, Bhatt DL, Steg PhG, et al. Icosapent ethyl reduces ischemic events in patients with a history of previous coronary artery bypass grafting: REDUCE-IT CABG. Circulation. 2021;144(23):1845–55. https://doi.org/10.1161/CIRCULATIONAHA.121.056290.
24. Jithia A, Bhatt DL, Friedman AN, et al. Benefits of icosapent ethyl across the range of kidney function in patients with established cardiovascular disease or diabetes: REDUCE-IT RENAL.

Circulation. 2021;144(22):1750–9. https://doi.org/10.1161/CIRCULATIONAHA.121.055560.
25. Singh N, Bhatt DL, Miller M, et al. Consistency of benefit of icosapent ethyl by background statin type in REDUCE-IT. J Am Coll Cardiol. 2022;79(2):220–2. https://doi.org/10.1016/j.jacc.2021.11.005.
26. Ridker PM, Rifai N, MacFadyen J, et al. Effects of randomized treatment with icosapent ethyl and a mineral oil comparator on interleukin-1β, interleukin-6, C-reactive protein, oxidized low-density lipoprotein cholesterol, homocysteine, lipoprotein(a), and lipoprotein-associated phospholipase A2: a REDUCE-IT Biomarker Substudy. Circulation. 2022. https://doi.org/10.1161/CIRCULATIONAHA.122.059410.
27. Selvaraj S, Bhatt DL, Steg PG, et al. Impact of icosapent ethyl on cardiovascular risk reduction in patients with heart failure in REDUCE-IT. J Am Heart Assoc. 2022;11(7):e024999. https://doi.org/10.1161/JAHA.121.024999.
28. Peterson BE, Bhatt DL, Steg PG, REDUCE-IT Investigators, et al. Treatment with icosapent ethyl to reduce ischemic events in patients with prior percutaneous coronary intervention: insights from REDUCE-IT PCI. J Am Heart Assoc. 2022;11(6):e022937. https://doi.org/10.1161/JAHA.121.022937.
29. Miller M, Bhatt DL, Steg PG, et al. Potential effects of icosapent ethyl on cardiovascular outcomes in cigarette smokers: REDUCE-IT smoking [published online ahead of print, 2022 Aug 11]. Eur Heart J Cardiovasc Pharmacother. 2022. https://doi.org/10.1093/ehjcvp/pvac045.
30. Daida H. Randomized trial for evaluation in secondary prevention efficacy of combination therapy–statin and eicosapentaenoic acid—RESPECT-EPA. In: Presented at: the American Heart Association Scientific Sessions, Chicago, IL, November 6, 2022.
31. Nishizaki Y, Miyauchi K, Iwata H, et al. Study protocol and baseline characteristics of Randomized trial for Evaluation in Secondary Prevention Efficacy of Combination Therapy-Statin and Eicosapentaenoic Acid: RESPECT-EPA, the combination of a randomized control trial and an observational biomarker study. Am Heart J. 2023;257:1–8. https://doi.org/10.1016/j.ahj.2022.11.008.
32. Watanabe T, Ando K, Daidoji H, et al. A randomized controlled trial of eicosapentaenoic acid in patients with coronary heart disease on statins. J Cardiol. 2017;70(6):537–44. https://doi.org/10.1016/j.jjcc.2017.07.007.
33. Budoff MJ, Bhatt DL, Kinninger A, et al. Effect of icosapent ethyl on progression of coronary atherosclerosis in patients with elevated triglycerides on statin therapy: final results of the EVAPORATE trial. Eur Heart J. 2020;41(40):3925–32. https://doi.org/10.1093/eurheartj/ehaa652.
34. Bryn Mawr Communications. Amarin's VAZKEPA recommended in UK nice final draft guidance for prevention of cardiovascular events in patients with raised triglycerides. Cardiac Interventions Today. Retrieved July 15, 2022, from https://citoday.com/news/amarins-vazkepa-recommended-in-uk-nice-final-draft-guidance-for-prevention-of-cardiovascular-events-in-patients-with-raised-triglycerides-1#:~:text=June%2010%2C%202022%E2%80%94The%20United,in%20adults%20who%20have%20raised. Accessed 15 Jul 2022.
35. Patel PN, Patel SM, Bhatt DL. Cardiovascular risk reduction with icosapent ethyl. Curr Opin Cardiol. 2019;34(6):721–7. https://doi.org/10.1097/HCO.0000000000000678.
36. Alfaddagh A, Kapoor K, Dardari ZA, et al. Omega-3 fatty acids, subclinical atherosclerosis, and cardiovascular events: implications for primary prevention. Atherosclerosis. 2022;353:11–9. https://doi.org/10.1016/j.atherosclerosis.2022.06.1018.
37. Nissen SE, Lincoff AM, Wolski K, et al. Association between achieved ω-3 fatty acid levels and major adverse cardiovascular outcomes in patients with high cardiovascular risk: a secondary analysis of the STRENGTH Trial. JAMA cardiology. 2021. https://doi.org/10.1001/jamacardio.2021.1157.
38. Olshansky B, Chung MK, Budoff MJ, et al. Mineral oil: safety and use as placebo in REDUCE-IT and other clinical studies. Eur Heart J Suppl. 2020;22(Supplement_J):J34–48. https://doi.org/10.1093/eurheartj/suaa117.
39. Ambrosy AP, Malik UI, Thomas RC, et al. Rationale and design of the pragmatic randomized trial of icosapent ethyl for high cardiovascular risk adults (MITIGATE). Am Heart J. 2021;235:54–64. https://doi.org/10.1016/j.ahj.2021.01.018.
40. A pragmatic randomized trial of icosapent ethyl for high-cardiovascular risk adults - full text view. A Pragmatic Randomized Trial of Icosapent Ethyl for High-Cardiovascular Risk Adults - Full Text View - ClinicalTrials.gov. (n.d.). Retrieved July 15, 2022, from https://clinicaltrials.gov/ct2/show/NCT04505098.
41. Derington CG, Bress AP, Herrick JS, et al. The potential population health impact of treating REDUCE-IT eligible US adults with Icosapent Ethyl. Am J Prev Cardiol. 2022;10:100345. https://doi.org/10.1016/j.ajpc.2022.100345.