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Reducing residual cardiovascular risk in Europe: Therapeutic implications of European medicines agency approval of icosapent ethyl/eicosapentaenoic acid

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ABSTRACT

Atherosclerotic cardiovascular disease (ASCVD) and its atherothrombotic complications impose a substantial disease burden in Europe, representing a cost of €210 billion per year for the European Union. Hypertriglyceridemia, a major risk factor for premature ASCVD, is present in more than 20% of the European population, and is a key feature of atherogenic dyslipidemia. Recent findings from the Progression of Early Subclinical Atherosclerosis (PESA) cohort in Spain showed that even in apparently healthy, middle-aged individuals without a history of cardiovascular (CV) risk, elevated triglyceride levels are associated with subclinical atherosclerosis and arterial inflammation. Emerging evidence from epidemiologic and genetic studies supports an independent causative role of triglycerides, triglyceride-rich lipoproteins, and their remnants in this pathology. Icosapent ethyl (IPE) is a highly purified, stable ethyl ester of eicosapentaenoic acid (EPA) that was initially approved by the United States Food and Drug Administration to treat severe hypertriglyceridemia, and subsequently received an expanded indication to reduce the risk of CV events in adult statin-treated patients. Approval was based on the pivotal, randomized, placebo-controlled, double-blind Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT), which showed that high-dose IPE (4 g/day) significantly reduced the risk of primary and secondary composite endpoints comprising major CV events and CV death relative to placebo. In 2021, the European Medicines Agency (EMA) approved IPE to reduce the risk of CV events in adult statin-treated patients at high CV risk with elevated triglyceride levels (≥1.7 mmol/L [≥150 mg/dL]) and established CV disease, or diabetes and at least one other CV risk factor. Clinical studies in Europe, which included patients with acute myocardial infarction, coronary artery disease, and those undergoing cardiac rehabilitation, established that 12.5% to 23.3% of these high-risk populations may benefit from treatment with IPE. Such clinical benefit may in part result from the moderate triglyceride-lowering properties of IPE/EPA; equally however, concentrations of atherogenic remnant particle-cholesterol are markedly reduced. Furthermore, IPE/EPA exerts pleiotropic actions beyond its lipid-lowering properties, which include modulation of endothelial function, attenuation of intraplaque inflammation and oxidative stress, and reduction in macrophage accumulation. Plasma phospholipids, into which EPA is primarily incorporated and transported, appear to serve as precursors for a series of anti-inflammatory metabolites involving the resolvins RvE1 to RvE3, a pathway which may confer cardioprotective benefits. In addition, plaque imaging data from the Effect of Icosapent Ethyl on Progression of Coronary Atherosclerosis in Patients With Elevated Triglycerides on Statin Therapy (EVAPORATE) and the Combination Therapy of Eicosapentaenoic Acid and Pitavastatin for Coronary Plaque Regression Evaluated by Integrated Backscatter Intravascular Ultrasonography (CHERRY) trials show that plaque stabilization may be favorably affected. These factors may act synergistically to stabilize atherosclerotic plaques and reduce CV risk. In addition to robust efficacy

Abbreviations: AA, arachidonic acid; ACS, acute coronary syndrome; AEs, adverse events; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; CYP450, cytochrome P450; DHA, docosahexaenoic acid; EMA, European Medicines Agency; EPA, eicosapentaenoic acid; ESC/EAS, European Society of Cardiology/European Atherosclerosis Society; EU, European Union; FCT, fibrous cap thickness; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; hsCRP, high-sensitivity C-reactive protein; HTG, hypertriglyceridemia; ICER, incremental cost-effectiveness ratio; IPE, icosapent ethyl; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event; MI, myocardial infarction; NAFLD, nonalcoholic fatty liver disease; NHANES, National Health and Nutrition Examination Survey; NNT, number needed to treat; OM3FAs, omega-3 fatty acids; PG, prostaglandin; QALY, quality-adjusted life-year; SAEs, serious adverse events; TG, triglyceride; TX, thromboxane; US FDA, United States Food and Drug Administration; TRL, triglyceride-rich lipoproteins; VLDL, very-low-density lipoprotein.

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data, multiple cost-utility studies across several countries indicate that IPE/EPA is a cost-effective treatment option that is favorably situated relative to some common willingness-to-pay thresholds.
This review will evaluate the relevance of hypertriglyceridemia to residual ASCVD burden in statin-treated dyslipidemic patients, the potential of IPE/EPA to reduce the risk of ASCVD and cardiovascular mortality in high-risk patient populations, and the mechanisms which may underlie these effects. Finally, the clinical implications of the EMA label for IPE will be critically appraised in light of the updated 2019 European Society of Cardiology/European Atherosclerosis Society guidelines on the management of dyslipidemia and the recent European Atherosclerosis Society consensus statement on triglyceride-rich lipoproteins and their remnants, together with considerations of its cost-effectiveness across several countries.

Contents

1. Introduction

Atherosclerotic cardiovascular disease (ASCVD) imposes a substantial burden in Europe, with a reported 34.9 million Europeans suffering from ischemic heart disease, 25.8 million with peripheral vascular disease, and 20.4 million with stroke (Timmis et al., 2020). These conditions contribute to an overall financial burden in the European Union (EU) totaling €210 billion annually (European Society of Cardiology, 2019; Timmis et al., 2020). One of the principal drivers of premature ASCVD is atherogenic dyslipidemia, which typically features elevated levels of triglycerides (TGs), TG-rich lipoproteins (TRL), and their remnants. This dyslipidemia is also characterized by subnormal levels of high-density lipoprotein cholesterol (HDL-C) and elevated concentrations of small, dense low-density lipoproteins (LDL) (Chapman et al., 2011; Ginsberg et al., 2021; Halcox et al., 2017). More than 20% of the European patient population has lipid levels suggestive of atherogenic dyslipidemia (Halcox et al., 2017). International Guidelines for clinical management of dyslipidemia recommend statins, or HMG-CoA reductase inhibitors, as first-line treatment (International Atherosclerosis Society, 2014a), but residual cardiovascular (CV) risk remains, even after LDL-C levels are controlled (Sampson, Fazio, & Linton, 2012). However, the evidence that LDL is a causal factor and thus a key therapeutic target in ASCVD is indisputable (Borén et al., 2020; Ference et al., 2017).

Multiple studies have demonstrated that hypertriglyceridemia (HTG) is an independent risk factor for ASCVD (Farnier, Zeller, Masson, & Cottin, 2021; Hokanson & Austin, 1996; Nordestgaard, Benn, Schnohr, & Tybjaerg-Hansen, 2007; Patel et al., 2004), and it is widely acknowledged that HTG is equally associated with increased risk for pancreatitis (Hansen, Madsen, Varbo, & Nordestgaard, 2020). It was only recently, however, that evidence from epidemiologic and genetic studies has accumulated to argue strongly for a causal relation between TGs, TRL, and their remnants and an increased risk of ASCVD-related events, including myocardial infarction (MI), ischemic stroke, and aortic valve stenosis (Chapman et al., 2011; Ference et al., 2019; Ginsberg et al., 2021; Kaltoft, Langsted, & Nordestgaard, 2020; Mach et al., 2020; Nordestgaard, 2016). Until recently, clinical trials involving TG-lowering agents, such as mixed omega-3 fatty acids (OM3FAs; containing both eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]), fibrates, and niacin have not consistently demonstrated reductions in CV risk or in CV mortality (Toth, 2016; The Risk and Prevention Study Collaborative Group, 2013).

It is relevant in this context that icosapent ethyl (IPE), a highly purified ethyl ester of EPA, was originally approved in 2012 by the United States Food and Drug Administration (US FDA) as an adjunct to diet to reduce TG levels in severe HTG (TG levels ≥5.6 mmol/L [≥500 mg/dL]) (Vascepa [package insert], 2019). Furthermore, the US label was expanded in 2019 to include an indication as adjunct treatment to maximally tolerated statin therapy to reduce the risk of MI, stroke, coronary revascularization, and unstable angina requiring hospitalization in patients with elevated TG levels (≥1.7 mmol/L [≥150 mg/dL]) and either established CV disease (CVD) or diabetes mellitus plus ≥2 additional risk factors for CVD (Vascepa [package insert], 2019). It is therefore of immediate relevance that approval of IPE was recently extended to Europe by the European Medicines Agency (EMA) for reduction of the risk of CV events in adult statin-treated patients at high CV risk with elevated TG levels (≥1.7 mmol/L [≥150 mg/dL]), and either established CVD or diabetes and ≥ 1 other CV risk factor (Vazkepa [summary of product characteristics], 2021).

In addition to its TG-lowering action, IPE/EPA exerts pleiotropic actions at the arterial wall that may impact the pathophysiology of atherosclerosis progression (Mason, Libby, & Bhatt, 2020). Indeed, given the prominent role of inflammation in this process, pro-inflammatory processes have become an attractive therapeutic target in ASCVD independent of lipid levels (Libby, 2021b). Therefore, it is of special relevance that EPA may promote resolution of inflammation and consequently be of relevance in treating these patients (Mason et al., 2020; Ridker et al., 2017). Such action of IPE/EPA is entirely consistent with findings in both the EVAPORATE (Effect of Icosapent Ethyl on Progression of Coronary Atherosclerosis in Patients With Elevated Triglycerides on Statin Therapy) and CHERRY (Combination Therapy of Eicosapentaenoic

Acid and Pitavastatin for Coronary Plaque Regression Evaluated by Integrated Backscatter Intravascular Ultrasonography) trials in patients with coronary atherosclerosis, in which imaging studies revealed both plaque regression and enhanced plaque stability independent of background statin treatment (Budoff et al., 2020; Watanabe et al., 2017).

The objectives of this review are to (1) identify the contributions of HTG to residual ASCVD burden in high-risk patients with well-controlled LDL-C levels; (2) summarize clinical trial data for IPE/EPA in reducing the risk of ASCVD, with focus on the findings of the Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT); (3) consider both the lipid-lowering characteristics of IPE/EPA and its pleiotropic mechanisms of action at the interface with the pathophysiology of atherosclerosis; (4) discuss the clinical implications of IPE's EMA label, including indicated risk populations, in light of updated European guidelines/consensus statements on management of dyslipidemia; and (5) review cost-effectiveness data of IPE across several countries.

2. HTG is associated with increased ASCVD risk and economic burden

HTG, defined as TG levels 1.7 mmol/L (>150 mg/dL), increases risk of ASCVD. While the European Guidelines do not specify treatment goals for TGs, they do note that TG levels <1.7 mmol/L (<150 mg/dL) indicate lower risk, while higher levels suggest assessing other risk factors, and recommend pharmacologic treatment for patients with TG levels >2.3 mmol/L (>200 mg/dL) after excluding secondary causes. HTG is apparent in ≈10% of adult patients in clinical practice worldwide (prevalence of HTG in Europe and in the United States is 29.6% and 25.9%, respectively) (Fan, Philip, Granowitz, Toth, & Wong, 2020; Qiao, 2006) and is driven in part by the growing epidemics of obesity and diabetes (Laufs, Parhofer, Ginsberg, & Hegele, 2020; Roth et al., 2020). Major causes of HTG may be attributed to genetic factors, as well as consumption of high fructose products and alcohol.

HTG frequently involves a polygenic background, in which variants in key genes of TG metabolism code for proteins with attenuated biological activity. In combination with aging, lifestyle factors, medications, and concomitant diseases, these genetic variations produce HTG states of variable severity (Virani et al., 2021). HTG that can be attributed solely to monogenic conditions (eg, lipoprotein lipase deficiency [formerly type 1 hyperlipidemia]) or a single secondary factor (eg, diabetes mellitus) is rare (Hegele et al., 2014; Laufs et al., 2020; Virani et al., 2021).

Abundant evidence from epidemiologic, clinical, and genetic studies (and notably Mendelian randomization analyses) support the independent, causative role of elevated levels of TG, TRL, and their remnants in the development of ASCVD (Budoff, 2016; Jorgensen et al., 2013; Lawler et al., 2020; Raposeiras-Roubin et al., 2021; Schwartz et al., 2015; Varbo et al., 2013). Mendelian randomization studies have centered on variants of genes whose translated proteins play key roles in the metabolism of TRL and their remnants, including apolipoprotein (apo)CIII, apoAV, lipoprotein lipase, and angiopoietin-like proteins 3, 4 and 8 (Ginsberg et al., 2021; Hegele et al., 2014). Such genetic analyses provide a strong basis for the contention that TG, TRL, and their remnants are causally related to elevated risk for premature ASCVD.

From the viewpoint of epidemiologic studies, pooled analyses of ≈100,000 individuals from the Copenhagen City Heart Study and the Copenhagen General Population Study, which adjusted for age, sex, and trial group, revealed that those with a mean non-fasting TG level of 6.6 mmol/L (580 mg/dL) exhibited significantly increased risks of MI (5.1-fold), ischemic heart disease (3.2-fold), ischemic stroke (3.2-fold), and all-cause mortality (2.2-fold) compared with patients with a mean non-fasting TG level of 0.8 mmol/L (70 mg/dL) (Nordestgaard & Varbo, 2014). Findings from an Italian study of outpatients with type 2 diabetes ($n = 1917$), which used multivariate analysis, similarly demonstrated that those with the highest TG levels (tertile 3) displayed an 87% increased risk of overall mortality over 10 years compared with those exhibiting the lowest TG levels (tertile 1; $P = 0.016$), regardless of body mass index, HbA1c, LDL-C, and medication use (Miselli, Nora, Passaro, Tomasi, & Zuliani, 2014).

As noted above, elevated TG levels are associated with residual CV risk, even in statin-treated patients with well-controlled LDL-C. Pivotal findings from the PROVE-IT TIMI 22 trial (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22) involved patients hospitalized for acute coronary syndrome (ACS) ($n = 4162$) and showed in an adjusted analysis that, independent of LDL-C levels, attainment of TG levels <1.7 mmol/L (<150 mg/dL) was associated with a 20% reduction in the risk of coronary heart disease (CHD) compared with TG levels ≥1.7 mmol/L (Miller et al., 2008). Moreover, in the MIRACL trial (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering) involving statin-treated patients with ACS ($n = 1501$) and a median LDL-C level of 1.5 mmol/L (120 mg/dL), the risk of a CV event (ie, CHD death, non-fatal MI, stroke, unstable angina, or cardiac arrest with resuscitation) was 51% higher in patients with fasting TG levels >2.2 mmol/L (>195 mg/dL) than in those with TG levels ≤1.5 mmol/L (≤135 mg/dL), after adjusting for multiple factors such as age, sex, and diabetes (Schwartz et al., 2015). More recently, a 2007–2014 National Health and Nutrition Examination Survey (NHANES) of US patients with diabetes ($n = 1448$) found that ≈77.5% of those with HTG had an estimated 10-year ASCVD risk of ≥7.5%, and that nearly 40% of patients with diabetes and mild to moderate elevations of TG were at moderate or high 10-year ASCVD risk (Fan, Philip, Granowitz, Toth, & Wong, 2019). Considered together, these genetic and epidemiologic findings highlight the importance of elevated concentrations of TG and TRL particles that transport TGs as risk factors not only for subclinical atherosclerosis and arterial inflammation but also for clinical CV events (Budoff, 2016; Jorgensen et al., 2013; Lawler et al., 2020; Raposeiras-Roubin et al., 2021; Schwartz et al., 2015; Varbo et al., 2013).

Beyond the elevated risk of ASCVD or pancreatitis, or both, HTG is intimately linked to additional healthcare resource use and costs. Real-world data comparing statin-treated patients with TG levels ≥1.7 mmol/L (≥150 mg/dL) versus those with TG levels <1.7 mmol/L demonstrated an ≈12% increase in total direct costs and ≈13% increase in inpatient hospital stays over ≈42 months (Toth, Philip, Hull, & Granowitz, 2019). In addition, data from NHANES in ≈18 million US patients showed that TG levels ≥1.7 mmol/L were associated with additional costs of $1730 per patient per year compared with levels <1.7 mmol/L (Case et al., 2019).

3. Therapeutic role of TG-lowering agents in reducing ASCVD risk

In line with guidelines for management of dyslipidemia, elevated ASCVD risk is conventionally reduced initially by initiation of statin treatment (Mach et al., 2020). Combination therapy with non-statin agents may then be introduced to reduce residual risk (Mach et al., 2020). It is however essential to emphasize that statin therapy may decrease TG levels in patients with HTG (baseline TG >2.8 mmol/L to <4.5 mmol/L [>250 mg/dL to <400 mg/dL]) in the range of 22% to 45% as a function of statin dose and baseline TG level (Stein, Lane, & Laskarzewski, 1998).

In light of the association between elevated TG levels and ASCVD risk, one would anticipate that "add-on" TG-lowering agents would provide cardioprotective benefit beyond those achieved with statin treatment. An overview of clinical trials examining such benefit is therefore warranted, with the present focus on EPA-only therapies.

3.1. EPA: Findings from JELIS, RESPECT-EPA and REDUCE-IT

CV Outcomes Trials of EPA/IPE

- The open-label JELIS study demonstrated a 19% reduction in major CV events with EPA 1.8 g/day in patients on low-dose statin therapy.
- In REDUCE-IT, which involved statin-treated patients aged ≥45 years with established CVD or aged ≥50 years with diabetes and ≥ 1 additional CV risk factor, IPE 2 g twice daily reduced the primary composite endpoint (CV death, MI, stroke, coronary revascularization, hospitalization for unstable angina) and the key secondary composite endpoint (CV death, MI, stroke) by 25% and 26%, respectively, versus placebo.
- Prespecified analyses of REDUCE-IT further highlighted benefit of IPE in reducing CV events, and especially in patients with diabetes.
- Rates of adverse events in REDUCE-IT were similar in the treatment and placebo groups. Incidence of atrial fibrillation was significantly higher in the IPE group versus placebo; however, this AE occurred more frequently in patients with a history of atrial fibrillation or flutter.

Encouraging data have been reported in clinical trials of EPA-only formulations. The JELIS study (Japan EPA Lipid Intervention Study) was an open-label trial that examined the use of low-dose EPA (1.8 g/d) in patients receiving low-dose statin therapy (Yokoyama et al., 2007). A 19% reduction in major coronary events was observed in patients who received EPA versus control treatment (ie, statin only; $P < 0.011$) (Yokoyama et al., 2007). However, it should be noted that patients were not enrolled on the basis of elevated TG levels, and that statin doses, while appropriate for the study population, were much lower than those used in other regions of the world (Boden, Baum, Toth, Fazio, & Bhatt, 2021).

An ongoing study in Japan, RESPECT-EPA is examining the effects of EPA (1.8 g/d) in statin-treated patients with established ASCVD. The primary endpoint is the first occurrence of CV death, non-fatal MI, non-fatal cerebral infarction, unstable angina requiring emergent hospitalization and coronary revascularization, and coronary revascularization based on clinical findings. This trial is expected to complete in 2022 (Jia, Koh, Al Rifai, Blumenthal, & Virani, 2020; UMIN Clinical Trials Registry, 2018).

REDUCE-IT was a phase 3b, randomized, double-blind, placebo-controlled trial that assessed the effect of IPE versus mineral oil placebo on the risk of CV events in statin-treated patients with elevated TG levels (1.5–5.6 mmol/L [135–499 mg/dL]) and LDL-C levels (1.1–2.6 mg/dL [41–100 mg/dL]) (Bhatt et al., 2019a). Patients aged ≥45 years with established CVD or aged ≥50 years with diabetes and ≥ 1 additional CV risk factor ($n = 8179$) were randomized to receive 4 g IPE (2 g twice daily with food) or placebo. Mineral oil was chosen as the placebo because it closely resembles IPE in color and consistency (Bhatt et al., 2019a). The primary efficacy endpoint was a composite of CV death, non-fatal MI, non-fatal stroke, coronary revascularization, or unstable angina (Bhatt et al., 2019a). The key secondary endpoint included the composite of CV death, non-fatal MI, or non-fatal stroke (Bhatt et al., 2019a). IPE was associated with a 25% reduction in the primary endpoint (17.2% of patients in the IPE group vs 22.0% in the placebo group; hazard ratio [HR], 0.75; 95% confidence interval [CI], 0.68–0.83; $P < 0.001$), with a number needed to treat (NNT) of 21 patients to avoid one primary event (Fig. 1) (Bhatt et al., 2019a). The key secondary endpoint occurred in 11.2% of patients in the IPE group versus 14.8% of patients in the placebo group (HR, 0.74; 95% CI, 0.65–0.83; $P < 0.001$), translating to a 26% reduction when comparing IPE to placebo and an NNT of 28 patients (Bhatt et al., 2019a).

Except for deaths from any cause, the IPE group had significantly lower relative risks of individual CV endpoints compared with placebo, including a 20% reduction in death due to CV causes (95% CI, 0.66–0.98), 31% reduction in MI (95% CI, 0.58–0.81), 28% reduction in stroke (95% CI, 0.55–0.93), and 31% reduction in sudden cardiac death (95% CI, 0.50–0.96) (Bhatt et al., 2019a). Baseline TG (≥1.7 mmol/L vs <1.7 mmol/L [≥150 vs <150 mg/dL] or ≥ 2.3 mmol/L vs <2.3 mmol/L [≥200 vs <200 mg/dL]) and LDL-C levels (≤1.7 mmol/L vs >1.7 mmol/L [≤67 mg/dL vs >67 mg/dL] to ≤2.2 mmol/L vs >2.2 mmol/L [≤84 mg/dL vs >84 mg/dL]) did not impact the primary or key secondary efficacy endpoints (Bhatt et al., 2019a). It is noteworthy, however, that as a CV biomarker, TG measurement is not sensitive to changes in levels of TG-rich lipoprotein–derived remnant particles, which are cholesterol-enriched (Borén et al., 2020; Langlois et al., 2020; Salinas & Chapman, 2020).

After a median follow-up of 4.9 years, treatment with IPE was associated with a 21.6% decrease in TG levels from baseline versus a 6.5%

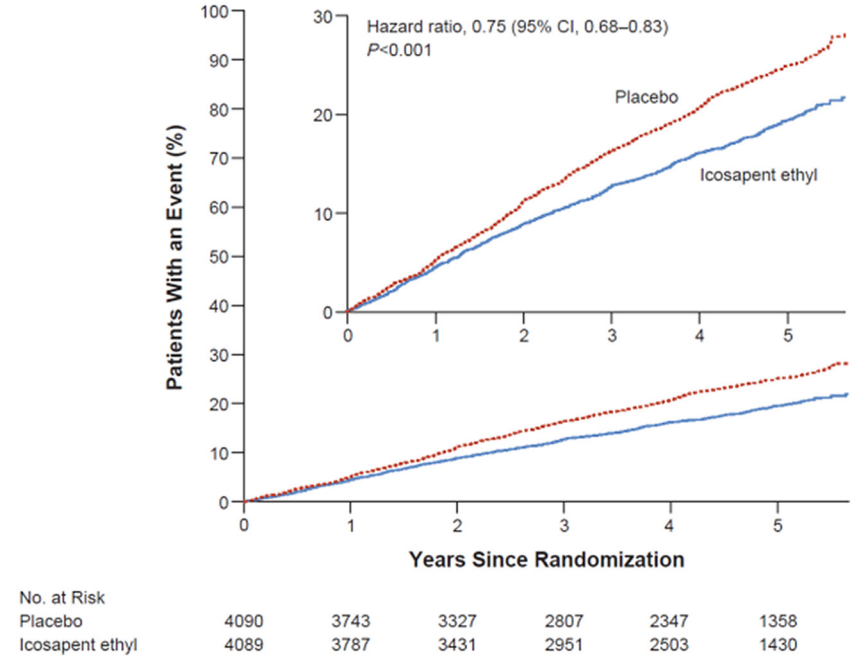

Fig. 1. REDUCE-IT total event primary endpoint (Bhatt et al., 2019a). Kaplan–Meier event curve for the primary efficacy composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularization, or unstable angina in the icosapent ethyl group and the placebo group, in a time-to-event analysis. The curve was visually truncated at 5.7 years because a limited number of events occurred beyond that time point; all patient data were included in the analyses. CI, confidence interval. From N Engl J Med, Bhatt DL, Steg G, Miller M, Brinton EA, Jacobson TA, Ketchum SB, et al., Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia, 380, 11–22. Copyright ©2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

decrease in the placebo group. A 3.1% increase in LDL-C levels from baseline occurred in the IPE group versus a 10.2% increase in the placebo group ($P < 0.001$). High-sensitivity CRP (hsCRP) levels were reduced by 12.6% in the IPE group and increased by ≈30% in the placebo group ($P < 0.001$). Significant increases in LDL-C and hsCRP levels in the placebo group were not expected, and since publication of REDUCE-IT, it has been suggested that the benefit of IPE on CV risk in REDUCE-IT may be attributed to the negative effects of mineral oil (Jo, Han, Kim, Eckel, & Koh, 2021; Sharma, Martin, & Blumenthal, 2020). In fact, one study investigated whether contrasting study results between REDUCE-IT and STRENGTH—a randomized controlled study of mixed OM3FAs 4 g/day versus corn oil placebo that was terminated early due to lack of demonstrated clinical benefit—can be attributed to differences in chosen placebo and their effects on lipid biomarkers and CRP; the study investigators concluded that differences in the effect of placebo (mineral oil vs corn oil) on lipid and CRP levels may be responsible for some of the contrasting results between the studies (Doi, Langsted, & Nordestgaard, 2021). However, correlating clinical benefit of EPA solely to changes in lipids and CRP fails to account for the pleiotropic mechanisms of action of EPA, which may underlie a substantial part of the clinical benefit seen in REDUCE-IT. Patients receiving IPE in REDUCE-IT displayed substantially elevated plasma EPA levels, which were strongly correlated with reduction in CV events (Bhatt et al., 2020); indeed, EPA's downstream effects may account for the bulk of the observed clinical benefit, rather than changes in the lipid profile and in CRP levels (Steg & Bhatt, 2021). The question of mineral oil placebo in REDUCE-IT has been examined in detail by regulatory bodies in the US and EU, with the European Public Assessment Report for Vazkepa reporting that "the remaining benefit of Vazkepa on CV outcome remains unambiguously clinically relevant" (2021).

Multiple prespecified analyses of REDUCE-IT further yielded encouraging data with regard to the effect of IPE on total ischemic events, revascularization, and stroke; pronounced benefits in patients with diabetes; and strong correlation of EPA levels with CV benefits (Table 1) (Bhatt et al., 2019b; Bhatt et al., 2020; Bhatt et al., 2021; Bhatt, Miller, et al., 2020; Peterson et al., 2021). For example, in REDUCE-IT Total Events, IPE reduced the risk for total primary endpoint events by 30% ($P < 0.0001$) and the key secondary composite endpoint by 28% ($P < 0.0001$) compared with placebo (Bhatt et al., 2019b). In REDUCE-IT Revascularization, treatment with IPE was associated with a 34% ($P < 0.0001$) reduction in first revascularization and a 36% ($P < 0.0001$) reduction in total revascularizations versus placebo (Peterson et al., 2021). Furthermore, in REDUCE-IT Diabetes involving the subset of patients with diabetes, IPE reduced first and total primary events by 23% ($P = 0.00005$) and 24% ($P = 0.0003$), respectively, compared with placebo (Bhatt, Brinton, et al., 2020).

Overall, rates of adverse events (AEs) were similar in the two treatment groups, including incidence of serious AEs (SAEs) leading to treatment discontinuation (Bhatt et al., 2019a). Rates of bleeding-related SAEs were higher in the IPE group (2.7%) than in the placebo group (2.1%), albeit none of the bleeding events were fatal. In addition, rates of atrial fibrillation and peripheral edema were significantly higher in the IPE group (5.3% [$P = 0.003$] and 6.5% [$P = 0.002$], respectively) than in the placebo group (3.9% and 5.0%, respectively), and hospitalization for atrial fibrillation or flutter was significantly higher with IPE than with placebo (3.1% vs 2.1%; $P = 0.004$). Although OM3FAs have been suggested as treatment for atrial fibrillation, they have not been shown to be effective for this purpose (Ofman, Peralta, Hoffmeister, Gaziano, & Djousse, 2013). In fact, other major clinical trials of mixed OM3FA formulations have also shown increased risk of AF in the OM3FA group versus the control group (Kalstad et al., 2020; Nicholls et al., 2020), although the mechanism responsible for the increased incidence of atrial fibrillation is not well understood. It should be noted that the incidence of atrial fibrillation seen in REDUCE-IT was greater among patients with a history of atrial fibrillation or atrial flutter. Conversely, anemia (4.7% vs 5.8%; $P = 0.03$), diarrhea (9.0% vs 11.1%; $P = 0.002$), and gastrointestinal AEs (33.0% vs 35.1%; $P = 0.04$) were significantly lower in the IPE group than in the placebo group. Overall, the FDA concluded that REDUCE-IT demonstrated that "the benefits of icosapent ethyl outweigh the risks for both the secondary and high-risk primary prevention subgroups (US FDA, 2019a)." Similarly, the EMA stated that "the side effects of Vazkepa were considered

Table 1
Summary of Prespecified REDUCE-IT Analyses.

Analysis	N	Outcome Measures	CV Outcomes Assessed	Results (IPE vs Placebo)	*P*-value
REDUCE-IT Total Events (Bhatt et al., 2019b)	8179	Risk of total primary and key secondary composite endpoint events	Primary endpoint: Composite of CV death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularization, or hospitalization for unstable angina	30% reduction in risk for total primary endpoint events	<0.0001
			Secondary endpoint: CV death, non-fatal myocardial infarction, or non-fatal stroke	28% reduction in risk for total secondary composite endpoint events	<0.0001
REDUCE-IT Stroke (Bhatt et al., 2021)	8179	Risk of ischemic stroke	First fatal and non-fatal strokes	28% reduction in risk for first fatal or non-fatal stroke	0.01
			Total fatal and non-fatal strokes	32% reduction in risk for total fatal and non-fatal stroke	0.008
			First ischemic stroke	36% reduction in risk for first ischemic stroke	0.002
			Total ischemic strokes	36% reduction in risk for total ischemic strokes	0.003
REDUCE-IT Diabetes (Bhatt, Brinton, et al., 2020)	4787	Risk of primary and secondary first and total events in patients with diabetes	Primary endpoint: CV death, myocardial infarction, stroke, coronary revascularization, or unstable angina	23% reduction in first primary endpoint	0.00005
				23% reduction in total primary endpoint	0.0003
			Secondary endpoint: CV death, myocardial infarction, or stroke	30% reduction in first secondary endpoint	0.000003
				29% reduction in total secondary endpoint	0.00005
REDUCE-IT Revascularization (Peterson et al., 2021)	8179	Risk of coronary revascularization	All coronary revascularizations, recurrent revascularizations, and revascularization subtypes	34% reduction in first coronary revascularization	<0.0001
				36% reduction in first and subsequent revascularizations	<0.0000001
				38% reduction in first emergent revascularization	0.016
				34% reduction in first urgent revascularization	<0.0001
				32% reduction in first elective revascularization	<0.0001
REDUCE-IT EPA (Bhatt, Miller, et al., 2020)	8179	Correlation between EPA levels and CV outcomes	Primary endpoint, key secondary endpoint, CV death, all-cause mortality, myocardial infarction, stroke, coronary revascularization, unstable angina, sudden cardiac death, cardiac arrest, and new heart failure	On-treatment EPA levels with IPE correlated with the primary endpoint, key secondary endpoint, CV death, all-cause mortality, myocardial infarction, stroke, coronary revascularization, unstable angina, sudden cardiac death, cardiac arrest, and new heart failure	<0.001 for all

CV, cardiovascular; EPA, eicosapentaenoic acid; IPE, icosapent ethyl; REDUCE-IT, Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial.

manageable" and that "Vazkepa's benefits are greater than its risks" (European Medicines Agency, 2021). The aforementioned incidences of bleeding, edema, and atrial fibrillation are included in the prescribing information (Vascepa [package insert], 2019; *Vazkepa [summary of product characteristics]*).

4. Mechanisms underlying reduction in cv outcomes with IPE/EPA: Beyond TG-lowering effects

It is difficult to attribute the significant reduction in CV events seen with IPE in REDUCE-IT solely to lowering of TG levels, given that TGs were only moderately reduced (Bhatt et al., 2019a; Harris, 2019; Zambon, Pirillo, Zambon, Norata, & Catapano, 2020), although it should be noted that IPE intervention significantly reduces levels of remnant cholesterol (Ballantyne et al., 2012; Ballantyne et al., 2016; Bays et al., 2012). Furthermore, a prespecified analysis of first event and total events by baseline TG tertiles found statistically significant reductions for first and total events across all TG tertiles (≥0.9 to ≤2.1 mmol/L, >2.1 to ≤2.8 mmol/L, and > 2.8 to ≤15.8 mmol/L [≥81 to ≤190 mg/dL, >190 to ≤250 mg/dL, and > 250 to ≤1401 mg/dL]). These data prompted the hypothesis that the mechanisms involved in lowering CV risk with EPA may go beyond simple TG reduction to include remnant particles, but also may implicate its non-lipid effects (Fig. 2A) (Bhatt et al., 2019c; Harris, 2019). One hypothesis focuses on the 4-fold increase in blood serum levels of EPA seen after treatment with IPE; significant ($P < 0.05$) increases in EPA levels were directly correlated with improvements in CV outcomes (Table 1) (Bhatt, Miller, et al., 2020). Alternative mechanisms cannot be excluded however, and therefore we examine the potential effects of IPE/EPA, be they direct or indirect, on critical aspects of plaque development, plaque stability, and ASCVD.

4.1. Pathophysiology of plaque development and ASCVD

Atherosclerosis is a chronic inflammatory disease of the arterial wall, and is characterized by a complex series of processes which underlie the initiation, formation, and progression of the atherosclerotic plaque (Borén et al., 2020; Libby, 2021a; Libby, 2021b). Multiple modifiable risk factors act in a synergistic and interactive manner to initiate plaque formation at sites of predilection in the arterial tree; such sites are characterized by turbulence in blood flow and involve endothelial cell activation due to negative shear stress at the wall (Borén et al., 2020; Korshunov, Schwartz, & Berk, 2007). Modifiable risk factors include not only dyslipidemia, but also smoking, hypertension, hemodynamic factors, oxidative stress, and diabetic hyperglycemia; dyslipidemia occurs frequently in the general population worldwide and is a prominent risk factor (Libby, 2021b; Yusuf et al., 2004).

Indeed, the retention and accumulation of apoB-containing lipoprotein particles, including LDL, very-low-density lipoproteins (VLDL), intermediate-density lipoproteins and their remnants, and lipoprotein (a), are critical components of plaque initiation and progression (Borén et al., 2020; Chapman, 2007; Ference et al., 2017). At such sites, infiltrating monocytes differentiate into adherent macrophages in the subendothelial space; subsequently, their phenotype is determined by the microenvironment. Macrophages displaying the M1 and M4 phenotypes secrete a spectrum of proinflammatory substances, including reactive oxygen species, inflammatory cytokines, proinflammatory eicosanoids, bioactive lipids, chemokines, growth factors, proteolytic enzymes and metalloproteases (Chistiakov, Bobryshev, & Orekhov, 2015; Erbel et al., 2015; Moreau et al., 1999; Tall & Yvan-Charvet, 2015; Williams, Fisher, & Greaves, 2012). A localized immunoinflammatory response results, involving a complex interplay of native and modified lipoprotein-derived lipids and lipoproteins with

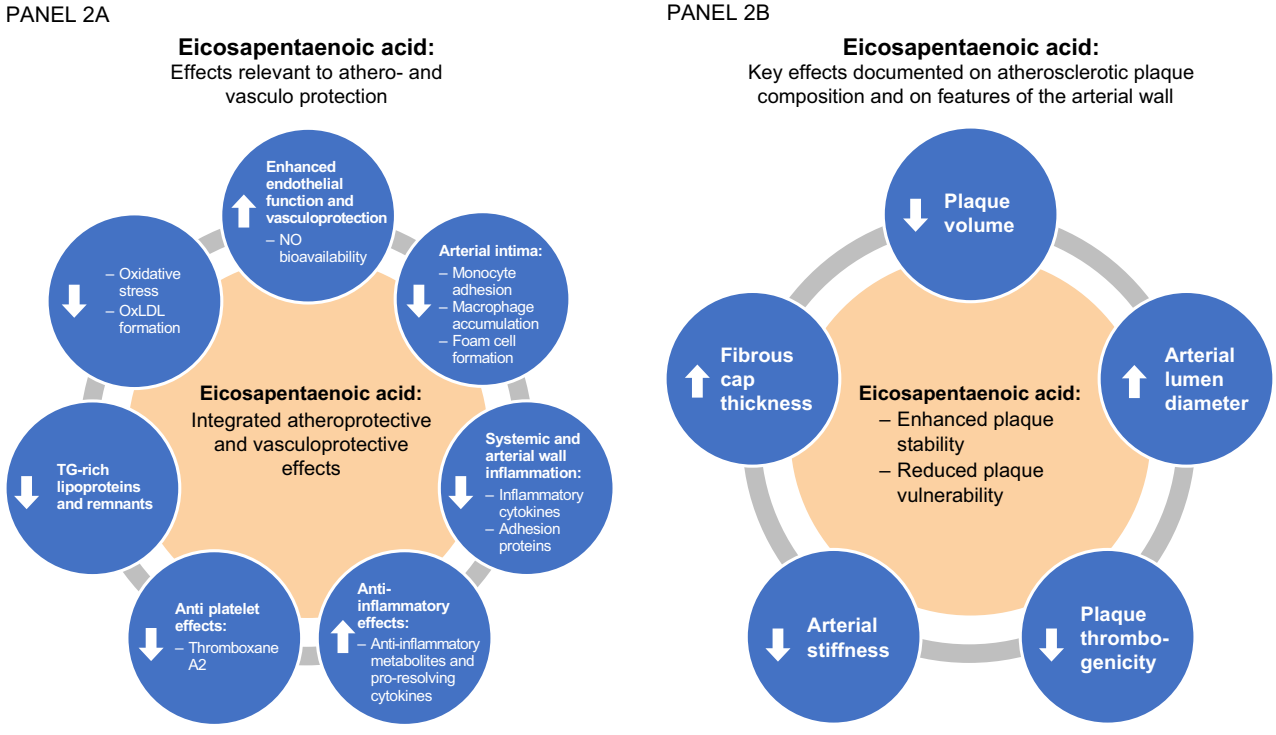

Fig. 2. Athero- and vasculoprotective actions of EPA (A) and its effects on atherosclerotic plaque (B) (Bhatt et al., 2019a; Budoff et al., 2020; Domei et al., 2013; Kashiyama et al., 2011; Kita et al., 2020; Nelson et al., 2021; Takaki et al., 2011; Watanabe et al., 2017; Yokoyama et al., 2007). **A.** EPA exerts multiple actions, both directly and indirectly, which mutually interact to favor both athero- and vasculoprotection. Arrows indicate increases or decreases in individual processes with EPA contributing to athero- and vasculoprotection. **B.** Randomized, double-blind, placebo-controlled clinical trials, notably EVAPORATE and CHERRY, have demonstrated that EPA exerts several key effects on atherosclerotic plaques in coronary arteries, which translate into enhanced plaque stabilization and reduced plaque vulnerability and ultimately into reduction in cardiovascular events as seen in the REDUCE-IT and JELIS trials. Arrows indicate increases or decreases in individual arterial wall properties with EPA. EPA, eicosapentaenoic acid. JELIS, Japan EPA Lipid Intervention Study; REDUCE-IT, Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial.

monocyte-derived macrophages and also with smooth muscle cells, dendritic cells, neutrophils, and lymphocytes (Borén et al., 2020; Libby, 2021a; Libby, 2021b; Williams et al., 2012). Uptake of both native and modified lipoproteins by macrophages and smooth muscle cells gives rise to formation of foam cells displaying intracellular cholesteryl ester droplets. Large extracellular pools of cholesterol-rich lipids are equally a hallmark feature of atherosclerotic arterial tissue (Stary et al., 1995). Plaque progression is typified by formation of a necrotic core involving accumulation of cellular debris resulting from defective efferocytosis of apoptotic cells; cholesterol monohydrate crystals are a prominent feature of necrotic cores (Fujiyoshi et al., 2019; Tabas & Lichtman, 2017). The lipid-rich core is progressively covered by smooth muscle cells and collagen-rich matrix immediately under the endothelium, thereby constituting the fibrous cap (Borén et al., 2020). Mechanisms favoring reduction in fibrous cap thickness (FCT), such as metalloprotease action, are intimately associated with the vulnerability of the plaque to rupture (Borén et al., 2020; Moreau et al., 1999). It is the formation of an occlusive or partially occlusive thrombus at the surface of an eroded or ruptured lesion that may ultimately result in an atherothrombotic, life-threatening event, such as MI or ischemic stroke (Borén et al., 2020; Chapman, 2007).

4.2. Reduction in CV events by IPE/EPA: Potential role of pleiotropic mechanisms of action

IPE/EPA Pleiotropic Mechanisms of Action

- Mechanism of action responsible for the significant reduction in CV events in REDUCE-IT cannot be attributed to lowering of TG levels alone, as reduction was modest (<20%).
- Other actions, including reduction of remnant particles and non-lipid effects could contribute to reduction in CV risk; these include inflammatory and antioxidant effects, attenuation of plaque macrophage accumulation, improved endothelial function, enhanced fibrous cap thickness and/or stability, and antiplatelet effects (Fig. 2A and B)
- Significant plaque regression and modification of plaque composition upon intervention with IPE/EPA was demonstrated in the EVAPORATE and CHERRY clinical trials, adding to existing evidence that EPA may confer CV benefit beyond TG lowering.(Fig. 2B)
- Strong correlation between on-treatment EPA levels and reduced CV events, as demonstrated in a subanalysis of REDUCE-IT, appears as a key factor underlying the considerable CV risk reduction.

The precise mechanisms implicated in the action of IPE/EPA on atherosclerotic plaque and its translation to reduction in CV events as seen in REDUCE-IT, have not been fully elucidated. Multiple — and potentially complementary — mechanisms are feasible, including reduction in concentrations of TRL and remnants, anti-inflammatory and antioxidant effects, attenuation of plaque macrophage accumulation, improved endothelial function, antiplatelet effects, and enhanced FCT and/or stability (Fig. 2A and B) (Mason et al., 2020; Nelson et al., 2021; Vazkepa [summary of product characteristics], 2021). All of these mechanisms can favorably impact the development, progression, and stabilization of atherosclerotic plaque, and are consistent with experimental findings in both preclinical studies and in the EVAPORATE and CHERRY imaging trials involving intervention with IPE/EPA (see below) (Fig. 2B) (Budoff et al., 2020; Watanabe et al., 2017).

4.2.1. Reduction of TRL and remnant cholesterol

High-dose EPA is well recognized for its TG-lowering effect, which involves reduction in hepatic production of VLDL associated with attenuated TG synthesis. The former downregulation of VLDL production results from inhibition of phosphatidic acid phosphatase/phosphohydrolase and diacylglycerol acyltransferase activities, enzymes central to TG synthesis; also, increased clearance of VLDL and chylomicrons occurs as a result of enhanced lipoprotein lipase activity (Nelson et al., 2021). Even though EPA reduces hepatic production of VLDL, EPA has been investigated in preclinical and clinical studies on nonalcoholic fatty liver disease (NAFLD) treatment. One recent mouse study showed that EPA enhances hepatic fatty acid beta-oxidation, reduces hepatic carbohydrate metabolism in the liver, and reduces hepatic inflammation, suggesting that it may impart beneficial effects in patients with NAFLD (Albracht-Schulte et al., 2019). Clinical trials in patients with NAFLD have indeed shown improvements in hepatic steatosis after treatment with OM3FAs (Spooner & Jump, 2019).

HTG is closely associated with elevated concentrations of cholesterol transported in remnant lipoproteins, now recognized as highly atherogenic particles (Ginsberg et al., 2021; Packard, Boren, & Taskinen, 2020; Saeed et al., 2018; Salinas & Chapman, 2020). In fact, remnant particles contain up to a fourfold greater content of cholesterol per particle compared with LDL, potentially resulting in increased atherogenicity versus LDL (Salinas & Chapman, 2020). It is therefore of immediate relevance that major reductions in remnant lipoprotein-cholesterol (RLP-C; up to 30%) have been observed in the phase 3 MARINE (Multi-Center, Placebo-Controlled, Randomized, Double-Blind, 12-week Study With an Open-label Extension) and ANCHOR (Effect of AMR101 (Ethyl Icosapentate) on Triglyceride Levels in Patients on Statins With High TG Levels) trials (Ballantyne et al., 2012; Ballantyne et al., 2016; Bays et al., 2012). These 12-week, double-blind studies in adult patients with HTG and statin-controlled LDL-C levels involved randomization to IPE 4 g/day, 2 g/day, or placebo, with TG cut-offs as follows: MARINE $n = 218$): ≥5.65 mmol/L and ≤ 22.6 mmol/L (≥500 and ≤ 2000 mg/dL); and ANCHOR ($n = 252$): ≥2.26 and < 5.65 mmol/L (≥200 and < 500 mg/dL) (Ballantyne et al., 2016) Median percent change in RLP-C from baseline to study termination was determined in remnant particles separated in an immunoaffinity assay; RLP-C levels were also calculated. High-dose IPE (4 g/day) significantly reduced directly measured RLP-C levels in both MARINE and ANCHOR (−29.8%, $P = 0.004$ and − 25.8%, $P = 0.0001$, respectively) versus placebo (Ballantyne et al., 2012; Ballantyne et al., 2016; Bays et al., 2012). Furthermore, directly measured RLP-C levels were reduced to a greater degree in patient subgroups with higher versus lower baseline TG levels, in patients receiving statins versus no statins (MARINE), and in patients receiving medium/higher-intensity versus lower-intensity statins (ANCHOR) (Ballantyne et al., 2016). Calculated and directly measured values for RLP-C at baseline, end of treatment, and percent change values (0.73–0.92; $P < 0.0001$ for both MARINE and ANCHOR) were strongly correlated, reinforcing the relevance of RLP-C as a biomarker of CV risk (Ballantyne et al., 2016). Clearly, high-dose IPE is efficacious in markedly reducing plasma levels of atherogenic remnant particles, key components of the atherogenic profile of apoB-containing particles (Ginsberg et al., 2021; Packard et al., 2020; Salinas & Chapman, 2020). It is notable that such effects are essentially undetected by plasma TG determination as performed in a standard lipid profile (Langlois et al., 2020); we cannot therefore exclude their potential contribution to the reduction in CV outcomes seen in REDUCE-IT (Bhatt et al., 2019a).

4.2.2. Anti-inflammatory effects

As previously mentioned, inflammation is central to the pathophysiology of atherosclerosis. OM3FAs may confer anti-inflammatory effects via competition with arachidonic acid (AA) for cyclooxygenase and lipoxygenase enzymes. In this way, polyunsaturated fatty acid catabolism is directed away from pro-inflammatory metabolites derived from AA (ie, 2-series prostaglandins and thromboxanes, and 4-series leukotrienes) and toward anti-inflammatory mediators derived from EPA and DHA. Specifically, EPA-derived lipoxygenase metabolites include resolvins RvE1 to RvE3 (Fig. 3), which have been shown to reduce leukotriene B4–induced proinflammatory signals and polymorphonuclear leukocyte migration, to augment phagocytosis of macrophages and production of cytokine interleukin-10, and to inhibit neutrophil chemotaxis (Nelson et al., 2021; Serhan & Levy, 2018). Anti-inflammatory lipoxygenase metabolites are also produced from DHA, including resolvins RvD1 to RvD4, maresin 1, and protectin D1 (Duvall & Levy, 2016; Serhan & Levy, 2018). The ratio of EPA to AA

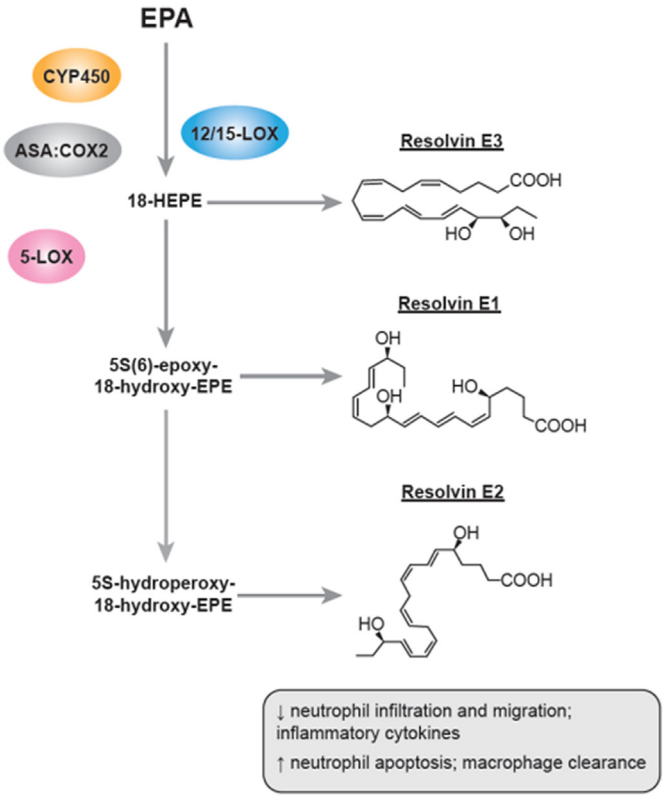

Fig. 3. Synthesis of anti-inflammatory metabolites (Duvall & Levy, 2016; Nelson et al., 2021). EPA may confer anti-inflammatory effects via competition with AA for cyclooxygenase and lipoxygenase enzymes. Whereas metabolism of AA results in formation of pro-inflammatory eicosanoids (not shown), metabolism of OM3FAs produces specialized proresolving mediators. E-series resolvins are generated by the conversion of EPA via aspirin acetylated COX-2 or CYP450 to 18R-hydroperoxy-EPE. Subsequently, 18R-HEPE is transformed via neutrophil-derived 5-LOX to another intermediary, which is then converted to RvE1 via enzymatic hydrolysis, or RvE2 via reduction. Alternatively, 18R-HEPE may be converted directly to E-series resolvin RvE3 via 12/15-LOX. ASA, acetylsalicylic acid; COX, cyclooxygenase; EPA, eicosapentaenoic acid; EPE, eicosapentaenoate; HEPE, hydroxyeicosapentaenoic acid; LOX, lipoxygenase. Reprinted from Eur J Pharmacol, 785, Duvall MG, Levy BD, DHA- and EPA-derived resolvins, protectins, and maresins in airway inflammation, 144–55, Copyright 2016, with permission from Elsevier.

determines whether the overall response is pro-inflammatory or anti-inflammatory; as such, addition of EPA can alter the EPA:AA ratio from a pro-inflammatory to an anti-inflammatory state (Nelson et al., 2021). In a study examining the effects of EPA (1, 2, or 4 g/d) in patients with major depressive disorder, a dose-dependent increase was observed in plasma concentrations of EPA-derived metabolites, including resolvins. The most robust response was observed in patients who received 4 g/d, consistent with the dose in REDUCE-IT (Bhatt et al., 2019a; Lamon-Fava et al., 2021). However, the clinical significance of these observations remains unclear (Vazkepa [summary of product characteristics], 2021).

In addition to metabolism by cyclooxygenase and lipoxygenase, OM3FAs are also metabolized by cytochrome P450 (CYP450) enzymes, namely epoxygenases, which results in the formation of inflammatory hydroxylated metabolites as well as anti-inflammatory fatty-acid epoxides (McReynolds, Morisseau, Wagner, & Hammock, 2020). Epoxygenases oxidize EPA to epoxyeicosatetraenoic acids and DHA to epoxydocosapentaenoic acids. These epoxy fatty acids express a multitude of beneficial properties, some of which include anti-inflammatory effects, anti-arrhythmic and analgesic actions, and protection against ischemia-reperfusion injury (Spector & Kim, 2015). We cannot exclude at present as to whether the anti-inflammatory action of hydroxylated metabolites of EPA may contribute to the overall CV benefit of EPA intervention as seen in REDUCE-IT or JELIS.

4.2.3. Anti-oxidant effects

EPA has been documented to exert effects on biological factors involved in antioxidative actions in vivo, as exemplified by upregulation of the expression of the antioxidant enzymes paraoxonase 1 and 2 in patients with type 2 diabetes (Golzari, Javanbakht, Ghaedi, Mohammadi, & Djalali, 2019). In vitro, EPA inhibits oxidation of apoB-containing lipoproteins, including LDL, small dense LDL, and VLDL; it is relevant that when EPA is subjected to oxidative stress, it undergoes oxidative modification as a function of the type of oxidant, typically resulting in formation of labile lipid hydroperoxides (Mason et al., 2020; Nelson et al., 2021).

4.2.4. Fibrous cap thickening and atherosclerotic plaque stability

Trial evidence supports the contention that IPE/EPA intervention, in combination with statin treatment and compared to a control group receiving statin alone, significantly improves FCT in vulnerable plaques. For example, in one subgroup analysis in which patients were stratified into 2 groups (<120 μm [thinner FCT] versus ≥120 μm [thicker FCT]) according to the median minimum FCT of 120 μm, ACS patients with minimum FCT <120 μm who received EPA (1.8 g/day; $n = 40$) for 8 months in combination with statin therapy displayed a significant increment in minimum FCT versus the statin monotherapy control group ($P = 0.02$) measured by optical coherence tomography (Kita et al., 2020). Similarly, in a study involving post-percutaneous intervention and a 9-month follow-up with optical coherence tomography in patients with untreated dyslipidemia and thin-cap fibroatheroma ($n = 31$), a greater degree of plaque stabilization, as evaluated by FCT, was observed with concomitant use of EPA and rosuvastatin as compared to statin alone (Nishio et al., 2014). The additive improvement in FCT conferred by EPA in these studies has been attributed to its anti-inflammatory effects on dendritic cells and reduction in T-lymphocytes (Nishio et al., 2014).

In addition to improvement in FCT, EPA has also been associated with plaque regression. In the randomized, double-blind, placebo-controlled EVAPORATE trial, Budoff and colleagues sought to evaluate whether IPE (4 g/day) intervention in statin-treated patients with coronary atherosclerosis and elevated TG levels (1.5–5.6 mmol/L [135–499 mg/dL]), as an adjunct to diet and statin therapy, might result in a greater reduction from baseline in plaque volume than that in the statin-treated placebo group, as measured by serial multidetector computed tomography. Remarkably, after an intervention period of 18 months, IPE reduced low-attenuation plaque volume by 17% from baseline compared with an increase of 109% in the placebo group ($P = 0.006$) (Budoff et al., 2020). In addition, there were significant differences in rates of progression between IPE and placebo groups from baseline at study end involving other plaque volume indices; these included total plaque (−9% vs 11%; $P = 0.002$), total noncalcified plaque (−19% vs 9%; $P = 0.0005$), and fibrofatty plaque (−34% vs 32%; $P = 0.0002$), all of which regressed in the IPE group and progressed in the placebo group. Importantly, the reduced rate of plaque progression in the IPE plus statin group was not accompanied by significant reductions in lipid levels from baseline (LDL-C, 0.06 mmol/L [2.4 mg/dL] vs 0.33 mmol/L [12.8 mg/dL]; $P = 0.23$; TG, 1.01 mmol/L [89.3 mg/dL] vs 1.04 mmol/L [92.1 mg/dL]; $P = 0.91$). In all likelihood, the attenuation in plaque progression – and even regression – resulting from IPE intervention is a contributing factor to the diminution in CV events documented in REDUCE-IT (Budoff et al., 2020).

Similarly, the CHERRY trial recruited patients with coronary heart disease who underwent percutaneous coronary intervention ($n = 193$). Patients were randomized in a 1:1 ratio to receive 4 mg/day

pitavastatin or pitavastatin 4 mg/day plus EPA 1800 mg/day. Imaging analyses showed that addition of EPA to statin therapy resulted in superior plaque regression and stabilization versus statin therapy alone, as demonstrated by significantly reduced total atheroma volume with combination therapy compared with statin monotherapy ($P < 0.0001$). A noteworthy finding from the trial was the significant correlation between the EPA:AA ratio and percentage change in lipid volume, indicating that EPA is an important contributor to stabilization of coronary plaque (Watanabe et al., 2017).

The key effects of EPA on coronary atherosclerotic plaques that translate to enhanced plaque stabilization and attenuated plaque vulnerability are shown schematically in Fig. 2B; favorable effects on arterial phenotype, including reduction in arterial stiffness and increase in lumen diameter, are integral features of the overall benefit on coronary vessels conferred by EPA (Budoff et al., 2020; Domei et al., 2013; Kashiyama et al., 2011; Kita et al., 2020; Takaki et al., 2011).

4.2.5. Antiplatelet effects

Resolvin E1, whose enzymatic formation is enhanced by EPA as compared to AA as substrate, regulates leukocyte extravasation, but also reduces platelet aggregation and potentially blocks initial platelet–leukocyte interactions (Nelson et al., 2021). EPA also reduces the production of the potent pro-aggregating agent thromboxane A2 (TXA2) from AA by shifting production to thromboxane A3 (TXA3), which is not pro-aggregating (Dyerberg, Bang, Stoffersen, Moncada, & Vane, 1978). On the other hand, production of prostaglandin I2 (PGI2) from AA, which is anti-aggregating, is not inhibited by EPA (Dyerberg & Jørgensen, 1980). EPA itself is also metabolized to the anti-aggregating prostaglandin I3 (PGI3) (Dyerberg et al., 1978), although less is converted when compared to the conversion of PGI2 from AA (Dyerberg & Jørgensen, 1980).

4.2.6. Endothelial function

Synthesized in endothelial cells by nitric oxide synthase, nitric oxide plays a key role in maintenance of normal endothelial function by modulating vascular dilator tone; regulating vascular permeability, platelet aggregation, and adherence; and recruiting immune cells circulating in the blood (Nelson et al., 2021). It is therefore relevant that EPA reverses endothelial dysfunction by increasing the ratio of nitric oxide to peroxynitrite (Nelson et al., 2021). In a series of in vitro experiments using human umbilical vein endothelial cells, one study evaluated the effects of combined treatment of EPA and the active metabolite of atorvastatin on endothelial cell function under oxidative stress. Combining EPA and the active metabolite of atorvastatin resulted in a significant increase in the NO/ONOO- release ratio following oxidized LDL exposure (Mason, Dawoud, Jacob, Sherratt, & Malinski, 2018).

5. IPE approval by EMA for reduction in cv events

In March 2021, the EMA approved Vazkepa, the first European Commission–approved treatment indicated to reduce the risk of CV events in adult statin-treated patients at high CV risk with elevated TG levels (≥1.7 mmol/L [≥150 mg/dL]) and established CVD or diabetes and ≥ 1 other CV risk factor (Vazkepa [summary of product characteristics], 2021). Patients with established CVD were defined as those aged ≥45 years with a documented history of coronary artery disease, cerebrovascular or carotid disease, or peripheral artery disease (Vazkepa [summary of product characteristics], 2021). Patients in the other risk group were defined as those aged ≥50 years with diabetes (type 1 or 2) requiring medical treatment, with ≥1 of the following: hypertension/receiving an antihypertensive medicinal product, age ≥ 55 (men) or ≥ 65 (women), low HDL-C levels, smoking, elevated hsCRP levels, renal impairment, micro- or macroalbuminuria, retinopathy, or reduced ankle brachial index (Vazkepa [summary of product characteristics], 2021).

6. Target patient populations for clinical benefit from treatment with IPE

Potential Benefit of IPE in the European Patient Population, Guideline Recommendations, and Cost-Effectiveness Studies

- The European population is highly vulnerable to CV events given the increased prevalence of modifiable risk factors, such as hypertension, smoking, diabetes, and sedentarity.
- While European guidelines for lipid management recommend use of lipid-lowering therapies, a considerable gap exists in the care of European patients.
- Multiple European registry studies, including those in France and Ireland, comprise patients at high CV risk consistent with those who participated in the REDUCE-IT clinical trial, and suggest that these patients may benefit from treatment with IPE.
- In light of strong data from REDUCE-IT, several European medical societies have updated their guidelines on the use of IPE for reducing CV risk.
- The ESC/EAS guidelines recommend IPE/EPA in combination with a statin for high-risk patients who have TG levels 1.5–5.6 mmol/L (135–499 mg/dL) even after treatment with statins, and the EAS Task Force recommends fibrate or IPE for high-risk and very-high-risk patients with mild to moderately elevated TG levels on a statin.
- Cost-effectiveness studies with IPE across Canada, US, Israel, and Australia indicate that IPE is a cost-effective treatment option.

Major modifiable risk factors for ASCVD are prominent in the European population; among them, hypertension, hypercholesterolemia, diabetes, obesity and smoking predominate and underlie a substantial burden of ASCVD (Timmis et al., 2020). Overall, the high prevalence of these risk factors, which were akin to those seen in patients participating in the REDUCE-IT trial, strongly suggests that European populations at high and very high CV risk may in all probability benefit from treatment with IPE.

Several European registry studies assessed the proportion of patients who may benefit from treatment with IPE based on eligibility criteria for REDUCE-IT (Belle et al., 2017; Ferrières et al., 2020; Hanssen et al., 2012;Picard et al., 2019; Sorbets et al., 2017). The French FAST-MI 2010 and 2015 registries included 9459 patients with acute MI; of the 3789 patients with a complete lipid profile, 12.5% were eligible to enroll in REDUCE-IT and receive IPE (Belle et al., 2017; Ferrières et al., 2020; Hanssen et al., 2012). Similarly, analysis of the large international CLARIFY registry in 45 countries, based on 24,146 patients with stable coronary artery disease, found that 15.5% were eligible to receive IPE (Picard et al., 2019; Sorbets et al., 2017). Analysis of data from patients ($n = 275$) in a cardiac rehabilitation center in Ireland revealed that up to 23.3% of patients could potentially benefit from treatment with IPE (Gaine, Coughlan, Maher, & Waters, 2020). In addition to secondary prevention, data from the NHANES survey (1999–2016) found that, of a weighted population of 3 million patients who met the REDUCE-IT eligibility criteria, 37% were primary prevention patients, presenting with diabetes and additional risk factors (Wong, Fan, Philip, Granowitz, & Toth, 2020). Table 3 identifies patient populations most likely to benefit from treatment with IPE, patients who may benefit, and patients who would probably not benefit, as based on REDUCE-IT criteria.

7. CV outcomes with TG-lowering therapies other than IPE/EPA

Clinical endpoint trials investigating CV outcomes with other TG-lowering agents, including mixed OM3FAs, niacin, and fibrates, have been extensively reviewed elsewhere (Boden et al., 2021; Chapman et al., 2011; Ganda, Bhatt, Mason, Miller, & Boden, 2018). Briefly, early data using mixed OM3FA preparations in patients with previous ASCVD showed reductions in composite CV endpoints (GISSI-HF Investigators, 2008); however, numerous subsequent trials using doses ranging from 400 mg/day to 4 g/day failed to demonstrate CV benefits across various risk populations (ASCEND Study Collaborative Group, et al., 2018; Kalstad et al., 2020; Kromhout, Giltay, & Geleijnse, 2010; Manson et al., 2019; Nicholls et al., 2020; ORIGIN Trial Investigators, 2012; Rauch et al., 2010). No trials to date have demonstrated

reductions in CV events with fibrates in statin-treated patients, with the exception of post hoc analyses (Chapman et al., 2011; Pradhan et al., 2018), although a clinical trial utilizing an innovative fibrate (pemafibrate) in patients with type 2 diabetes (PROMINENT; Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients With Diabetes) is ongoing (Pradhan et al., 2018).

Finally, it is important to note that many patients use non-prescription formulations of DHA + EPA, typically purchased as fish oil dietary supplements (Sherratt, Lero, & Mason, 2020). It is critical to recognize that these products are classified as foods, which are not subject to the same rigorous regulatory review as medications (Chatzopoulou, Eriksson, & Eriksson, 2020) and uniformly lack sufficient scientific evidence to support CV benefit (Sherratt et al., 2020). Furthermore, these supplements tend to have lower amounts of OM3FAs than specified on the label, while at the same time exceeding international recommendations for oxidation markers; equally, they may contain additional fats and oils that may increase CV risk (Albert et al., 2015; Sherratt et al., 2020).

8. Guideline recommendations on clinical use of TG-lowering therapies

The 2019 European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines for the management of dyslipidemia recommend the use of lipid-lowering therapies in patients with CHD, regardless of LDL-C levels (Mach et al., 2020); however, the EUROASPIRE V survey of hospitalized patients with CHD ($n = 8261$) across 27 countries in Europe, conducted in 2017 over the course of 4 months, found that patients are not receiving guideline-recommended care (De Backer et al., 2019). Moreover, the recent DA VINCI study, an 18-country, European, cross-sectional, observational study spanning from June 2017 to November 2018 that included patients prescribed lipid-lowering therapy for primary or secondary prevention in primary or secondary care, revealed that major gaps between clinical guidelines and clinical practice for lipid management persist, and will be exacerbated by the 2019 ESC/EAS guidelines, which recommend an even lower goal for LDL-C in high-risk patients (1.4 mmol/L [55 mg/dL]) (Ray et al., 2021).

The ESC/EAS guidelines recommend IPE/EPA in combination with a statin for high-risk patients who have TG levels 1.5–5.6 mmol/L (135–499 mg/dL) despite statin therapy (Mach et al., 2020). Fibrates may be considered in combination with statins for primary prevention or in high-risk patients who are at LDL-C goal with TG levels >2.3 mmol/L (>200 mg/dL) (Mach et al., 2020).

The recent EAS Task Force practical guidance statement recommends treatment with either a fibrate or IPE for high-risk (eg, type 2 diabetes mellitus) and very-high-risk (eg, documented ASCVD) patients with mild to moderately elevated TG levels (>2.3 and < 5.6 mmol/L [>200 and < 500 mg/dL]) on statin therapy (Averna et al., 2021). As per EMA recommendation, mixed OM3FAs at 1 g/day are not effective for secondary CV prevention in patients with a history of MI (European Medicines Agency, 2020). Most recently, the 2021 ESC guidelines on CVD prevention in clinical practice recommend IPE in combination with a statin for high-risk patients with TG levels >1.5 mmol/L (>135 mg/dL) despite statin treatment and lifestyle measures (Visseren et al., 2021).

9. Cost- effectiveness of IPE/EPA across multiple countries

Cost-effectiveness studies of IPE in the EU are not yet available. However, several incremental cost-effectiveness ratio (ICER) studies evaluating the cost-effectiveness of IPE across Canada, the US, Israel, and Australia have yielded encouraging data (Table 2) (Ademi, Ofori-Asenso, Zomer, Owen, & Liew, 2021; Arbel, Aboalhasan, Hammerman, & Azuri, 2021; Gao, Moodie, & Li, 2019; Lachaine, Charron, Gregoire, Hegele, & Leiter, 2020; Synnott, McQueen, Ollendorf, Campbell, & Pearson, 2020; Weintraub et al., 2020; Zhang et al., 2020).

Table 2
From IPE EMA Label to Patient Profile.

Anticipated Level of Benefit	Patient Profile[a]
Patients most likely to benefit from IPE	Patients that fulfill all recruitment criteria for REDUCE-IT and could potentially have been included in the trial on this basis
Patients who may benefit from IPE	Patients with a characteristic that did not meet the eligibility criteria to participate in REDUCE-IT (eg, too old, too obese, TG levels too high, taking PCSK9 inhibitors, comorbidities, concomitant drugs, etc) but who otherwise could have been considered for inclusion in the study
Patients least likely to benefit from IPE	Patients with characteristics far outside the inclusion criteria for REDUCE-IT (eg, severe alcoholism, very high TG levels, strong secondary factors for HTG, etc)

HTG, hypertriglyceridemia; IPE, icosapent ethyl; PCSK9, proprotein convertase subtilisin/kexin type 9; REDUCE-IT, Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial; TG, triglyceride.
[a] Please refer to Bhatt D, et al. *N Engl J Med*. 2019;380:11–22, for a comprehensive list of inclusion and exclusion criteria in REDUCE-IT.

A US study observed that at the estimated annual net price of $1625, the ICER was $18,000 per quality-adjusted life-year (QALY) for IPE versus medical management alone (Synnott et al., 2020). Similarly, a further study showed that the ICER in primary prevention was $36,118 per QALY. The cost-effectiveness of IPE in combination with statin therapy versus statin therapy alone over a 20-year time horizon at a willingness-to-pay threshold was estimated at AU$ 50,000 in an Australian analysis (Ademi et al., 2021). IPE in combination with statin therapy was associated with an ICER of AU$ 45,036 per QALY gained; IPE and statin therapy produced an ICER of AU$ 96,136 per QALY gained in the primary setting, and an ICER of AU$ 35,935 per QALY gained in the secondary setting (Ademi et al., 2021). A Canadian cost-utility analysis comparing IPE to placebo for the reduction of ischemic CV events found that treatment corresponded to an ICER of $42,797 per QALY gained, and concluded that IPE was cost-effective per a threshold of $50,000 per QALY gained (Lachaine et al., 2020). Finally, a cost analysis study from Israel comparing the cost value of IPE for primary versus secondary prevention demonstrated that the cost-needed-to-treat to prevent one major adverse CV event (MACE) was $842,726 for primary prevention versus $199,969 for secondary prevention; this translated to a prevention of 4762 MACE versus 20,069 MACE for primary or secondary prevention, respectively, given an annual investment of $819 million over 4.9 years (Arbel et al., 2021).

10. Conclusions

On the basis of the evidence presented herein, our principal conclusions are:

1. High-dose IPE (4 g/day), the ethyl ester and immediate precursor of EPA, significantly reduces ischemic CV events, coronary revascularization, unstable angina, and CV death by 25% in high-risk patient populations; these populations principally involved patients with established CVD or with diabetes and other risk factors, or both (Bhatt et al., 2019a).
2. Elevated circulating levels of EPA are strongly correlated with improvement in clinical outcomes (Bhatt, Miller, et al., 2020).
3. Randomized, double-bind, placebo-controlled imaging trials in patients with coronary atherosclerosis treated with EPA have convincingly documented plaque regression; moreover, favorable effects on plaque stability were observed, including increase in thickness of plaque fibrous caps in vulnerable lesions (Kita et al., 2020).

Table 3
Cost-Effectiveness of IPE.

Study	Country	Type of Analysis	Time Horizon	IPE Price	Results
The Cost-Effectiveness of Icosapent Ethyl in Combination With Statin Therapy Compared With Statin Alone for Cardiovascular Risk Reduction (Ademi et al., 2021)	Australia	CUA and CEA (cost per QALY and cost per YoLS)	20 years	AU$ 1637 (AU$ 4.49/day)	ICER: AU $45,036 per QALY and AU $38,480 per YoLS; Primary prevention: AU$ 96,136 per QALY, AU $113,916 per YoLS; Secondary prevention: AU$ 35,935 per QALY, AU $29,250 per YoLS
Cost-Effectiveness of Icosapent Ethyl in REDUCE-IT (Weintraub et al., 2020)	USA	CUA (cost per QALY)	Lifetime	US$ 4.16/day (WAC tested in sensitivity analysis)	The mean costs for IPE and placebo in trial were US$ 23,926 and US$ 24,563 and lifetime US$ 87,077 and US$ 88,912, respectively
Icosapent Ethyl for Primary Versus Secondary Prevention of Major Adverse Cardiovascular Events in Hypertriglyceridemia – Value for Money Analysis (Arbel et al., 2021)	Israel	NNT/CNT-based analysis corresponding to ICER's annual budget impact threshold to estimate number of preventable MACE	4.9	Cost of IPE estimated as 75% of the published US National Average Drug Acquisition Cost (US$ 2915 baseline annual cost)	US$ 819 million worth of IPE can avoid 20,069 MACE for secondary prevention and 4762 MACE for primary prevention
Scenario Analyses of Lifetime Cost-Effectiveness of Icosapent Ethyl in REDUCE-IT (Zhang et al., 2020)	USA	CUA (cost per QALY)	Lifetime	US$ 4.16/day (WAC and Optum costs tested in sensitivity analysis)	IPE cost less than the standard of care both in-trial ($23,926 vs $24,563) and over the lifetime ($87,077 vs $88,912) and yielded more QALYs than the standard of care (3.34 vs 3.27 in-trial and 11.61 vs 11.35 lifetime)
The Effectiveness and Value of Rivaroxaban and Icosapent Ethyl as Additive Therapies for Cardiovascular Disease (Synnott et al., 2020)	USA	CUA and CEA (cost per QALY, cost per LYG and evLYG) for IPE and rivaroxaban	Lifetime	Estimated annual net price: US$ 1625	ICER: US$ 18,000 per QALY for IPE vs medical management alone; US$ 17,000 per LYG and US$ 17,000 per evLYG
Cost-Effectiveness of Icosapent Ethyl (IPE) for the Reduction of the Risk of Ischemic Cardiovascular Events in Canada (Lachaine et al., 2020)	Canada	CUA (cost per QALY)	20 years	Unknown	ICER: CA$ 42,797 per QALY gained (SD: CA$ 15,884)

AU, Australia; CA, Canada; CEA, cost-effectiveness analysis; CNT, cost needed to treat; CUA, cost-utility analysis; evLYG, equal value of life years gained; ICER, incremental cost-effectiveness ratio; IPE, icosapent ethyl; LYG, life years gained; MACE, major adverse cardiovascular event; N/A, not applicable; NNT, number needed to treat; QALY, quality-adjusted life-year; SD, standard deviation; WAC, wholesale acquisition cost; USA, United States of America; YoLS, years of life saved.

4. Plaque imaging findings for coronary atherosclerotic plaques are consistent with attenuation of intra-plaque inflammation (Budoff et al., 2020), and are consistent with a spectrum of anti-inflammatory actions of EPA and its metabolites. Such actions potentially involve a range of resolvins (ie, RvE1–RvE3), specifically derived from EPA.
5. TG lowering by EPA (15%–20%) presents as a minor component of overall clinical benefit (Bhatt et al., 2019a); by contrast, marked reduction in atherogenic remnant-like particle-cholesterol (26%–30%) has been consistently observed in phase 3 trials involving high-dose IPE (4 g/day) (Ballantyne et al., 2016). Importantly, remnant particles contain up to a fourfold greater content of cholesterol per particle (up to 10,000) than LDL (up to 2700), and may therefore exhibit greater atherogenicity per particle than LDL (Ginsberg et al., 2021).
6. The effects of IPE/EPA have been demonstrated to be independent of statin treatment, as control groups receiving statin alone were included in both major clinical trials (Bhatt et al., 2019a; Yokoyama et al., 2007).
7. The clinical benefit of IPE was independent of both baseline LDL-C and TG levels on statin treatment (Bhatt et al., 2019a).
8. The clinical benefits of IPE/EPA appear to be distinct from those of DHA and other omega-3 fatty acids, possibly reflecting distinct mechanisms of action (Bradberry & Hilleman, 2013; Mason et al., 2020).
9. The strength and consistency of evidence regarding efficacy of IPE in reducing CV events outweighs its associated increased risks of bleeding-related serious AEs and atrial fibrillation, ultimately favoring its use for CVD risk reduction (US FDA, 2019b).
10. IPE is now approved in the EU to reduce the risk of CV events in adult statin-treated patients at high CV risk with elevated TG levels (≥5.6 mmol/L [≥150 mg/dL]) and established CVD, or diabetes and at least 1 other CV risk factor (Vazkepa [summary of product characteristics], 2021). Such approval enables use of IPE in secondary prevention and in high-risk primary prevention in a large European patient population known to display high residual CV risk on statin monotherapy.
11. Although the cost-effectiveness of IPE has yet to be documented in the EU, multiple cost analyses across several countries indicate that IPE is a cost-effective option for patients with established CVD, or for those in primary prevention at high risk (Ademi et al., 2021; Arbel et al., 2021; Lachaine et al., 2020; Synnott et al., 2020).
12. Recent ESC/EAS guidelines for the management of dyslipidemia recommend that OM3FAs (IPE; 4 g/day) should be considered in combination with a statin in high-risk (or above) patients with TG levels between 1.5 and 5.6 mmol/L (135–499 mg/dL) despite statin treatment (Class IIa, level B) (Mach et al., 2020).

Clearly, IPE/EPA constitutes an important addition to our arsenal of non-statin lipid-lowering agents in Europe, and is relevant to CV risk reduction across a wide range of clinical disorders featuring primary HTG, frequently of genetic origin, and also to secondary HTG states (Hegele et al., 2014; Hegele et al., 2020). The latter disorders typically involve an atherogenic dyslipidemic phenotype, and as such are manifest in type 2 diabetes, prediabetic states such as metabolic syndrome, chronic renal disease, autoimmune diseases and HIV-associated dyslipidemia, and commonly feature elevated CV risk (Chapman et al., 2011; Farnier et al., 2021; Ginsberg et al., 2021; Hansen et al., 2020; International Atherosclerosis Society, 2014b; Laufs et al., 2020; Mach et al., 2020; Packard et al., 2020; Sampson et al., 2012; Subramanian & Chait, 2012; Virani et al., 2021).

Declaration of Competing Interest

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