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REVIEW

Icosapent ethyl: safely reducing cardiovascular risk in adults with elevated triglycerides

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ABSTRACT

Introduction: In patients at high cardiovascular risk, the rate of events remains elevated despite traditional, evidence-based lipid-lowering therapy. Residual hypertriglyceridemia is an important contributor to this risk. However, prior medications with triglyceride-lowering effects have not reduced adverse clinical outcomes in the statin era.

Areas covered: The present review summarizes evidence and recommendations related to triglyceride-lowering therapy in the primary and secondary preventive settings. We provide an overview of findings from recent meta-analyses, important observational studies, and a detailed description of landmark trials, including the Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT). We further review recommendations from current guidelines.

Expert opinion: Icosapent ethyl is a stable, highly purified ethyl ester of eicosapentaenoic acid that safely and effectively reduces cardiovascular events in the contemporary setting. It is prescribed at a dose of 2 grams twice daily and is indicated in patients at high cardiovascular risk who have fasting or non-fasting triglyceride levels ≥150 mg/dl despite maximally tolerated statin treatment, or in individuals with triglyceride levels ≥500 mg/dl. Conversely, omega-3 fatty acid preparations containing a combination of eicosapentaenoic acid and docosahexaenoic acid are not indicated for reduction of cardiovascular risk and should be actively deprescribed.

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1. Introduction

According to the 2017 Global Burden of Diseases, Injuries, and Risk Factors Study, atherosclerotic cardiovascular disease remains the most common cause of death worldwide and constitutes an increasingly important threat to global health [1, 2]. In 2017, approximately 17.8 million deaths were attributed to cardiovascular disease, a number that is expected to exceed 22.2 million by 2030 [1]. Among Americans ≥20 years of age, an estimated 18.2 million individuals have coronary artery disease, and 7.0 million have had a stroke [3]. 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) play a pivotal role in reducing the risk of cardiovascular events in primary and secondary preventive settings and are unanimously recommended by international guidelines for both these purposes [4-7]. However, a substantial residual cardiovascular risk may remain despite such evidence-based lipoprotein lowering treatment [8–10].

Numerous studies have shown an independent and seemingly causal relationship between triglyceride concentrations and residual cardiovascular risk [11–14], but prior medications targeting triglyceride or high-density lipoprotein cholesterol levels, e.g. fibrates and niacin, have not demonstrated an ability to reduce adverse clinical outcomes in the statin era [15–20]. The importance of identifying a medication that effectively lowers triglyceride concentrations and, potentially via multifactorial mechanisms, subsequent cardiovascular events is further emphasized by the rising prevalence of obesity, a critical risk factor for hypertriglyceridemia [21–23].

2. Observational evidence for omega-3 fatty acids

Several decades ago, it was postulated that high seal and whale consumption might explain the low rates of death from coronary artery disease among Greenland Inuit [24–26]. These individuals had significantly lower plasma concentrations of total cholesterol and triglycerides, and significantly higher concentrations of high-density lipoprotein cholesterol than both Greenland Inuit living in Denmark and native Danes [27–30]. Similar findings were since reported for other communities with a high fish intake [31,32]. Reduced platelet aggregation and longer bleeding times were also described among persons with a high consumption of fish [33,34].

In 1985, investigators from the Zutphen Study reported that there was an inverse dose-response relationship between fish consumption and death from coronary disease during 20 years of follow-up in 852 middle-aged men without baseline coronary heart disease [35]. The degree of fish consumption correlated with intake of monounsaturated and polyunsaturated fat. In a subgroup of 552 individuals, the risk of stroke was also lower among those with persistent

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Article highlights

- In patients at high cardiovascular risk, the rate of events remains elevated despite traditional, evidence-based lipid-lowering therapy with statins, and residual hypertriglyceridemia is an important contributor to this risk
- Icosapent ethyl safely and effectively reduces the risk of incident cardiovascular events in patients at high cardiovascular risk with fasting or non-fasting triglyceride levels 150-499 mg/dl despite statin treatment, and it is also indicated in individuals with triglyceride levels ≥500 mg/dl to lower triglycerides to try and reduce the risk of pancreatitis
- Omega-3 fatty acid preparations containing a combination of eicosapentaenoic acid and docosahexaenoic acid are not indicated for reduction of cardiovascular risk and should be actively deprescribed

fish consumption [36]. Likewise, data from the Chicago Western Electric Study showed that among 1822 middle-aged men free from cardiovascular disease at baseline, the 30-year risk of fatal myocardial infarction was significantly reduced among those with a higher degree of fish intake, though a beneficial effect on stroke was not seen [37,38].

Many observational studies corroborating the ability of n-3 (omega-3) fatty acids to reduce triglyceride levels and various types of cardiovascular events have since emerged [39,40]. The lowering of triglyceride levels appears to be dose-dependent and displays substantial interindividual variability, but with greater absolute risk reductions among those with higher baseline concentrations [41]. Nevertheless, typical doses found in dietary supplements have not consistently been shown to produce substantial reductions in triglycerides or have antithrombotic effects [40].

3. Chemistry and potential mechanisms of action for omega-3 fatty acids

The three key omega-3 fatty acids involved in human physiology are alpha-linolenic acid (ALA) derived from plant oils, and eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) derived largely from fish oils. The term omega-3 indicates the presence of a carbon-carbon double bond three carbons from the terminal or omega methyl group of the fatty acid chain [41–43]. Proposed mechanisms for reduction of circulating triglyceride concentrations include reduced hepatic production of very low-density lipoprotein, increased chylomicron clearance, stimulation of lipoprotein lipase activity, reduced de novo lipogenesis, increased beta-oxidation, reduced delivery of fatty acids to the liver, reduced hepatic enzyme activity for triglyceride synthesis, and a relative increase in hepatic phospholipid synthesis [44–50].

EPA serves as an enzymatic precursor for thromboxane A_3 and prostaglandin I_3, which have neutral and inhibitory effects on platelet aggregation, respectively [51]. Both eicosanoids appear to be produced in subjects who consume at least 4 grams of EPA daily [52,53]. Individuals who ingest 4 grams or more of EPA daily may also have lower thromboxane A_2 synthesis and increased prostaglandin I_2 synthesis, augmenting the inhibitory effect on platelets [53–57]. Other potentially beneficial effects of omega-3 fatty acids include those on blood pressure, endothelial function, atherosclerotic plaques, insulin resistance, and inflammation [58]. New insights indicate differences among omega-3 fatty acids that may favor EPA over DHA with respect to plaque stabilization. In particular, EPA inhibits cholesterol crystal formation, stabilizes membrane structure, reverses endothelial dysfunction [57,58,65], and produces sustained inhibition of lipoprotein and membrane lipid oxidation [59,60]. The benefits of EPA and its metabolites on triglyceride levels may also in part be due to activation of the peroxisome proliferator-activator receptor alpha (PPAR-α) [61,62]. The distinct membrane interactions, effects on oxidation, and tissue distributions of EPA and DHA are depicted in Figure 1. In other words, there is no single unifying explanation for the potential benefits of omega-3 fatty acids on cardiovascular disease [40].

4. Evidence from randomized controlled trials of omega-3 fatty acids

Many randomized controlled trials and subsequent meta-analyses have been conducted for various omega-3 fatty acid formulations [63]. Nevertheless, results from clinical trials have not been entirely consistent, and contemporary data do not support routine use of omega-3 fatty acids for reduction of cardiovascular events [64–67]. For example, a 2020 meta-analysis of 86 randomized controlled trials found no effect of increasing omega-3 fatty acid intake on all-cause mortality (risk ratio (RR) 0.97, 95% confidence interval (CI): 0.93 to 1.01), and only marginal evidence for reduction of cardiovascular mortality (RR 0.92, 95% CI: 0.86 to 0.99) and coronary heart disease mortality (RR 0.90, 95% CI: 0.81 to 1.00) [67].

In the 2*2 factorial, randomized, controlled Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI-Prevenzione) trial, 11,324 patients with a myocardial infarction within the last 3 months were randomized to receive omega-3 fatty acids (1000 mg daily of EPA and DHA in an average ratio of 1:2), vitamin E (300 mg daily), both, or neither [68]. At 3.5 years, treatment with omega-3 fatty acids was associated with a significant reduction in the risk of the primary composite endpoint of death, non-fatal myocardial infarction, or non-fatal stroke (RR 0.90, 95% CI: 0.82 to 0.99), but not the main secondary composite endpoint of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke (RR 0.89, 95% CI: 0.80 to 1.01). Of note, since patients were recruited between 1993 and 1995, less than 5% were receiving traditional lipid-lowering therapy at baseline.

The more recently published A Study of Cardiovascular Events in Diabetes (ASCEND; n = 15,480) trial and Vitamin D and Omega-3 Trial (VITAL; n = 25,871) examined the use of omega-3 fatty acids (1000 mg daily of EPA and DHA in an average ratio of 1.3:1) in the primary preventive setting in individuals with diabetes and those predominantly without diabetes, respectively [69,70]. Neither trial was able to detect a significant reduction in the primary composite ischemic endpoint with omega-3 fatty acid supplementation (ASCEND: RR 0.97, 95% CI: 0.87 to 1.08; P = 0.55; VITAL: hazard ratio (HR) 0.92, 95% CI: 0.80 to 1.06; P = 0.24). However, the prevalence of lipid-lowering therapy was much higher than in GISSI-Prevenzione (~75% in ASCEND and ~38% in VITAL) [68-70].

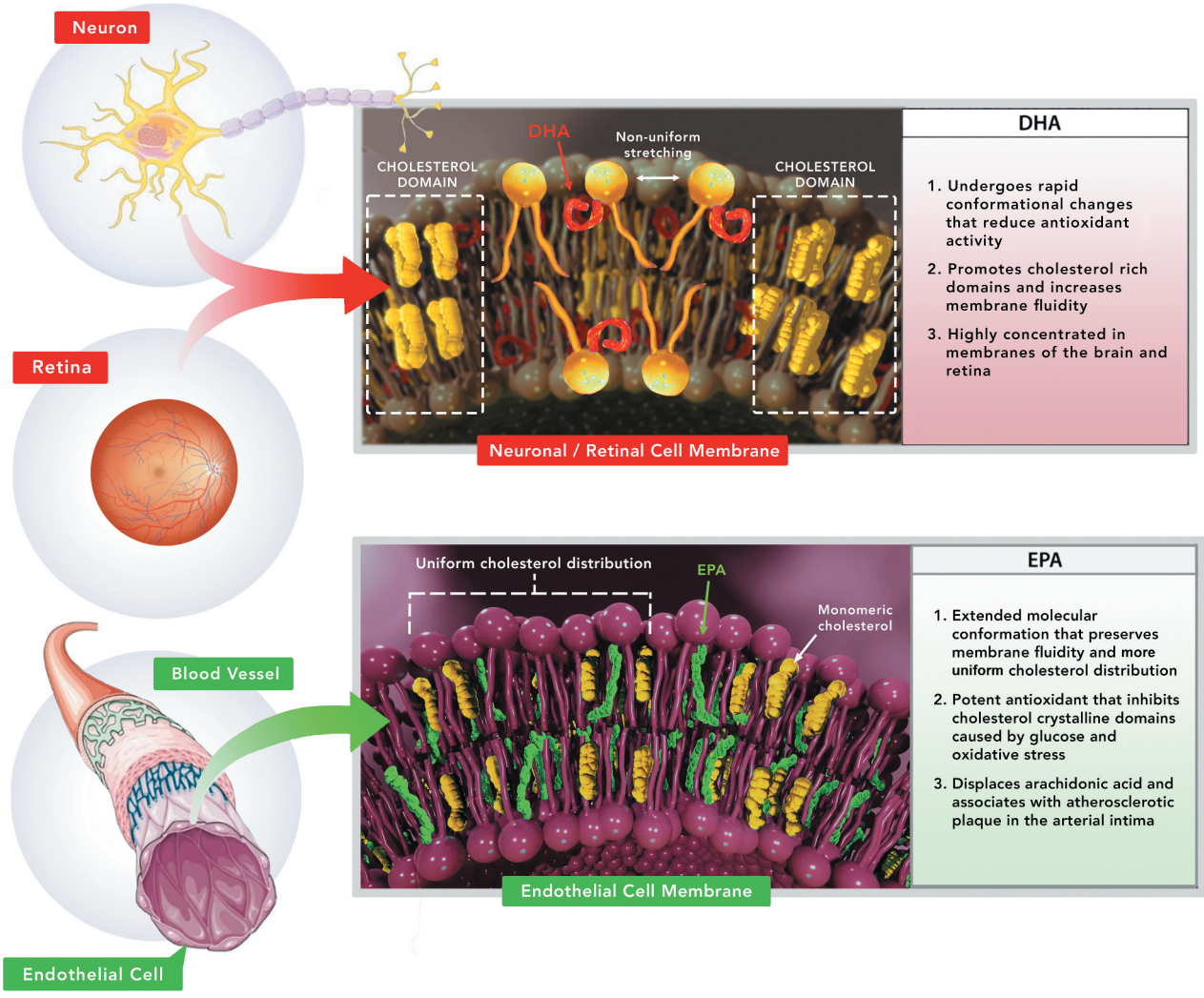

Figure 1. Distinct membrane interactions and tissue distributions of eicosapentaenoic acid and docosahexaenoic acid.
Abbreviations: DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid.

5. Differential effects and potential safety issues for dietary supplements

The above findings underscore the general lack of efficacy of mixed, low-dose omega-3 fatty acids for reduction of cardiovascular risk in contemporary clinical practice. While it is possible that negative study results may have been due to subtherapeutic doses, there appear to be potential differential effects between various preparations. The evidence base is weaker for ALA than for the predominantly marine-derived omega-3 fatty acids [64,67,71]. Furthermore, while both EPA and DHA lower triglycerides, DHA may also increase low-density lipoprotein cholesterol [72–77]. These considerations are particularly important as several mixed omega-3 formulations are approved as prescription medications which may hinder optimal treatment of patients with dyslipidemia [78].

Qualitative and quantitative differences between prescription medications and dietary supplements have been well characterized [79]. While dietary fish oil supplements are widely consumed [80–82], they should not be used for treatment of medical conditions as they are not subjected to careful regulatory approval and oversight by the U.S. Food and Drug Administration (FDA) [78,83,84]. Loosely regulated as food products, dietary fish oil supplements are considered safe until proven otherwise while prescription medications require proof of both clinical safety and efficacy with ongoing manufacturing oversight [85]. Testing of fish oil supplements has identified issues with variable amounts of EPA and DHA, lipid oxidation products, and significant levels of saturated fat and other environmental contaminants that may actually be harmful to patients with cardiovascular risk [86–90]. In the absence of clinical outcome evidence and FDA oversight, dietary supplements containing omega-3 fatty acids cannot be recommended to reduce triglycerides or cardiovascular risk.

6. Evidence from Japanese randomized controlled trials of icosapent ethyl

Few studies have examined the efficacy of EPA alone. The Japan EPA Lipid Intervention Study (JELIS) was a controlled trial in which 18,645 participants with a total cholesterol level

≥6.5 mmol/l were randomized to receive either highly purified EPA ethyl ester 600 mg thrice daily plus statin or statin alone [91]. Mean daily statin doses were 10 mg for pravastatin and 5.6 mg for simvastatin. At a mean of 4.6 years, the risk of the primary composite endpoint of any major coronary event was significantly reduced in the EPA group (HR 0.81, 95% CI: 0.69 to 0.95; P = 0.01). Results were comparable between patients with or without a history of coronary artery disease. Low-density lipoprotein cholesterol reduction was similar in the two study groups (25%), but triglyceride reduction was more pronounced in those allocated to EPA (9% versus 4%, P < 0.001) [90]. EPA appeared to be associated with a greater relative reduction of the primary endpoint among patients with a triglyceride concentration ≥150 mg/dl and a high-density lipoprotein concentration <40 mg/dl (HR 0.47, 95% CI: 0.23 to 0.98; P = 0.04) [92]. The risk of incident events also correlated with on-treatment plasma EPA levels [93].

The Combination Therapy of Eicosapentaenoic Acid and Pitavastatin for Coronary Plaque Regression Evaluated by Integrated Backscatter Intravascular Ultrasonography (CHERRY) study randomized 193 patients with stable coronary artery disease or an acute coronary syndrome who underwent percutaneous coronary intervention to either highly purified EPA 1800 mg daily plus pitavastatin 4 mg daily or pitavastatin alone and followed them for 6–8 months [94]. The primary endpoint comprised changes in coronary plaque tissue characteristics as assessed by intravascular ultrasound. Several measures, including total atheroma volume regression and lipid volume regression were significantly more pronounced in the combination therapy group [95].

7. Evidence from largely western randomized controlled trials of icosapent ethyl

The Multi-center, plAcebo-controlled, Randomized, double-blINd, 12-week study with an open-label Extension (MARINE) and the Effect of AMR101 (Ethyl Icosapentate) on Triglyceride Levels in Patients on Statins With High Triglyceride Levels (ANCHOR) trials examined, in a randomized, placebo-controlled fashion, the efficacy of icosapent ethyl among 229 individuals with a triglyceride concentration 500–2000 mg/dl and 702 patients at high cardiovascular risk on statin therapy with a residual triglyceride concentration 200–499 mg/dl, respectively [96,97]. Icosapent ethyl, a stable, highly purified ethyl ester of EPA, was administered at doses of either 1 gram twice daily or 2 grams twice daily. Both doses resulted in significant reduction in triglyceride levels without affecting low-density lipoprotein cholesterol levels, but effects were more pronounced for the 2 grams twice daily regimen. The safety profile of icosapent ethyl was similar to that of placebo. High-sensitivity C-reactive protein concentrations were also reduced with icosapent ethyl versus placebo [98].

These promising results paved the way for the Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT) [99]. Patients with either established atherosclerosis (secondary prevention) or diabetes plus additional cardiovascular risk factors (primary prevention) who had received a statin for ≥4 weeks were eligible for inclusion. Furthermore, a fasting triglyceride concentration of 135–499 mg/dl and a low-density lipoprotein concentration of 41–100 mg/dl were required. A total of 8179 participants were enrolled and randomly assigned to either icosapent ethyl 2 grams twice daily or placebo. At a median of 4.9 years, the risk of the primary efficacy endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularization, or unstable angina was significantly reduced in the icosapent ethyl group (HR 0.75, 95% CI: 0.68 to 0.83; P < 0.001), as was the risk of the key secondary endpoint of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke (HR 0.74, 95% CI: 0.65 to 0.83; P < 0.001) [100–102]. In fact, all atherosclerotic cardiovascular endpoints were significantly reduced in patients randomized to icosapent ethyl, including cardiovascular death (HR 0.80, 95% CI: 0.66 to 0.98; P = 0.03) and total (first and subsequent) ischemic events (rate ratio 0.70; 95% CI: 0.62 to 0.78; P < 0.001) [103,104]. Considering the subgroup of 3146 patients enrolled in the United States, all-cause mortality was also reduced with icosapent ethyl (HR 0.70, 95% CI: 0.55 to 0.90; P = 0.004) [105]. Finally, the benefits of icosapent ethyl were consistent across baseline triglyceride concentration tertiles [106]. Interestingly, the efficacy of icosapent ethyl was greater than would be expected based on attained triglyceride levels, lending strength to the concept of EPA having multiple pleiotropic effects beyond triglyceride reduction [100–103].

Adverse events were overall equally distributed between the two groups, irrespective of severity (Table 1). Rates of serious adverse bleeding events, including hemorrhagic stroke, other serious central nervous system bleeding, and gastrointestinal bleeding, were not significantly increased in the icosapent ethyl group (2.7% versus 2.1%, P = 0.06), though, when considering minor bleeding as well, all bleeding treatment-emergent adverse events were significantly increased (11.8% versus 9.9%, P = 0.006). Diarrhea (9.0% versus 11.1%, P = 0.002) and anemia (4.7% versus 5.8%, P = 0.03) were among the safety events more commonly observed in the placebo group. Conversely, constipation (5.4% versus 3.6%, P < 0.001) and peripheral edema (6.5% versus 5.0%, P = 0.002) were more common in the icosapent ethyl group. Furthermore, while the rate of hospitalization for atrial fibrillation or atrial flutter was significantly higher for icosapent ethyl (3.1% versus 2.1%, P = 0.004), the risk of stroke in the trial was not (HR 0.72, 95% CI: 0.55 to 0.93; P = 0.01) [100]. Key features of completed randomized controlled trials of EPA products are summarized in Table 2.

Table 1. Treatment-emergent adverse events in Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT) [100].

	Icosapent ethyl (N = 4089)	Placebo (N = 4090)	P-value for difference
Subjects with ≥1 TEAE	3343 (81.8%)	3326 (81.3%)	0.63
TEAE leading to study drug withdrawal	321 (7.9%)	335 (8.2%)	0.60
Serious TEAE	1252 (30.6%)	1254 (30.7%)	0.98
Serious TEAE leading to study drug withdrawal	88 (2.2%)	88 (2.2%)	1.00
Serious TEAE leading to death	94 (2.3%)	102 (2.5%)	0.61

Abbreviation: TEAE = treatment-emergent adverse event.

Table 2. Key completed randomized controlled trials of eicosapentaenoic acid.

Study	Main Inclusion Criteria	Intervention	Control	Sample Size	Primary Endpoint	Primary Follow-Up Duration
JELIS [91]	Age 50–75 years (men) or postmenopausal to 75 years (women) + With or without coronary artery disease + TC ≥6.5 mmol/l (LDL-C ≥4.4 mmol/l)	EPA ethyl ester 600 mg thrice daily + pravastatin ≥10 mg daily or simvastatin ≥5 mg daily	Pravastatin ≥10 mg daily or simvastatin ≥5 mg daily	18,645	A composite of any major coronary event, including sudden cardiac death, fatal and non-fatal myocardial infarction, and other non-fatal events including unstable angina pectoris, angioplasty, stenting, or coronary artery bypass grafting	4.6 years
CHERRY [95]	Age ≥20 years + Stable angina pectoris or Acute coronary syndrome + TC ≥220 mg/dl or LDL-C ≥140 mg/dl or Cholesterol-lowering deemed necessary when LDL-C ≥100 mg/dl or TC ≥180 mg/dl + Coronary plaque Successful percutaneous coronary intervention with intravascular ultrasound guidance	EPA 1800 mg daily + pitavastatin 4 mg daily	Pitavastatin 4 mg daily	193	Change in coronary plaque tissue characteristics as evaluated by integrated backscatter intravascular ultrasound	6–8 months
MARINE [96]	Age ≥18 years + TG 500–2000 mg/dl	Icosapent ethyl 1 gram twice daily or 2 grams twice daily	Placebo	229	Placebo-corrected median percentage of change in TG from baseline	12 weeks
ANCHOR [97]	Age ≥18 years + High risk for coronary heart disease On statin therapy + TG 200–499 mg/dl LDL-C 40–99 mg/dl	Icosapent ethyl 1 gram twice daily or 2 grams twice daily	Placebo	702	Placebo-corrected median percentage of change in TG from baseline	12 weeks
REDUCE-IT [100]	Age ≥45 years (established cardiovascular disease) or Age ≥50 years (diabetes and an additional risk factor) + TG 135–499 mg/dl LDL-C 41–100 mg/dl On statin therapy	Icosapent ethyl 2 grams twice daily	Placebo	8179	A composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularization, or unstable angina	4.9 years

Abbreviations: EPA = eicosapentaenoic acid, LDL-C = low-density lipoprotein cholesterol concentration, TC = total cholesterol concentration, TG = triglyceride concentration.

8. Contemporary guidelines and recommendations

Several international societies have published updated clinical practice guidelines on the use of icosapent ethyl in individuals with hypertriglyceridemia who are at high risk for cardiovascular events [6,107–109]. The 2019 scientific statement from the National Lipid Association (NLA) recommends icosapent ethyl at a dose of 2 grams twice daily for risk reduction in patients aged ≥45 years with clinical atherosclerotic cardiovascular disease, or with medically treated diabetes mellitus plus at least one additional risk factor, who have fasting triglyceride concentrations 135–499 mg/dl despite high-intensity or maximally tolerated statin (class of recommendation: I) [107]. Likewise, the 2019 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines advise that icosapent ethyl be considered in patients at high risk who have triglyceride levels 135–499 mg/dl despite statin treatment (class of recommendation: IIa) [6]. The American Diabetes Association's (ADA) 2020 Standards of Medical Care in Diabetes recommend consideration of icosapent ethyl in patients with atherosclerotic cardiovascular disease or other cardiovascular risk factors on a statin whose low-density lipoprotein cholesterol levels are controlled, but whose triglyceride concentrations are 135–499 mg/dl (class of recommendation: Level A) [108]. Similar recommendations are provided by the American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) [109].

The medication label was expanded by the FDA from triglyceride reduction only in those with severe hypertriglyceridemia ≥500 mg/dl to include reduction of cardiovascular event risk in statin-treated patients with triglyceride concentrations ≥150 mg/dl who have either established cardiovascular disease or diabetes with at least two other cardiovascular risk factors [110,111]. While REDUCE-IT required fasting triglycerides, the FDA labeling does not require that the triglyceride measurement be in a fasting state. The trial also required statin use, while the FDA label states maximally tolerated statin therapy, which for some patients who are statin intolerant may mean no statin. Health Canada has approved icosapent ethyl to reduce the risk of cardiovascular events (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularization, or hospitalization for unstable angina) in statin-treated patients with elevated triglycerides who are at high risk of cardiovascular events due to either established cardiovascular disease or diabetes and at least one other cardiovascular risk factor [111]. Based on lack of positive clinical trial outcome data, the European Medicines Agency (EMA) recently concluded that other omega-3 fatty acid medications which contain a combination of EPA and DHA at a dose of 1000 mg daily were not effective in preventing recurrent cardiovascular events, an authorization these medications had otherwise held since 2000 [112]. Icosapent ethyl has recently been approved by the EMA.

9. Other randomized controlled trials

Other trials of triglyceride lowering medications provide additional insights into the potential mechanisms of action for icosapent ethyl as well as different omega-3 fatty acid formulations. The randomized, double-blind, placebo-controlled Effect of Vascepa on Improving Coronary Atherosclerosis in People With High Triglycerides Taking Statin Therapy (EVAPORATE) trial evaluated the effects of icosapent ethyl 4 g/day on coronary atherosclerotic plaque volume as assessed by coronary CT angiography [113]. The prespecified interim analysis showed a significant reduction in total (non-calcified plus calcified) plaque volume at 9 months [114], a finding that was confirmed by the final study results at 18 months [115]. The open-label Randomized trial for Evaluation in Secondary Prevention Efficacy of Combination Therapy – Statin and Eicosapentaenoic Acid (RESPECT-EPA) has recruited 3900 patients with stable coronary artery disease receiving a statin, randomized them to EPA 1800 mg daily or no EPA, and is currently following them for incident atherosclerotic cardiovascular events [116].

Considering mixed omega-3 fatty acid formulations, the Long-Term Outcomes Study to Assess Statin Residual Risk Reduction with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia (STRENGTH) was prematurely terminated because of lack of any benefit with EPA (~550 mg) and DHA (~200 mg) free carboxylic acids in patients at high risk for cardiovascular events who were on optimal statin therapy, despite a significant reduction in triglycerides [117,118]. This underscores the importance of the type, not only quantity, of omega-3 fatty acid consumed, as the total dose of the preparation was 4 g/day. The randomized, double-blind, placebo-controlled OMega-3 fatty acids in Elderly patients with Myocardial Infarction (OMEMI) trial tested the utility of a supplement consisting of 1.8 g/day of mixed EPA and DHA to reduce cardiovascular outcomes, but in older individuals with a recent myocardial infarction [119]. This trial was also negative.

Finally, the Pemafibrate to Reduce Cardiovascular OutcoMes by Reducing Triglycerides IN patiENts With diabeTes (PROMINENT) trial is examining whether the selective PPAR-α modulator (SPPARM-α) pemafibrate can reduce cardiovascular events in patients with type 2 diabetes, hypertriglyceridemia, and low high-density lipoprotein cholesterol [120]. Detailed characteristics of these studies are summarized in Table 3.

10. Expert opinion

In patients at high cardiovascular risk, the rate of events remains elevated despite traditional, evidence-based lipid-lowering therapy. Residual hypertriglyceridemia is an important contributor to this risk and is a potent predictor of an elevated rate of ischemic events. However, the majority of medications aimed at reducing triglyceride levels have failed to demonstrate a reduction in adverse clinical outcomes in the statin era. Although various combinations of EPA and DHA have been tested in high-risk patients [122], only icosapent ethyl, a stable, highly purified ethyl ester of EPA, safely and effectively reduces incident cardiovascular events in the contemporary setting.

Indeed, the large, randomized REDUCE-IT trial demonstrated considerable reductions in atherosclerotic

Table 3. Additional randomized controlled trials of triglyceride lowering medications.

Study	Main Inclusion Criteria	Intervention	Control	Sample Size	Primary Endpoint	(Expected) Primary Follow-Up Duration
EVAPORATE [113]	Age 30–85 years + TG 200–499 mg/dl LDL-C ≥40 and ≤115 mg/dl on statin therapy + Stenosis of ≥20% in one coronary artery by invasive angiography or MDCTA	Icosapent ethyl 2 grams twice daily	Placebo	80	Rate of change in low-attenuation plaque volume from baseline to final assessment as measured by MDCTA	18 months
RESPECT-EPA [116]	Age 20–79 years + On statin therapy + Established coronary artery disease	EPA 1800 mg once daily	None	3900	A composite of cardiovascular death, non-fatal myocardial infarction, non-fatal cerebral infarction, unstable angina requiring emergent hospitalization and coronary revascularization, or coronary revascularization	5 years
STRENGTH [117]	Age ≥18 years (established cardiovascular disease) or Age ≥40 years (men) or ≥50 years (women) (diabetes with an additional risk factor) or Age >50 years (men) or >60 years (women) (with an additional risk factor) + LDL-C <100 mg/dl or LDL-C ≥100 if treated with high-intensity or maximally tolerated statin TG 180–500 mg/dl and HDL-C < 42 mg/dl (men) or <47 mg/dl (women)	EPA + DHA carboxylic acids 4 grams once daily	Placebo	13,078	A composite of cardiovascular death, myocardial infarction, stroke, coronary revascularization, or hospitalization for unstable angina	3.5 years
OMEMI [121]	Age 70–82 years + Type 1, 2, or 4 myocardial infarction within 2–8 weeks	EPA+DHA 600 mg thrice daily	Placebo	1027	A composite of total mortality, first non-fatal recurring myocardial infarction, stroke, or revascularization	2 years
PROMINENT [120]	Age ≥18 years (established cardiovascular disease) or Age ≥50 years (men) or ≥55 years (women) (no established cardiovascular disease) + Type 2 diabetes TG level 200–499 mg/dl HDL-C level ≤40 mg/dl + On moderate-to-high intensity statin therapy or LDL-C ≤70 mg/dl or Statin intolerant and LDL-C ≤100 mg/dl	Pemafibrate 0.2 mg twice daily	Placebo	10,391	A composite of non-fatal myocardial infarction, non-fatal ischemic stroke, hospitalization for unstable angina requiring urgent coronary revascularization, or cardiovascular death	5 years

Abbreviations: DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, HDL-C = high-density lipoprotein cholesterol concentration, LDL-C = low-density lipoprotein cholesterol concentration, MDCTA = multi-detector computed tomography angiography, TG = triglyceride concentration.

cardiovascular events (both first and total), without an overall increase in the risk of adverse events with icosapent ethyl versus placebo. There were significant reductions in the individual endpoints of myocardial infarction, stroke, coronary revascularization, hospitalization for unstable angina, and cardiovascular death. Potential reductions in all-cause mortality were also seen. The medication improves the lipid profile, decreases coronary atherosclerotic plaque volume, and reduces markers of inflammation, providing mechanistic explanations for its clinical benefits. The salutary effects on plaque volume are evident within 9 months, with evidence of clinical reductions in cardiovascular events starting even before that timepoint. Several markers of unstable plaque are reduced as well. Accordingly, icosapent ethyl, prescribed at a dose of 2 grams twice daily, is warranted in adult patients at high cardiovascular risk, i.e., established atherosclerotic disease or diabetes with additional risk factors, who have triglyceride levels 135–499 mg/dl despite statin treatment (or who cannot take a statin because of intolerance), or in individuals with triglyceride levels ≥500 mg/dl, irrespective of additional risk factors. Conversely, omega-3 fatty acid preparations containing a combination of EPA and DHA at typical dietary supplement doses do not provide clinically meaningful lowering of triglyceride concentrations, are not indicated for reduction of cardiovascular risk, and should be actively deprescribed.

The body of evidence supporting icosapent ethyl is rapidly growing, with several mechanistic studies underway. Elegant experiments assessing the differential effects of various omega-3 fatty acids on cell membrane preparations will provide further insights into molecular mechanisms of EPA that produce downstream beneficial effects, such as attenuating inflammation. It is already clear that the benefits of icosapent ethyl are mediated largely through EPA and are independent of baseline triglyceride levels. Thus, while the REDUCE-IT trial used elevated triglycerides to enrich the rate of ischemic events, the results likely apply to patients with lower triglyceride levels than what was studied, assuming such patients are otherwise at high cardiovascular risk. In conclusion, icosapent ethyl will have an increasingly important impact on cardiovascular risk reduction given the growing population of patients with hypertriglyceridemia and other associated risk factors. The evaluations of cost-effectiveness in both primary and secondary prevention have been quite favorable, particularly when compared with more expensive therapies such as the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, alirocumab, and evolocumab [123,124]. Studies of the generalizability of REDUCE-IT have shown that tens of millions of people worldwide could derive benefit from this medication [125–127]. Implementation of this effective and safe therapy should be a priority in healthcare systems worldwide.

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Declaration of interest

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