

UCLA

UCLA Previously Published Works

Title

The Evolving Role of Omega 3 Fatty Acids in Cardiovascular Disease: Is Icosapent Ethyl the Answer?

Permalink

<https://escholarship.org/uc/item/7w17n118>

Journal

Heart International, 15(1)

ISSN

1826-1868

Authors

Lakshmanan, Suvasini
Budoff, Matthew J

Publication Date

2021

DOI

10.17925/hi.2021.15.1.7

Peer reviewed

The Evolving Role of Omega 3 Fatty Acids in Cardiovascular Disease: Is Icosapent Ethyl the Answer?

Suvasini Lakshmanan and Matthew J Budoff

The Lundquist Institute for Biomedical Innovation, Harbor-UCLA Medical Center, Los Angeles, CA, USA

DOI: <https://doi.org/10.17925/HI.2021.15.1.7>

Atherosclerotic cardiovascular disease (ASCVD) remains the leading cause of morbidity and mortality globally. Despite significant advances in pharmacotherapies and the beneficial effects of statin therapy on ASCVD outcomes and progression of atherosclerosis, residual cardiovascular (CV) risk remains. Extensive evidence has identified the contribution of atherogenic dyslipidaemia, which is particularly characterised by elevated triglycerides (TGL) as a key driver of CV risk, even if low-density lipoprotein cholesterol levels are well controlled. Epidemiologic and genetic/Mendelian randomisation studies have demonstrated that elevated TGL levels serve as an independent marker for an increased risk of ischaemic events, highlighting TGLs as a suitable therapeutic target. Clinical studies have shown that omega 3 fatty acids (OM3FA) are effective in lowering TGLs; however, to date, trials and meta-analyses of combined OM3FA products have not demonstrated any clinical CV outcome benefit in patients receiving statins. However, icosapent ethyl (IPE) – a highly purified, stable ethyl ester of eicosapentaenoic acid (EPA) – has been rigorously demonstrated in multiple studies to be a useful adjunctive therapy to address residual CV risk. EPA is an omega-3 polyunsaturated fatty acid that is incorporated into membrane phospholipid bilayers and is reported to exert multiple beneficial effects along the pathway of coronary atherosclerosis. In this brief review, we will provide an overview of the mode of action of IPE in coronary atherosclerosis, the robust clinical evidence and trial data supporting its use, and expert consensus/recommendations on its use in specific populations, as an adjunct to existing anti-atherosclerotic therapies.

Keywords

Icosapent ethyl, coronary atherosclerosis, atherosclerotic cardiovascular disease

Disclosure: Suvasini Lakshmanan has no financial or non-financial relationships or activities to declare in relation to this article. Matthew Budoff has received honoraria from Amarin Pharmaceuticals.

Review Process: Double-blind peer review

Compliance with Ethics: This article involves a review of literature and does not report on new clinical data, or any studies with human or animal subjects performed by either of the authors

Authorship: The named author meets the criteria of the International Committee of Medical Journal Editors for authorship for this manuscript, takes responsibility for the integrity of the work as a whole and has given final approval for the version to be published.

Access: This article is freely accessible at touchCARDIO.com © Touch Medical Media 2021.

Received: 4 January 2021

Accepted: 18 February 2021

Published Online: 15 July 2021

Citation: *Heart International*. 2021;15(1):7–13

Corresponding Author: Suvasini Lakshmanan, Lundquist Institute of Biomedical Innovation and Research, 1124 W Carson Street, Torrance, CA 90502 USA. E: suvasini.lakshmanan@lundquist.org

Support: No funding was received in the publication of this article.

There are several beneficial effects of statins on the progression of atherosclerosis, and there have been significant advancements in pharmacotherapies for atherosclerotic cardiovascular disease (ASCVD). However, substantial residual cardiovascular (CV) risk remains, and there is an unmet need to reduce the residual risk of cardiovascular disease (CVD) events.¹ There is increased focus on the role of atherogenic dyslipidaemia, particularly elevated triglycerides (TGL), as important mediators of residual risk, which is highlighted in epidemiologic and genetic/Mendelian randomisation studies and supports the hypothesis of elevated TGLs as a suitable therapeutic target.²⁻⁴ Clinical studies have shown that omega 3 fatty acids (OM3FA) are effective in lowering TGLs; however, to date, trials and meta-analyses of combined OM3FA products have not demonstrated any clinical CV outcome benefit in patients receiving statins.⁵ Icosapent ethyl (IPE), a highly purified, stable ethyl ester of eicosapentaenoic acid (EPA), has emerged as a useful adjunctive therapy to address residual CV risk in recent trials.⁶⁻⁹ In this brief review, we will provide an overview of the mode of action of IPE in coronary atherosclerosis, the robust clinical evidence and trial data supporting its use, and expert consensus/recommendations on its use in specific populations, as an adjunct to existing anti-atherosclerotic therapies.

Insights from trials of omega 3 fatty acid preparations

Based on epidemiological associations between OM3FAs and reduced CV morbidity and mortality in populations with CV risk, numerous randomised clinical trials have studied the benefit of OM3FAs on clinical outcomes.^{10,11} As we explore the evolution of OM3FA in CV clinical trials, we note that most earlier studies in OM3FAs included dietary supplements or heterogeneous preparations of combinations of docosahexaenoic acid (DHA) and EPA, and have failed to show significant improvement in CV risk and incidence of CV events (*Table 1*).¹²⁻²⁷

The initial trials of OM3FA included dietary supplements, as in the Alpha Omega trial (ClinicalTrials.gov identifier: NCT00127452; 400 mg per day of EPA-DHA) and the OMEGA trial (ClinicalTrials.gov identifier: NCT00251134; 1g per day of EPA-DHA), where low-dose supplementation with EPA-DHA failed to demonstrate significant reductions in CV events in high-risk patients with a history of myocardial infarction (MI).¹⁴⁻¹⁷ The ASCEND study (A Study of CV Events in Diabetes; ClinicalTrials.gov identifier: NCT00135226) compared the effect of 1 g of OM3FAs (a mixture of DHA and EPA) or placebo (olive oil) on CV outcomes, in a high-risk population with diabetes with no known history of CVD (primary prevention).^{19,20} After a mean follow-up of 7.4 years, there was no significant difference in the risk of serious vascular events between the two

Table 1: An overview of major cardiovascular outcomes trials of omega 3 fatty acids

Study	Population	Number of participants	Follow-up period	Therapy	Outcomes	Treatment effect
Alpha Omega Trial (Study of Omega-3 Fatty Acids and Coronary Mortality; NCT00127452) ^{14,15}	Patients with a history of MI	4,837	40 months	One of four therapies (addition to guideline directed treatment): a margarine with a combination of EPA and DHA (daily intake of 400 mg of EPA-DHA), a margarine supplemented with ALA (daily intake of 2 g of ALA), a margarine with EPA-DHA and ALA, or placebo	Primary endpoint: rate of major CV events, which comprised fatal and nonfatal CV events and cardiac interventions	No significant differences between EPA-DHA versus placebo. Primary endpoint: (HR with EPA-DHA 1.01, 95% CI 0.87–1.17; p=0.93)
OMEGA trial (Effect of Omega 3-Fatty Acids on the Reduction of Sudden Cardiac Death After Myocardial Infarction; NCT00251134) ^{16,17}	Survivors of acute MI	3,851	365 days	Omega-3-acid ethyl esters-90 (1 g/d for 1 year) versus placebo	Primary endpoint: rate of sudden cardiac death. Secondary end point: total mortality and non-fatal clinical events	Event rates: OM3FA versus placebo <ul style="list-style-type: none"> • Sudden cardiac death: 1.5% and 1.5%, respectively (p=0.84) • Total mortality: 4.6% and 3.7%, respectively (p=0.18) • Major adverse cerebrovascular and cardiovascular events: 10.4% and 8.8%, respectively (p=0.1) • Revascularisation: 27.6% and 29.1%, respectively (p=0.34)
GISSI-P study (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico - Prevenzione) ¹⁸	Participants with recent MI (≤3 months prior)	11,324	42 months	Supplements of n-3 PUFA (a combination of EPA-DHA; 1 g daily, n=2836), vitamin E (300 mg daily, n=2830), both (n=2830), or none (control, n=2828)	Primary combined efficacy endpoint was death, non-fatal MI, and stroke. Intention-to-treat analyses were done according to a factorial design (two-way) and by treatment group (four-way)	n-3 PUFA significantly lowered the risk of the primary endpoint: RR 0.90, 95% CI 0.82–0.99 for two-way analysis; RR 0.85, 95% CI 0.74–0.98 for four-way analysis
ASCEND (A Study of Cardiovascular Events in Diabetes; NCT00135226) ^{19,20}	Patients with diabetes without known CVD	15,480	Median follow-up: 7.4 years	1 g of OM3FAs (a mixture of DHA and EPA) or placebo (olive oil) daily	Primary endpoint: a first serious vascular event (i.e., non-fatal MI or stroke, transient ischaemic attack, or vascular death, excluding confirmed intracranial haemorrhage). Secondary outcome: composite of a first serious vascular event or any arterial revascularization	No significant differences in primary and secondary endpoints between OM3FA and placebo. Primary endpoint: OM3FA versus placebo: (rate ratio 0.97, 95% CI 0.87–1.08; p=0.55) Secondary endpoint: (rate ratio 1.00, 95% CI 0.91–1.09)
VITAL (Vitamin D and Omega-3 Trial; NCT01169259) ^{21,22}	Primary prevention of CVD and cancer	25,871	Median follow-up: 5.3 years	Vitamin D3 and OM3FAs at a dose of 1 g per day (containing 380 mg of DHA and 460 mg of EPA) or placebo	Primary end points: major CV events and invasive cancer of any type. Secondary end points: individual components of the composite CV endpoint, the composite end point plus coronary revascularisation (expanded composite of CV events), site-specific cancers, and death from cancer	Primary endpoint, major CV event, OM3FA versus placebo: (HR 0.92; p=0.24). No significant differences in secondary endpoints between the two groups

Table 1: Cont.

Study	Population	Number of participants	Follow-up period	Therapy	Outcomes	Treatment effect
JELIS (Japan EPA Lipid Intervention Study) ²³	Patients for primary or secondary prevention, with total cholesterol of 251 mg/dL or greater	18,645	Mean follow up of 4.6 years	A highly purified prescription EPA ethyl ester (1.8 g/day) in addition to statins versus statins only (no placebo)	Primary endpoint: major coronary events (sudden cardiac death, fatal and non-fatal MI, unstable angina, angioplasty, stenting, or coronary artery bypass graft)	Primary endpoint: 2.8% patients in the EPA group versus 3.5% in the control group (19% RRR; p=0.011). Secondary prevention subgroup: 8.7% in the EPA group versus 10.7% in the control group (19% RRR; p=0.048). Primary prevention group: 1.4% in the EPA group versus 1.7% in the control group (18% RRR; p=0.13)
REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial; NCT01492361) ^{7,8}	Patients with established CVD (70.7% in secondary prevention) or with diabetes and other cardiac risk factors (29.3% in primary prevention), on statins and with a fasting triglyceride level of 135–499 mg/dL and a LDL-C level of 41–100 mg/dL	8,179	Median follow-up of 4.9 years	2 g of icosapent ethyl twice daily (total daily dose, 4 g) or mineral oil placebo	Primary end point: composite of CV death, nonfatal MI, non-fatal stroke, coronary revascularization or unstable angina	Primary endpoint: 17.2% of the patients in the IPE group, versus 22.0% in the placebo group (HR 0.75, 95% CI 0.68–0.83; p<0.001). Secondary prevention cohort: 19.3% in IPE arm versus 25.5% in placebo arm (HR 0.73, 95% CI 0.65–0.81). Primary prevention cohort: 12.2% in IPE group versus 13.6% in placebo group (HR 0.88, 95% CI 0.70–1.10; p=0.14). Rates of additional ischaemic endpoints: significantly lower in the IPE arm, including the rate of CV death (4.3% versus 5.2%; HR 0.80; 95% CI 0.66–0.98; p=0.03)
STRENGTH (STatin Residual Risk Reduction With EpaNova in HiGH Cardiovascular Risk PatientS With Hypertriglyceridemia; NCT02104817) ^{24,25}	Statin-treated patients with atherogenic dyslipidaemia (hypertriglyceridaemia) and low levels of HDL-C and high CV risk	13,078	Early termination of study due to futility of treatment. Median follow-up: 42 months	4 g per day of omega-3 carboxylic acid combination of EPA and DHA versus corn oil, as an adjunct to statins	Primary efficacy measure: composite of CV death, non-fatal MI, non-fatal stroke, coronary revascularisation, or unstable angina requiring hospitalisation	Primary endpoint: 12% on OM3FA versus 12.2% on corn oil (HR 0.99, 95% CI 0.90–1.09; p=0.84)
OMEMI (OMega-3 fatty acids in Elderly with Myocardial Infarction; NCT01841944) ^{26,27}	Secondary prevention in elderly (age: 70–82 years) patients with a recent (2–8 weeks) AMI	1,027	2 years	1.8 g OM3FA combination (930 mg EPA and 660 mg DHA) versus placebo (corn oil) daily to standard of care	Primary endpoint: composite of non-fatal AMI, unscheduled revascularisation, stroke, all-cause death, hospitalisation for heart failure	No significant differences in primary endpoint in the two groups. Primary endpoint: 21.4% of patients on OM3FA versus 20.0% on placebo (HR 1.08, 95% CI 0.82–1.41; p=0.60)

ALA = alpha linolenic acid; AMI = acute myocardial infarction; CI = confidence interval; CV = cardiovascular; CVD = cardiovascular disease; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; HDL-C = high-density lipoprotein cholesterol; HR = hazard ratio; IPE = icosapent ethyl; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; RR = relative risk; RRR = relative risk reduction.

groups (8.9% of patients in treatment group versus 9.2% in the placebo group, rate ratio 0.97, 95% confidence interval [CI] 0.87–1.08).^{19,20} In another primary prevention trial of CVD, the Vitamin D and Omega-3 Trial (VITAL; ClinicalTrials.gov identifier: NCT01169259) randomised 25,871 participants in a two-by-two factorial design, and reported no significant reduction in the rate of major CV events in the treatment group who received vitamin D3/OM3FAs at a dose of 1 g per day (containing 380 mg of DHA and

460 mg of EPA; hazard ratio [HR] 0.92, 95% CI 0.80–1.06).^{21,22} Most recently, the STatin Residual Risk Reduction With EpaNova in HiGH Cardiovascular Risk PatientS With Hypertriglyceridemia (STRENGTH) trial (ClinicalTrials.gov identifier: NCT02104817) randomised 13,078 participants and compared a mixture of EPA and DHA with corn oil in statin-treated participants with high CVD risk, hypertriglyceridaemia, and low levels of high-density lipoprotein cholesterol (HDL-C).^{24,25}

The trial failed to demonstrate significant CV benefit and was terminated early for futility. Furthermore, the OMega-3 fatty acids in Elderly with Myocardial Infarction (OMEMI; ClinicalTrials.gov identifier: NCT01841944) trial evaluated the effects of adding 1.8 g OM3FA (a combination of 930 mg EPA and 660 mg DHA) versus placebo (corn oil) daily to standard-of-care treatment in a vulnerable cohort of elderly patients with a recent (2–8 weeks) acute MI.^{26,27} There was no reduction in clinical events in the elderly patients treated with OM3FA for 2 years (primary endpoint: 21.4% on OM3FA versus 20% on placebo; HR 1.08, 95% CI 0.82–1.41; $p=0.60$).

The clinical benefits of EPA were highlighted in JELIS (Japan EPA Lipid Intervention Study), an open label, randomised trial where 18,645 statin-treated participants (primary prevention cohort of 14,981 participants and secondary prevention cohort included 3,664 participants) were randomised to treatment with 1.8 g/day EPA ethyl ester, a highly purified OM3FA, or statin alone (no placebo).²³ Unlike previous OM3FA trials, which used combinations of EPA-DHA, JELIS examined the effectiveness of a highly purified prescription EPA ethyl ester, as an adjunct to statins. Significant reduction in ASCVD events were observed in the EPA treatment group (HR 0.81, 95% CI 0.69–0.95; $p=0.011$), with consistent benefits across primary and secondary prevention cohorts. The differential trial results of heterogeneous OM3FA combinations and purified EPA preparations bring to our attention important insights with respect to the composition and purity of OM3FAs and dosage levels of EPA, which were incorporated in REDUCE-IT.

The Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial

The Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT) was a randomised, double-blinded, placebo-controlled trial and sought to evaluate if treatment with 4 g/day of IPE (a highly purified ethyl ester of EPA), as an adjunct to statins would lower the incidence of ischaemic events in vulnerable patients at risk for ASCVD (primary and secondary prevention) and residually elevated fasting TGL (135–499 mg/dL).²⁸

Randomised participants in the primary prevention stratum (29.3%) were required to be ≥ 50 years of age, with diabetes mellitus and at least one additional CV risk factor; and those in the secondary prevention stratum were required to be ≥ 45 years of age and with established CV disease. REDUCE-IT investigators randomised 8,179 participants to receive 4 g per day of IPE, compared with a mineral oil placebo. In a landmark outcome, treatments with IPE reduced the incidence of ischaemic CV events by 25% (HR 0.75, 95% CI 0.68–0.83; $p=0.00000001$), when compared with placebo.⁷ Furthermore, when stratified by risk category, both primary (HR 0.81, 95% CI 0.62–1.06) and secondary (HR 0.71, 95% CI 0.63–0.82) prevention cohorts demonstrated meaningful reductions in the incidence of primary and secondary endpoints. A follow-up analysis demonstrated a consistent and significant benefit of reduction in event burden with IPE, when the totality of subsequent ischaemic events were incorporated (HR 0.70, 95% CI 0.62–0.78; $p=0.0000000036$).²⁹ A subgroup analysis of high-risk patients with diabetes revealed robust clinical benefits, irrespective of patients' history of CVD at baseline.³⁰ In terms of benefits with rates of revascularization, IPE further lowered the need for first and subsequent coronary revascularizations, including both percutaneous coronary intervention (PCI) and coronary artery bypass grafting.³¹ These findings from REDUCE-IT underscore the sharp contrast in results from previous outcome trials of heterogeneous OM3FA preparations, and highlight the robust benefits and generalisability of IPE in a broad population of at-risk patients.³² The mounting evidence in support of IPE

leads us to understand the unique mechanisms of action of EPA, the significance of dosage, purity and composition of OM3FA preparations, and its distinct effects on coronary atherosclerosis.

Mechanisms of action: Icosapent ethyl pleiotropy

Although REDUCE-IT was designed to recruit participants with persistently elevated TGL, the results across subgroups suggest that at least some of the effects of IPE on the incidence of CV events may be mediated by effects beyond the reduction of TGL and lipoproteins.⁶ First, the degree of benefit observed with treatment by IPE was similar and significant across all tertiles of baseline and attained/on-treatment TGL levels. Second, the magnitude of observed benefit of 25% relative risk reduction for the primary composite endpoint cannot be correlated with the magnitude of differences in TGL levels between the treatment arms.⁹ These data from REDUCE-IT and emerging evidence from numerous studies suggest a myriad of beneficial effects of EPA that contribute to CV risk reduction beyond the effects on lipid biomarkers and TGL levels.

Studies suggest unique beneficial effects of IPE that include a wide spectrum of downstream effects on cell membrane stabilisation, improved endothelial function, lipid oxidation, and anti-thrombotic and anti-inflammatory properties.³³ These mechanisms attest to the drug's categorisation as being potentially pleiotropic. Emerging evidence continues to validate the biologic plausibility of actions of EPA as an anti-atherosclerotic agent, with effects along the pathophysiological cascade of coronary atherosclerosis, from initiation of plaque formation to plaque progression, stability and rupture.³⁴ The Effect of Vascepa on Progression of Coronary Atherosclerosis in Persons With Elevated Triglycerides on Statin Therapy (EVAPORATE) trial (ClinicalTrials.gov identifier: NCT02926027) sought to understand the mechanistic effects of IPE as an adjunct to statins on coronary plaque characteristics and volumes by serial coronary computed tomography angiography (CCTA), in a population with CVD with persistently high TGLs, similar to REDUCE-IT.^{35,36} IPE demonstrated slowed rates of progression of most coronary plaque types at 9 months, with sustained and significant benefits at 18 months, including regression of high-risk plaque characteristics/low attenuated plaque volume, compared with placebo.^{37,38} In a follow-up analysis, IPE, when added to statin therapy, was associated with increased fibrous cap thickness at 9 months, suggesting reduction in vulnerable plaque features, leading to a more stable plaque phenotype.³⁹ Similarly, the Combination therapy of eicosapentaenoic acid and pitavastatin for coronary plaque regression evaluated by integrated backscatter intravascular ultrasonography (CHERRY) trial investigated the effects of EPA/pitavastatin (PTV) (EPA 1,800 mg/day and PTV 4 mg/day) versus PTV only, on coronary plaque progression and stability features analysed by integrated backscatter intravascular ultrasound, in patients with known CVD who had undergone recent PCI.⁴⁰ They demonstrated significantly reduced coronary plaque volumes and increased plaque stabilisation in combination EPA/PTV therapy versus statins alone.

In addition to lowering TGL, the beneficial effects of IPE on lipoprotein loading in the initial steps of atherogenesis are significant. Treatment with IPE is shown to lower circulating atherogenic lipoproteins, including apoB, and lipoprotein-associated phospholipase A2, highlighting its anti-oxidant properties.^{41,42} Atherosclerosis has been identified as a chronic inflammatory condition, with maladaptive immune-inflammatory responses being described as the key pathophysiologic mechanism contributing to initiation, propagation and progression of atherosclerosis.⁴³ A favourable impact on markers

of inflammation has been demonstrated in clinical studies; the Effect of AMR101 (Ethyl Icosapentate) on Triglyceride (Tg) Levels in Patients on Statins With High Tg Levels (≥ 200 and < 500 mg/dL) (ANCHOR) and Efficacy and Safety of AMR101 (Ethyl Icosapentate) in Patients With Fasting Triglyceride (Tg) Levels ≥ 500 and ≤ 2000 mg/dL (MARINE) trials showed that EPA significantly reduced high-sensitivity C-reactive protein (hsCRP) in participants with residually elevated TGL and in a sub-analysis of patients with metabolic syndrome.⁴⁴⁻⁴⁷ In summary, the role of EPA in reducing the circulating load of major atherogenic lipoproteins beyond TGL, along with concomitant anti-oxidant and anti-inflammatory activity, regulates the cascade of atherosclerosis, which likely leads to a profound impact on adverse CV outcomes.

Distinct mechanistic effects of eicosapentaenoic acid versus docosahexaenoic acid

The differential and distinct mechanisms of action of EPA and DHA on factors related to coronary atherogenesis, may explain the differences in results of outcome trials of OM3FA preparations, such as REDUCE-IT and STRENGTH. In a pre-specified analysis of REDUCE-IT, the degree of, and time to, CV benefit from IPE was closely related to the serum EPA levels achieved, with a 37% relative risk reduction observed in the highest EPA tertile, which was 2.5-fold greater than in the lowest tertile ($p < 0.0001$).⁴⁸ The magnitude of CV benefits in REDUCE-IT is likely strongly correlated with on-treatment serum EPA levels via IPE, compared with changes in CV biomarkers such as low-density lipoprotein cholesterol (LDL-C) or hsCRP. A potential explanation for the robust CV benefits in REDUCE-IT can be linked to the higher dosage of EPA and the specific formulation of IPE, which has not been studied in prior trials, including those with combination mixtures of EPA-DHA. In a sub-analysis of the EVAPORATE trial, higher serum EPA levels were shown to predict regression of prognostically relevant coronary plaque volumes, total non-calcified plaque, and total plaque on CCTA.⁴⁹ These results build on existing evidence to strongly suggest EPA levels act as a key mediator to mechanisms of benefit with IPE.⁴⁸

There is increasing evidence to demonstrate the distinct effects of EPA and DHA on coronary atherosclerotic pathways through the differential influence on membrane structure, oxidation of lipids, inflammation and endothelial function.³³ The favourable molecular structure and lipophilic nature of EPA, in contrast to DHA, contributes to the increase in membrane stability, improved lipoprotein clearance and reduced inflammation.⁵⁰ However, studies indicate that DHA influences membrane fluidity and structure in a non-uniform manner, and promotes the formation of cholesterol-rich domains that are pro-atherogenic and promote the formation of unstable atherosclerotic plaques.⁵¹ EPA also exhibits important anti-oxidant properties that are not reproduced with DHA even under hyperglycaemic states.⁵² EPA and DHA are known to have different effects on the LDL receptor, as DHA may reduce LDL receptor expression and LDL particle clearance, while EPA enhances the clearance of LDL particles. Most importantly, the anti-inflammatory effect of EPA has been demonstrated in clinical trials with significant reductions in serum inflammatory biomarkers, which has not been consistently demonstrated in trials with EPA/DHA mixtures.^{33,53} In MARINE and ANCHOR, IPE significantly decreased TGLs without raising LDL-C, unlike DHA, which can increase LDL levels.⁵⁴ Imaging trials further allude to the differential effects of pure EPA preparations on coronary atherosclerosis versus EPA/DHA combinations. The CHERRY and EVAPORATE trials highlight the early and substantial effects of EPA on the reduction of atherothrombotic burden, demonstrated by a reduction of coronary plaque volumes in the EPA group compared to placebo. In contrast, no significant differences in coronary plaque progression were observed when comparing statin-treated subjects with stable coronary

artery disease, who received OM3FA (1.86 g of eicosapentaenoic acid and 1.5 g of docosahexaenoic acid daily) versus no omega-3 (control) for 30 months.⁵⁵

Beyond the unique effects of EPA and DHA on several factors related to coronary atherogenesis, the inconsistencies in observed benefits related to EPA alone versus combination of EPA plus DHA, remains to be completely understood. Mechanistic studies are needed to explore if the addition of DHA may diminish or negate the beneficial properties of EPA, which could explain some of the discordant results observed in the REDUCE-IT and STRENGTH trials.

There has been some interest in the effect of different placebos used in the REDUCE-IT trial (mineral oil) versus the STRENGTH trial (corn oil) on the differential outcomes of the trials. Concerns have been raised regarding the validity of results in the REDUCE-IT trial, in part questioning the stipulated biological activity of the mineral oil placebo linked to observed changes in cardiac biomarkers in the placebo arm of the trial. In a post-hoc analysis comparing serial CCTA in the mineral oil placebo arm in EVAPORATE to a cellulose-based placebo cohort in the GARLIC5 study, no differences were observed in the rate of coronary plaque progression in the two groups.^{56,57} In addition, consistent and significant benefits of EPA on coronary atherosclerosis and CV outcomes have been demonstrated in Japanese populations in the open-label CHERRY and JELIS trials, where no placebo comparator groups were included.^{40,58}

A detailed review of literature has shown that mineral-oil-related changes in TGL, low-density lipoprotein cholesterol and other biomarkers have been mostly inconsistent across studies, and are not clinically meaningful to explain the substantially positive results of REDUCE-IT.⁵⁹ In a review of REDUCE-IT by the US Food and Drug Administration (FDA), they concluded that the magnitude of difference in outcomes between IPE and mineral oil groups could not be explained by the stipulated harmful effects of mineral oil placebo.⁶⁰ Therefore, a summary of current evidence supports the validity of CV benefits with IPE in the REDUCE-IT and EVAPORATE trials, and attests to the results not being influenced by the small amount of mineral oil used in the placebo capsules.

Clinical implications

IPE has received support from leading medical bodies across the world for its robust clinical efficacy, well-established safety profile and cost effectiveness, making it an important addition to address residual CV risk.⁶¹

Currently, IPE is the first and only available medication approved by the FDA, 'to be used as an adjunct to maximally tolerated statin therapy to reduce the risk of myocardial infarction, stroke, coronary revascularisation, and unstable angina requiring hospitalisation in adult patients with elevated TG levels (≥ 150 mg/dL [1.69 mmol/L]) and established CV disease or diabetes mellitus and two or more additional risk factors for CV disease'.⁶² Based on the findings from REDUCE-IT, the European Society of Cardiology guidelines recommend the use of IPE for residually elevated TGL levels, despite statins (class IIa, level B recommendation). The American Diabetes Association's 2020 'Standards of Medical Care in Diabetes' and the National Lipid Association recommend the addition of IPE as an adjunct to statins to lower residually elevated TGL in primary prevention cohorts/high-risk patients with diabetes and ≥ 1 additional CV risk factor.^{63,64}

Adverse effects

In the REDUCE-IT population, the overall rates of adverse events during the trial or the rates of serious events associated with discontinuation of

treatment (drug or placebo) were comparable between the two groups. Participants in the treatment group had higher rates of new onset atrial fibrillation in the IPE arm compared with the placebo group (5.3% versus 3.9%), and a relatively higher incidence of hospitalisations for atrial fibrillation or flutter (3.1% versus 2.1%, $p=0.004$). Given the physiological anti-thrombotic and antiplatelet effects of OM3FA/EPA, bleeding rates were closely monitored in the trial. The rates of serious bleeding events were more frequent in the treatment group, 2.7% versus 2.1% ($p=0.06$), with no reports of fatal bleeding events in both groups.⁷ There were no significant differences between IPE and placebo in rates of adjudicated haemorrhagic stroke (0.3% versus 0.2%, $p=0.55$) or gastrointestinal bleeding (1.5% versus 1.1%, $p=0.15$) in the two groups.

Importantly, the overall safety profile of 4 g per day of IPE has been well documented with no change in benefit/risk assessments of the trial, when rates of atrial fibrillation and/or serious bleeding events were incorporated into the endpoint ascertainment in *post-hoc* analyses.⁶⁵

Expanding the indications for future use of icosapent ethyl

The substantial, consistent and clinically meaningful results across CV endpoints and subgroups (primary and secondary prevention cohorts) in REDUCE-IT has fuelled tremendous interest in extrapolating the application and clinical utility of IPE to additional high-risk patient subgroups, beyond the patients included in current guidelines.

Remarkably, the clinical benefits of IPE that were observed in REDUCE-IT were independent of baseline or attained TGL levels.⁶⁶ It is also important to highlight that 10% of the participants included in REDUCE-IT had normal TGL levels, and their relative risk reductions were comparable to patients with higher TGL levels.^{9,67} These data further suggest that the CV risk reductions observed with IPE were largely related to changes in serum EPA levels and its associated pleiotropic effects, and not mere changes in lipid biomarker or TGL levels. Multiple registry and cost-effectiveness analyses have identified a large proportion of patients at higher risk of CVD who could potentially benefit from IPE and the application of REDUCE-IT results, irrespective of serum TGL levels.^{32,68,69} Another important subgroup of participants that could be considered for the potential expanded role of IPE may be high-risk patients with known coronary atherosclerosis or diabetes mellitus with normal TGL levels. Another subset who may benefit from IPE beyond the current guideline recommendations may include patients who are intolerant to statins (representing nearly 4 million adults in the USA) with elevated TGL ≥ 150 mg/dL and high CV risk.

In summary, IPE offers an exciting therapeutic option to the multitude of anti-atherosclerotic and preventive therapies that are emerging, and can contribute to an improvement in CV outcomes across a spectrum of CV risk. Future studies must continue to examine and elucidate the myriad of plausible mechanisms of action of IPE in coronary atherosclerosis, and explore its beneficial applications and use in wider populations. □

- Fruchart JC, Davignon J, Hermans MP, et al. Residual macrovascular risk in 2013: what have we learned? *Cardiovasc Diabetol.* 2014;13:26.
- Nichols GA, Philip S, Reynolds K, et al. Increased cardiovascular risk in hypertriglyceridemic patients with statin-controlled LDL cholesterol. *J Clin Endocrinol Metab.* 2018;103:3019–27.
- Klempfner R, Erez A, Sagit BZ, et al. Elevated triglyceride level is independently associated with increased all-cause mortality in patients with established coronary heart disease: twenty-two-year follow-up of the Bezafibrate Infarction Prevention Study and Registry. *Circ Cardiovasc Qual Outcomes.* 2016;9:100–8.
- Toth PP, Granowitz C, Hull M, et al. High triglycerides are associated with increased cardiovascular events, medical costs, and resource use: a real-world administrative claims analysis of statin-treated patients with high residual cardiovascular risk. *J Am Heart Assoc.* 2018;7:e008740.
- Kastelein JJ, Maki KC, Susekov A, et al. Omega-3 free fatty acids for the treatment of severe hypertriglyceridemia: the Epanova for Lowering Very high triglycerides (EVOLVE) trial. *J Clin Lipidol.* 2014;8:94–106.
- Patel PN, Patel SM, Bhatt DL. Cardiovascular risk reduction with icosapent ethyl. *Curr Opin Cardiol.* 2019;34:721–7.
- Bhatt DL, Steg PG, Miller M, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med.* 2019;380:11–22.
- ClinicalTrials.gov. A study of AMR101 to evaluate its ability to reduce cardiovascular events in high risk patients with hypertriglyceridemia and on statin. The primary objective is to evaluate the effect of 4 g/day AMR101 for preventing the occurrence of a first major cardiovascular event. (REDUCE-IT). ClinicalTrials.gov Identifier: NCT01492361. Available at: <https://clinicaltrials.gov/ct2/show/NCT01492361> (accessed 8 July 2021).
- Bhatt DL, Steg PG, Miller M, et al. Reduction in first and total ischemic events with icosapent ethyl across baseline triglyceride tertiles. *J Am Coll Cardiol.* 2019;74:1159–61.
- Mozaffarian D, Wu JH. Omega-3 fatty acids and cardiovascular disease: effects on risk factors, molecular pathways, and clinical events. *J Am Coll Cardiol.* 2011;58:2047–67.
- Watanabe Y, Tatsuno I. Omega-3 polyunsaturated fatty acids for cardiovascular diseases: present, past and future. *Expert Rev Clin Pharmacol.* 2017;10:865–73.
- Wang X, Verma S, Mason RP, Bhatt DL. The road to approval: a perspective on the role of icosapent ethyl in cardiovascular risk reduction. *Curr Diab Rep.* 2020;20:65.
- Aung T, Halsey J, Kromhout D, et al. Associations of omega-3 fatty acid supplement use with cardiovascular disease risks: meta-analysis of 10 trials involving 77,917 individuals. *JAMA Cardiol.* 2018;3:225–34.
- Kromhout D, Gillay EJ, Geleijnse JM. n-3 fatty acids and cardiovascular events after myocardial infarction. *N Engl J Med.* 2010;363:2015–26.
- ClinicalTrials.gov. Alpha Omega Trial: study of omega-3 fatty acids and coronary mortality. ClinicalTrials.gov Identifier: NCT00127452. Available at: <https://clinicaltrials.gov/ct2/show/NCT00127452> (accessed 8 July 2021).
- Rauch B, Schiele R, Schneider S, et al. OMEGA, a randomized, placebo-controlled trial to test the effect of highly purified omega-3 fatty acids on top of modern guideline-adjusted therapy after myocardial infarction. *Circulation.* 2010;122:2152–9.
- ClinicalTrials.gov. OMEGA-Study: effect of omega 3-fatty acids on the reduction of sudden cardiac death after myocardial infarction (OMEGA). ClinicalTrials.gov Identifier: NCT00251134. Available at: <https://clinicaltrials.gov/ct2/show/NCT00251134> (accessed 8 July 2021).
- GISSI-Prevenzione Investigators (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico). Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. *Lancet.* 1999;354:447–55.
- Bowman L, Maffham M, Wallendszus K, et al. Effects of n-3 fatty acid supplements in diabetes mellitus. *N Engl J Med.* 2018;379:1540–50.
- ClinicalTrials.gov. ASCEND: a study of cardiovascular events in diabetes. ClinicalTrials.gov Identifier: NCT00135226. Available at: <https://clinicaltrials.gov/ct2/show/NCT00135226> (accessed 8 July 2021).
- Manson JE, Cook NR, Lee IM, et al. Marine n-3 fatty acids and prevention of cardiovascular disease and cancer. *N Engl J Med.* 2019;380:23–32.
- ClinicalTrials.gov. Vitamin D and omega-3 trial (VITAL) (VITAL). ClinicalTrials.gov Identifier: NCT01169259. Available at: <https://clinicaltrials.gov/ct2/show/NCT01169259> (accessed 8 July 2021).
- Yokoyama M, Origasa H, Matsuzaki M, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet.* 2007;369:1090–8.
- Nicholls SJ, Lincoff AM, Garcia M, et al. Effect of high-dose omega-3 fatty acids vs corn oil on major adverse cardiovascular events in patients at high cardiovascular risk: the STRENGTH randomized clinical trial. *JAMA.* 2020;324:2268–80.
- ClinicalTrials.gov. Outcomes study to assess statin residual risk reduction with Epanova in high CV risk patients with hypertriglyceridemia (STRENGTH). ClinicalTrials.gov Identifier: NCT02104817. Available at: <https://clinicaltrials.gov/ct2/show/NCT02104817> (accessed 8 July 2021).
- Kalstad AA, Myhre PL, Laake K, et al. Effects of n-3 fatty acid supplements in elderly patients after myocardial infarction: a randomized controlled trial. *Circulation.* 2021;143:528–39.
- ClinicalTrials.gov. Omega-3 fatty acids in elderly patients with acute myocardial infarction (OMEMI). ClinicalTrials.gov Identifier: NCT01841944. Available at: <https://clinicaltrials.gov/ct2/show/NCT01841944> (accessed 8 July 2021).
- Bhatt DL, Steg PG, Brinton EA, et al. Rationale and design of REDUCE-IT: reduction of cardiovascular events with icosapent ethyl-intervention trial. *Clin Cardiol.* 2017;40:138–48.
- Bhatt DL, Steg PG, Miller M, et al. Effects of icosapent ethyl on total ischemic events: from REDUCE-IT. *J Am Coll Cardiol.* 2019;73:2791–802.
- Bhatt DL, Brinton EA, Miller M, et al. 4-LB. Substantial cardiovascular benefit from icosapent ethyl in patients with diabetes: REDUCE-IT DIABETES. *Diabetes.* 2020;69(Suppl. 1). DOI: 10.2337/db20-4-LB.
- Peterson BE, Bhatt DL, Steg PG, et al. Reduction in revascularization with icosapent ethyl: insights from REDUCE-IT REVASC. *Circulation.* 2020;143:33–44.
- Picard F, Bhatt DL, Ducrocq G, et al. Generalizability of the REDUCE-IT trial in patients with stable coronary artery disease. *J Am Coll Cardiol.* 2019;73:1362–4.
- Mason RP, Libby P, Bhatt DL. Emerging mechanisms of cardiovascular protection for the omega-3 fatty acid eicosapentaenoic acid. *Arterioscler Thromb Vasc Biol.* 2020;40:1135–47.
- Nelson JR, Wani O, May HT, Budoff M. Potential benefits of eicosapentaenoic acid on atherosclerotic plaques. *Vasc Pharmacol.* 2017;91:1–9.
- Budoff M, Muhlestein JB, Le VT, et al. Effect of Vascepa (icosapent ethyl) on progression of coronary atherosclerosis in patients with elevated triglycerides (200–499 mg/dL) on statin therapy: rationale and design of the EVAPORATE study. *Clin Cardiol.* 2018;41:13–9.
- ClinicalTrials.gov. Effect of Vascepa on improving coronary atherosclerosis in people with high triglycerides taking statin therapy (EVAPORATE). ClinicalTrials.gov Identifier: NCT02926027. Available at: <https://clinicaltrials.gov/ct2/show/NCT02926027> (accessed 8 July 2021).
- Budoff MJ, Muhlestein JB, Bhatt DL, et al. 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;117:1070–77.
- 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;41:3925–32.
- Lakshmanan S, Buckler A, Bhatt DL, et al. Effect of icosapent ethyl on changes in coronary plaque characteristics at 9 months in patients with elevated triglycerides on statin therapy: insights from EVAPORATE. *Circulation.* 2020;142:A15389.
- 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;70:537–44.
- Miller M, Ballantyne CM, Bays HE, et al. Effects of icosapent ethyl (eicosapentaenoic acid ethyl ester) on atherogenic lipid/lipoprotein, apolipoprotein, and inflammatory parameters in patients with elevated high-sensitivity C-reactive protein (from the ANCHOR Study). *Am J Cardiol.* 2019;124:696–701.
- Ballantyne CM, Bays HE, Philip S, et al. Icosapent ethyl (eicosapentaenoic acid ethyl ester): effects on remnant-like particle cholesterol from the MARINE and ANCHOR studies. *Atherosclerosis.* 2016;253:81–7.
- Ross R. Atherosclerosis—an inflammatory disease. *N Engl J Med.* 1999;340:115–26.
- Bays HE, Ballantyne CM, Braeckman RA, et al. Icosapent ethyl, a pure ethyl ester of eicosapentaenoic acid: effects on circulating markers of inflammation from the MARINE and ANCHOR studies. *Am J Cardiovasc Drugs.* 2013;13:37–46.
- ClinicalTrials.gov. Effect of AMR101 (ethyl icosapentate) on triglyceride (Tg) levels in patients on statins with high Tg levels (≥ 200 and < 500 mg/dL) (ANCHOR). ClinicalTrials.gov Identifier: NCT01047501. Available at: <https://clinicaltrials.gov/ct2/show/NCT01047501> (accessed 8 July 2021).
- Bays HE, Ballantyne CM, Braeckman RA, et al. Icosapent ethyl (eicosapentaenoic acid ethyl ester): effects upon

- high-sensitivity c-reactive protein and lipid parameters in patients with metabolic syndrome. *Metab Syndr Relat Disord*. 2015;13:239–47.
47. ClinicalTrials.gov. Efficacy and safety of AMR101 (ethyl icosapentate) in patients with fasting triglyceride (Tg) levels ≥ 500 and ≤ 2000 mg/dL (MARINE). ClinicalTrials.gov Identifier: NCT01047683. Available at: <https://clinicaltrials.gov/ct2/show/NCT01047683> (accessed 8 July 2021).
 48. Bhatt DL, Steg PG, Miller M, et al. EPA levels and cardiovascular outcomes in the reduction of cardiovascular events with icosapent ethyl—intervention trial. Presented at: American College of Cardiology Scientific Sessions 2020, Chicago, IL, USA/Virtual, 30 March 2020.
 49. Lakshmanan S, Shekar C, Kinninger A, et al. Achieved eicosapentaenoic acid (EPA) levels predict regression of coronary plaque volumes by coronary computed tomography angiography (CCTA) in the EVAPORATE trial. *Circulation*. 2020;142:A14687.
 50. Sherratt SCR, Juliano RA, Mason RP. Eicosapentaenoic acid (EPA) has optimal chain length and degree of unsaturation to inhibit oxidation of small dense LDL and membrane cholesterol domains as compared to related fatty acids in vitro. *Biochim Biophys Acta Biomembr*. 2020;1862:183254.
 51. Mason RP, Jacob RF, Shrivastava S, et al. Eicosapentaenoic acid reduces membrane fluidity, inhibits cholesterol domain formation, and normalizes bilayer width in atherosclerotic-like model membranes. *Biochim Biophys Acta*. 2016;1858:3131–40.
 52. Preston Mason R. New insights into mechanisms of action for omega-3 fatty acids in atherothrombotic cardiovascular disease. *Curr Atherosclerosis Rep*. 2019;21:2.
 53. Dunbar RL, Nicholls SJ, Maki KC, et al. Effects of omega-3 carboxylic acids on lipoprotein particles and other cardiovascular risk markers in high-risk statin-treated patients with residual hypertriglyceridemia: a randomized, controlled, double-blind trial. *Lipids Health Dis*. 2015;14:98.
 54. Allaire J, Couture P, Leclerc M, et al. A randomized, crossover, head-to-head comparison of eicosapentaenoic acid and docosahexaenoic acid supplementation to reduce inflammation markers in men and women: the Comparing EPA to DHA (ComparED) Study. *Am J Clin Nutr*. 2016;104:280–7.
 55. Alfaddagh A, Elajami TK, Ashfaque H, et al. Effect of eicosapentaenoic and docosahexaenoic acids added to statin therapy on coronary artery plaque in patients with coronary artery disease: a randomized clinical trial. *J Am Heart Assoc*. 2017;6:e006981.
 56. Lakshmanan S, Shekar C, Kinninger A, et al. Comparison of mineral oil and non-mineral oil placebo on coronary plaque progression by coronary computed tomography angiography. *Cardiovasc Res*. 2020;116:479–82.
 57. Shaikh K, Kinninger A, Cherukuri L, et al. Aged garlic extract reduces low attenuation plaque in coronary arteries of patients with diabetes: a randomized, double-blind, placebo-controlled study. *Exp Ther Med*. 2020;19:1457–61.
 58. Saito Y, Yokoyama M, Origasa H, et al. Effects of EPA on coronary artery disease in hypercholesterolemic patients with multiple risk factors: sub-analysis of primary prevention cases from the Japan EPA Lipid Intervention Study (JELIS). *Atherosclerosis*. 2008;200:135–40.
 59. 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:J34–48.
 60. United States Food and Drug Administration. Endocrinologic and Metabolic Drugs Advisory Committee Briefing Document. Vascepa (icosapent ethyl) R-IN; 76–77, 112–114. 2019. Available at: www.fda.gov/media/132479/download (accessed 1 March 2021).
 61. Weintraub WS, Bhatt D, Zhang Z, et al. Cost-effectiveness of icosapent ethyl in US REDUCE-IT patients. *J Am Coll Cardiol*. 2020;75(Suppl. 1):1914.
 62. Reduction of cardiovascular risk with icosapent ethyl (Vascepa). *Med Lett Drugs Ther*. 2020;62:17–8.
 63. American Diabetes Association. Cardiovascular disease and risk management: standards of medical care in diabetes—2020. *Diabetes Care*. 2020;43(Suppl. 1):S111–34.
 64. Orringer CE, Jacobson TA, Maki KC. National Lipid Association Scientific Statement on the use of icosapent ethyl in statin-treated patients with elevated triglycerides and high or very-high ASCVD risk. *J Clin Lipidol*. 2019;13:860–72.
 65. Parhofer KG, Chapman MJ, Nordestgaard BG. Efficacy and safety of icosapent ethyl in hypertriglyceridaemia: a recap. *Eur Heart J Suppl*. 2020;22:J21–33.
 66. Boden WE, Baum S, Toth PP, et al. Impact of expanded FDA indication for icosapent ethyl on enhanced cardiovascular residual risk reduction. *Future Cardiol*. 2021;17:155–74.
 67. Bhatt DL, Steg PG, Miller M, et al. Reply: ischemic event reduction and triglycerides. *J Am Coll Cardiol*. 2019;74:1849–50.
 68. Fan W, Philip S, Granowitz C, et al. Residual hypertriglyceridemia and estimated atherosclerotic cardiovascular disease risk by statin use in U.S. adults with diabetes: National Health and Nutrition Examination Survey 2007–2014. *Diabetes Care*. 2019;42:2307–14.
 69. Ferrières J, Bataille V, Puymirat E, et al. Applicability of the REDUCE-IT trial to the FAST-MI registry. Are the results of randomized trials relevant in routine clinical practice? *Clin Cardiol*. 2020;43:1260–5.