Targeting hypertriglyceridemia to mitigate cardiovascular risk: A review

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ABSTRACT

A causal relationship between elevated triglycerides and cardiovascular disease is controversial, as trials of triglyceride-lowering treatments have not shown significant impact on cardiovascular outcomes. However, hypertriglyceridemia is associated with atherogenesis and risk for acute cardiovascular events that persist despite optimal statin treatment. Although most trials of triglyceride-lowering treatments have been negative, in trials of niacin and fibrates, subgroup analyses in patients with higher baseline triglycerides and lower HDL-C levels suggest reduced incidence of cardiovascular endpoints. The REDUCE-IT trial demonstrated that addition of purified prescription eicosapentaenoic acid (icosapent ethyl) 4 g/day in high-risk patients with triglyceride levels 135–499 mg/dL and optimized statin treatment significantly reduced cardiovascular events versus placebo (hazard ratio 0.75; 95% confidence interval 0.68–0.83; P < 0.001). Benefit was seen regardless of baseline and on-treatment triglyceride levels, suggesting that other effects of eicosapentaenoic acid besides triglyceride reduction may have played a role.

1. Introduction

The American Heart Association has long recognized that elevated triglyceride (TG) levels are a marker of cardiovascular disease (CVD) risk [1]. TG and TG-rich lipoproteins (TRLs) are among the atherogenic lipids and lipoproteins believed to be both causal and prognostic factors for atherosclerotic CV disease (ASCVD) [2,3]. Although there is pathophysiologic evidence for a role of TG in ASCVD, as well as observational and clinical trial data supporting the association between elevated TG levels and CV event risk [4,5], until recently primary endpoints of clinical trials of TG-lowering agents including fibric acid derivatives, niacin, and omega-3 fish oils have failed to show CV event risk reduction [6–13]. The objective of this review is to examine the biochemical and clinical evidence for the role of elevated TG levels in ASCVD and to place the results of CV outcomes trials of TG-lowering agents, including the recent Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT) [14], into proper context.

2. Biology of TG levels and ASCVD event risk

Although hypertriglyceridemia most commonly occurs secondary to conditions such as metabolic syndrome, diabetes mellitus, and central obesity, it can also be caused by various medications as well as primary genetic causes; these are summarized in Table 1 [15]. In some individuals, such as those with primary hypertriglyceridemia, excess alcohol consumption, or pregnancy, TG levels can rise to >1000 mg/dL, a significant risk factor for acute pancreatitis requiring immediate treatment [15–17].

Hypertriglyceridemia results from increased production of TRLs (ie, chylomicrons and very-low-density lipoproteins), decreased catabolism of TRLs, or a combination of the two, leading to an excess of TRLs and changes in the composition of key lipoprotein particles, including low- and high-density lipoproteins (LDL and HDL) [1]. In the setting of hypertriglyceridemia, cholesterol ester transfer protein transfers TGs out of TRLs in exchange for cholesterol esters from HDL and LDL particles. As the HDL and LDL particles become progressively more enriched with TGs, they become better substrates for lipolysis by hepatic lipase, resulting in HDL catabolism and increased formation of smaller, denser LDL particles. This produces “atherogenic dyslipidemia,” with high TRLs, increased numbers of small, dense LDL, and low serum levels of HDL. In people with hypertriglyceridemia, HDL may be dysfunctional and less likely to participate in reverse cholesterol transport, while small, dense LDL particles may be more susceptible to oxidative modification and reduced clearance. Hypertriglyceridemia is also associated with increased remnant lipoprotein particles (RLPs), which include very-low-density lipoproteins and intermediate-density lipoproteins) due to inadequate lipoprotein lipase (LPL) activity, such that RLPs are not lipolyzed and converted to LDL particles. RLPs are pro-atherogenic, as
3. Clinical evidence for the association of TGs and CV event risk

Several studies have shown that elevated TG levels correlate with elevated ASCVD event risk. In an analysis of 1836 consecutive patients who underwent coronary revascularization, risk of CV death over the subsequent 10 years was significantly associated with higher TG levels (P = 0.002), even after adjusting for total cholesterol and HDL cholesterol (HDL-C) [30].

The 3. Strong Heart Study reported the effects of TGs in a community-based, prospective cohort of 3216 Native Americans and found that elevated (≥150 mg/dL) fasting TG levels and low (<40 mg/dL) HDL-C levels were associated with increased risk of incident CHD and ischemic stroke, particularly in individuals with diabetes or LDL cholesterol (LDL-C) ≥130 mg/dL, independent of other risk factors [31]. A recent analysis from the Atherosclerosis Risk in Communities Study and the Framingham Offspring Study found that ASCVD risk rose rapidly across the entire range of TG levels starting below 100 mg/dL [32].

Two claims-based analyses of the Optum Research Database examined the association between hypertriglyceridemia (TG levels 200–499 mg/dL, TG levels ≥150 mg/dL) and CV events in statin-treated individuals aged ≥45 years with documented diabetes and/or ASCVD [33, 34]. The cohort with TG levels 200–499 mg/dL was more likely to have an initial major CV event than a propensity-matched cohort with TG levels <150 mg/dL (hazard ratio [HR] 1.349; 95% confidence interval [CI] 1.23–1.49; P < 0.001) [33]. Likewise, the cohort with TG levels ≥150 mg/dL was more likely to have an initial major CV event than the propensity-matched cohort (HR 1.26; 95% CI 1.19–1.34; P < 0.001) [34]. These results remained statistically significant even after adjusting for HDL-C levels.

In an analysis of baseline fasting TG levels from 2307 patients with type 2 diabetes and CVD in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial, higher TG levels were associated with major adverse CV events [35]. While elevated TG levels are an established marker for increased risk of CVD, the causal relationship is less certain. A large meta-analysis of epidemiologic data found that although higher TG levels are associated with increased CHD risk, the correlation was substantially attenuated after adjusting for established risk factors, especially HDL-C [36].

Data also suggest that lower TG levels are associated with reduced CV event risk. In the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22 trial (PROVE-IT TIMI 22), patients who received statin treatment following hospitalization for acute coronary syndrome had a lower risk of further CHD events if on-treatment TG levels were <150 mg/dL [4]. For each 10% lowering of on-treatment TG levels, there was a 2.7% reduction in incidence of subsequent CHD events (P = 0.003) [4]. In addition, Mendelian randomization analyses evaluating participants in the UK Biobank study or in one of 62 cohort, case-controlled, or cross-sectional studies conducted in North America or Europe found that TG-lowering LPL variants and LDL-C-lowering LDL-receptor variants were associated with a similar lower risk of CHD per unit difference in apo B [37].

Elevated RLPs, which are associated with hypertriglyceridemia, have also been correlated with CV events. An analysis of the Copenhagen City Heart Study found that a 39 mg/dL increase in non-fasting RLPs was associated with a 2.8-fold risk in ischemic heart disease [38]. Similar results were reported in an analysis of the Jackson Heart and Framingham Offspring Cohort studies [39]. Even after adjustment for other CV event risk factors, increased RLP remained a predictor of CHD (HR 1.18; 95% CI 1.00–1.39; P = 0.049).

Taken together, these data indicate that elevated TG and TRL levels and related markers are at least prognostic for ASCVD risk, and are potentially causative. A recent National Health and Nutrition Examination Survey (NHANES)-based analysis found that >25% of US adults have elevated TG levels, including statin-treated patients; it was estimated that over the next decade, there will be >3.4 million ASCVD events in patients
with LDL-C levels <100 mg/dl who have TG levels ≥150 mg/dl, with ~1 million of these events occurring in statin users [40]. This high number of events predicted in statin-treated patients highlights the presence of CV event risk even in patients with controlled LDL-C [2].

4. CV outcomes trials of niacin and fibrates

Although there is evidence that lower TG levels are associated with reduced ASCVD event risk, most CV outcomes trials of TG-lowering treatments, such as niacin and fibrates, have failed to show clinical benefit (Table 2). None of these studies sought to randomize patients with hypertriglyceridemia, and neither of the 2 studies evaluating the efficacy of combining niacin with statin treatment demonstrated CV event risk reduction. The Atherosclerosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) investigators studied the effect of niacin in patients with elevated TG levels and low HDL-C levels who received intensive statin therapy [41]. In the niacin group, median TG levels decreased from 164 mg/dl at baseline to 120 mg/dl after 2 years, while median HDL-C levels increased from 35 mg/dl to 42 mg/dl. Despite improvements in the plasma lipid profile with niacin, there was no difference between treatment groups in the composite primary CV endpoint (HR 1.02; 95% CI 0.87–1.21; P = 0.80). However, in a subgroup of patients with TG levels >200 mg/dl and HDL-C levels <32 mg/dl, CV event risk decreased with niacin versus placebo (HR 0.64; P = 0.032) [42]. The Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE), which investigated niacin in combination with laropiprant when added to simvastatin ± ezetimibe, also failed to show clinical benefit with niacin for major vascular events (rate ratio 0.96; 95% CI 0.90–1.03; P = 0.29) [7]. An exploratory subgroup analysis of HPS2-THRIVE in patients with low HDL-C levels and TG levels >151 mg/dl found that niacin was not associated with reduction in incidence of major vascular events.

Studies of fibrates have yielded equivocal results. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid study, in which fenofibrate was added to open-label simvastatin in patients with diabetes, found that although the fenofibrate group experienced a mean reduction in TG levels of 42 mg/dl, there was no corresponding benefit in the primary composite CV endpoint (HR 0.92; 95% CI 0.79–1.08; P = 0.32) [8]. There was, however, a trend toward better outcomes in fenofibrate-treated patients who had TG levels in the upper tertile (>204 mg/dl) and HDL-C levels in the lowest tertile (<34 mg/dl) (P = 0.057) [8]. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial randomized patients with type 2 diabetes to fenofibrate or placebo [9]; after 4 months, there was a 29% decrease in TG, 5% increase in HDL-C, and a 12% decrease in LDL-C levels. The primary CV endpoint, first occurrence of non-fatal MI or CHD death, was not significantly different between groups (HR 0.89; 95% CI 0.75–1.05; P = 0.16). The overall finding of the FIELD study was likely impacted by the fact that more patients in the placebo arm (17%) were treated with a non-study

### Table 2
Cardiovascular outcomes trials of niacin and fibrates.

| Trial          | Intervention                                                                 | Patient Population                                                                 | Primary Endpoint                                                                 | Primary Endpoint Met? | HR/RR for Intervention |
|---------------|-------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|------------------------|------------------------|
| **Tries of Niacin** |                                                                                |                                                                                   |                                                                                  |                        |                        |
| AIM-HIGH [41] | Extended-release niacin 1500–2000 mg/day plus simvastatin                     | 3414 adults aged ≥45 years receiving high-intensity statin therapy with established CV disease, HDL-C <40 mg/dl, and TG 150-400 mg/dl | CHD death, non-fatal MI, ischemic stroke, hospitalization >23 h for ACS, or symptom-driven coronary or cerebral revascularization | No                     | HR 1.02; 95% CI 0.87–1.21; P = 0.80 |
| HPS2-THRIVE [7] | Niacin ER 1 g/day in combination with laropiprant 20 mg for 4 weeks followed by ER niacin 2 g/day in combination with 40 mg/day for 3–6 weeks vs placebo for secondary prevention | 25,673 adults aged 50–80 years with a history of MI, cerebrovascular disease, peripheral artery disease, or diabetes mellitus with evidence of symptomatic coronary disease; all patients were on statins ± ezetimibe. No lipid level-based inclusion criteria. | Major vascular events (non-fatal MI, death from coronary causes, stroke of any type, or coronary or non-coronary revascularization) | No                     | RR 0.96; 95% CI 0.90–1.03; P = 0.29 |
| **Tries of Fibrates** |                                                                                |                                                                                   |                                                                                  |                        |                        |
| FIELD [9]     | Fenofibrate 200 mg micronized per day vs placebo for primary prevention       | 9795 adults aged 50–75 years with type 2 diabetes and not using a statin or other lipid-modifying drugs; total cholesterol 116–251 mg/dl, plus either a total cholesterol/HDL-C ratio of ≥4.0:1 or TG 88.6–442.9 mg/dl | First occurrence of non-fatal MI or death from CHD | No                     | HR 0.89; 95% CI 0.75–1.05; P = 0.16 |
| ACCORD Lipid [8] | Fenofibrate 160 mg/day initially (later adjusted to eGFR) + simvastatin vs placebo + simvastatin | 5518 adults with type 2 diabetes aged 40–79 years if evidence of clinical CV disease, or aged 55–79 years if evidence of subclinical CV disease or at least 2 additional risk factors; LDL-C 60–180 mg/dl, and HDL-C <35 mg/dl for women and African-American patients (<50 mg/dl for all other groups) | First occurrence of major CV event, including non-fatal MI, non-fatal stroke, or death from CV causes | No                     | HR 0.92; 95% CI 0.79–1.08; P = 0.32 |
| BIP [43]      | Bezafibrate 400 mg/day vs placebo                                             | 3122 adults aged 45–74 years with a history of MI ≥ 6 months to <5 years before enrollment, and/or stable angina pectoris with total serum cholesterol 180–250 mg/dl, LDL-C <180 mg/dl (<160 mg/dl for patients <50 years of age), HDL-C <45 mg/dl, and TG ≤ 300 mg/dl; excluded patients using lipid-modifying drugs | Fatal MI, non-fatal MI, or sudden death | No                     | 9.4% risk reduction; P = 0.26 |

ACCORD, Action to Control Cardiovascular Risk in Diabetes; ACS, acute coronary syndrome; AIM-HIGH, Atherosclerosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes; BIP, Bezafibrate Infarction Prevention; CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; ER, extended release; FIELD, Fenofibrate Intervention and Event Lowering in Diabetes; HDL-C, high-density lipoprotein cholesterol; HPS2-THRIVE, Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; RR, rate ratio; TG, triglycerides.
lipid-lowering drug (mainly statins) at any point during the study than the fenofibrate arm (8%). A significant reduction in total CVD events was observed (HR 0.89; 95% CI 0.80–0.99; P = 0.035) and driven by reduction of non-fatal MI and coronary revascularization. In the Beza-
brate Infarction Prevention (BIP) study [43], patients with a history of MI and/or stable angina were randomized to bezafibrate or placebo. Although there was a 21% reduction in TG and an increase in HDL-C levels sustained for 5 years, there was no significant reduction in risk of the composite CV endpoint after a mean 6.2 years of follow-up (risk reduction 9.4%; P = 0.26). A subgroup analysis of the BIP study by TG level found that elevated baseline TG levels were significantly associated with a greater reduction in CV endpoints with bezafibrate, with a 39.5% reduction in the primary endpoint versus a 7.9% reduction in those with TG levels <150 mg/dL (relative risk [RR] 0.57; 95% CI 0.35–0.93) [43]. The ongoing Pema-
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5. OMEGA-3 fatty acids and CV risk

There has been interest in omega-3 fatty acids (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) for prevention of CVD due to a low CVD incidence in populations that consume high amounts of fatty fish [45]. Short-term studies have shown that omega-3 fatty acids (2–4 g/day) can reduce plasma TG levels [46–50]. A number of CV outcomes studies have been conducted in patients receiving omega-3 fatty acids (Table 3 and discussed below).

Table 3
Cardiovascular outcomes trials of omega-3 fatty acids.

| Trial                        | Intervention                      | Patient Population | Statin Use                                      | Primary Endpoint                                                                 | Primary Endpoint Met? | HR/OR/RR for Intervention |
|------------------------------|-----------------------------------|--------------------|------------------------------------------------|-----------------------------------------------------------------------------------|------------------------|-----------------------------|
| GISSI Prevenzione [51]       | 1 g omega-3 fatty acids (EPA:DHA in a 1:2 ratio) vs no supplement for secondary prevention | 11,324 patients within 3 months after MI; no lipid level–based inclusion criteria | Not established as preventive care standard at time of study | Co–primary endpoints: (1) death, non–fatal MI, and non–fatal stroke; (2) CV death, non–fatal MI, and non–fatal stroke | Yes | (1) RR 0.85; 95% CI 0.74–0.98 (2) RR 0.80; 95% CI 0.68–0.95 |
| OMEGA [10]                  | 1 g omega-3 fatty acids (DHA 380 mg + EPA 460 mg) vs 1 g olive oil for secondary prevention | 3851 patients who had experienced acute MI within 3–14 days of randomization; no lipid level–based inclusion criteria | >90% on statins at discharge post-MI | Sudden cardiac death | No | OR 0.95; 95% CI 0.56–1.60; P = 0.84 |
| VITAL [12]                  | 1 g omega-3 fatty acid (DHA 380 mg + EPA 460 mg) vs placebo for primary prevention | 25,871 men ≥50 years of age or women ≥55 years of age; no lipid level–based inclusion criteria | >35% on statins | MI, stroke, and CV death | No | HR 0.92; 95% CI 0.80–1.06; P = 0.24 |
| ASCEND [11]                 | Omega-3 fatty acids (DHA 380 mg + EPA 460 mg) vs placebo | 15,480 diabetic patients aged ≥40 years, but with no evidence of CV disease; no lipid level–based inclusion criteria | ≤75% on statins | Serious vascular events | No | RR 0.97; 95% CI 0.87–1.08; P = 0.55 |
| Trials of EPA alone         |                                    |                    |                                                 |                                                                                    |                        |                             |
| JELIS [60]                  | EPA 1.8 g/day + statin vs statin alone for primary and secondary prevention | 5859 men aged 40–75 years and 12,786 postmenopausal women up to 75 years with hypercholesterolemia (total cholesterol >251 mg/dL; corresponding to LDL-C >170 mg/dL) | 98% on statins | Major coronary events including sudden cardiac death, fatal and non-fatal MI, unstable angina pectoris, angioiasty, stenting, or coronary artery bypass grafting | Yes | HR 0.81; 95% CI 0.69–0.95; P = 0.011 |
| REDUCE-IT [14]              | Icosapent ethyl 4 g/day + statin vs placebo + statin | 8179 adults aged ≥45 years with established CV disease or ≥50 years with type 2 diabetes and ≥1 additional CV event risk factor; TG 135–499 mg/dL, and LDL-C 41–110 mg/dL | >99% on statins | Composite of CV death, non-fatal MI, non-fatal stroke, coronary revascularization, or unstable angina in a time–to–event analysis | Yes | HR 0.75; 95% CI 0.68–0.83; P < 0.001 |

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Table 3, A Study of Cardiovascular Events in Diabetes; CI, confidence interval; CV, cardiovascular; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; GISSI-Prevenzione, Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto miocardico; HR, hazard ratio; JELIS, Japan EPA Lipid Intervention Study; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; OMEGA, Randomized, Placebo-Controlled Trial to Test the Effect of Highly Purified Omega-3 Fatty Acids on Top of Modern Guideline-Adjusted Therapy After Myocardial Infarction; OR, odds ratio; REDUCE-IT, Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial; RR, rate ratio; TG, triglycerides; VITAL, Vitamin D and Omega-3 Trial.
(DHA 380 mg + EPA 460 mg) or placebo, in addition to standard-of-care treatment. There was no difference between treatment arms in the rate of the primary endpoint of sudden cardiac death (1.5%, both groups; odds ratio [OR] 0.95; 95% CI 0.56–1.60; P = 0.84). In A Study of Cardiovascular Events in Diabetes (ASCEND) [11], patients with diabetes received combination omega-3 fatty acids (DHA 380 mg + EPA 460 mg) or placebo. After a mean follow-up of 7.4 years, there was no difference in occurrence of serious vascular events (8.9%, omega-3 fatty acid group, 9.2%, placebo; RR 0.97; 95% CI 0.87–1.08; P = 0.55). Most recently, in the Vitamin D and Omega-3 Trial (VITAL), patients received 1 g/day of combination omega-3 fatty acids (DHA 380 mg + EPA 460 mg), vitamin D₃ supplementation, or placebo [12,13]. After 5.3 years of follow-up, neither the omega-3 fatty acid product nor vitamin D₃ was associated with a significantly lower incidence of major CV events (HR 0.97; 95% CI 0.85–1.12; P = 0.69). Most recently, the Outcomes Study to Assess Statin Residual Risk Reduction With Epanova in High CV Risk Patients With Hypertriglyceridemia (STRENGTH) trial [56], a phase 3 study of combination omega-3 carboxylic acids (4 g/day EPA + DHA), was discontinued prior to completion given that the drug was unlikely to demonstrate any clinical benefit among patients with dyslipidemia (TG levels ≥180 mg/dL and <500 mg/dL; HDL-C <42 mg/dL in men or <47 mg/dL in women) considered to be at high risk for future CV disease events [56–58].

Thus, the collective clinical data do not support the efficacy of DHA + EPA combination omega-3 fatty acids for ASCVD event risk reduction. As with most studies of fibrates and niacin, these DHA + EPA studies, with the exception of STRENGTH, did not specifically enroll patients with hypertriglyceridemia. In addition, doses of omega-3 fatty acids were generally low (<1 g/day), and may have been inadequate for CV event risk reduction. However, the discontinued STRENGTH trial did enroll patients with elevated TG levels, and employed a higher dose of 4 g/day EPA + DHA, yet still failed to demonstrate benefit [56–58]. The ongoing Omega-3 Fatty Acids in Elderly Patients With Myocardial Infarction (OMEMI) study will provide additional insights into 1.8 g/day DHA + EPA combination omega-3 fatty acids in statin-treated patients for reduction of persistent CV event risk specific to the elderly population [59].

5.2. CV outcomes studies of EPA-only omega-3 fatty acids

Studies of purified EPA in combination with statins have yielded more favorable results (Table 3). The open-label Japan EPA Lipid Intervention Study (JELIS) included 18,645 patients with hypercholesterolemia [60]. Patients received EPA 600 mg three times daily on a background of pravastatin 10 mg or simvastatin 5 mg. After 4.6 years of follow-up, EPA plus statin demonstrated a 19% reduction in the primary CV composite endpoint of major coronary events versus statin alone in the total study population (HR 0.81; 95% CI 0.69–0.95; P = 0.011); however, this remained statistically significant only for secondary prevention and not primary prevention. In addition, the only individual endpoint that reached statistical significance was hospitalization for unstable angina (HR 0.72; 95% CI 0.55–0.95, Fig. 1) [60]. JELIS was restricted to a Japanese population and thus may not be generalizable to other populations. Additional limitations include the open-label design, very low doses of background statin therapy, and use of a relatively low EPA dose (1.8 g/day).

The recently published multicenter, international study REDUCE-IT investigatedicosapent ethyl (high-purity EPA) 2 g twice daily versus placebo in patients with TG levels 135–499 mg/dL who were either ≥45 years of age with established CVD or ≥50 years of age with type 2 diabetes and at least one additional CV risk factor [14]. This was an aggressively statin-treated population with mean baseline LDL-C level of 75 mg/dL. After a median 4.9 years of follow-up, a primary composite CV endpoint (defined as CV death, non-fatal MI, non-fatal stroke, coronary revascularization, or unstable angina) occurred in 17.2% of patients in the icosapent ethyl group versus 22.0% in the placebo group (HR 0.75; 95% CI 0.68–0.83; P < 0.001; Fig. 2). Similar results were seen for the key secondary endpoint of CV death, non-fatal MI, or non-fatal stroke, which occurred in 11.2% of patients in the icosapent ethyl group versus 14.8% in the placebo group (HR 0.74; 95% CI 0.65–0.83; P < 0.001).

Overall, icosapent ethyl reduced CV deaths by 20% compared with placebo. Among patients enrolled in REDUCE-IT in the United States, there was a significant 30% and 34% relative risk reduction in all-cause and CV-related mortality, respectively, in the icosapent ethyl group compared with the placebo group [61].

REDUCE-IT was the first international outcomes study of a lipid-lowering agent to demonstrate significant CV event risk reduction when targeting persistent risk beyond LDL-C lowering in statin-treated patients. As a result, several leading health authorities issued guideline updates incorporating REDUCE-IT findings, and the US Food and Drug Administration approved icosapent ethyl as an adjunct to statin therapy to reduce the risk of MI, stroke, coronary revascularization, and unstable angina requiring hospitalization in adult patients with elevated TG levels (≥150 mg/dL) and established CVD or diabetes mellitus and two or more additional risk factors for CVD. Health Canada has also recently approved icosapent ethyl for all five major adverse CV events, including CV death, as part of the prespecified REDUCE-IT composite endpoint. The American Diabetes Association, the (US) National Lipid Association, and the European Society of Cardiology and European Atherosclerosis Society all recommend that addition of icosapent ethyl be considered in high-risk patients who have TG levels 135–499 mg/dL despite statin treatment [62–64]. The American Heart Association issued a Science Advisory stating that the results of REDUCE-IT support use of icosapent ethyl for reducing ASCVD risk in high-risk patients with hypertriglyceridemia on statin therapy [65]. The effectiveness of EPA treatment in REDUCE-IT,

Table 3. Clinical Endpoints and Hazard Ratio with 95% Confidence Interval

| Clinical Endpoint | Hazard Ratio with 95% CI | P-value |
|-------------------|-------------------------|---------|
| Sudden cardiac death¹ | 1.00 | 0.736 |
| Fatal MI¹ | 0.995 |
| Non-fatal MI¹ | 0.963 |
| Unstable angina¹ | 0.321 |
| CABG or PTCA¹ | 0.338 |
| Sudden cardiac death² | 1.00 |
| Fatal MI² | 0.400 |
| Non-fatal MI² | 0.967 |
| Unstable angina² | 0.421 |
| CABG or PTCA² | 0.150 |
| Stroke | 0.019² |
| 0.019² | 0.019² |
| 0.243 | 0.785 |
coupled with the discontinuation of the STRENGTH trial given that the EPA+DHA carboxylic acid compound used was deemed unlikely to demonstrate a benefit in patients, suggest that these effects may be specific to EPA, rather than a class effect of omega-3 fatty acids [57,61]. The clinical benefit seen with icosapent ethyl in REDUCE-IT was achieved regardless of baseline or on-treatment TG levels [14]. Similarly, the relatively modest decrease in TG levels in JELIS does not fully explain the observed clinical benefit of EPA treatment [60]. A recent meta-analysis of omega-3 fatty acid studies including REDUCE-IT supported a reduction in the risk of CVD endpoints [66]; however, a meta-analysis of TG-lowering treatments suggested that the CVD risk reduction associated with TG level lowering alone was relatively modest after exclusion of REDUCE-IT [67]. While elevated TG levels have been identified in some studies as an independent CVD risk factor [68,69], there is some evidence to the contrary. For example, another recent meta-analysis found that while an elevated TG level in patients with type 2 diabetes was associated with an increased risk of CVD, this association was lost after adjusting for other blood lipid parameters [70]. In REDUCE-IT, changes in EPA levels, not in lipid biomarker and inflammatory parameters, accounted for most of the study’s relative risk reduction for the primary and secondary endpoints [71]. Nonetheless, patients in REDUCE-IT with elevated TG levels and the associated high risk of ASCVD events were shown to benefit from EPA treatment. Taken together, this suggests that pleiotropic effects of EPA beyond TG lowering may contribute to CV event risk reduction.

The open-label, parallel-group Randomized Trial for Evaluation in Secondary Prevention Efficacy of Combination Therapy–Statin and Eicosapentaenoic Acid (RESPPECT-EPA) [72] and the Effect of Vascepa on Improving Coronary Atherosclerosis in People with High Triglycerides Taking Statin Therapy (EVAPORATE) trial [73] will provide additional insights into the role of EPA in statin-treated patients for reduction of persistent CV event risk and progression of coronary atherosclerosis, respectively. A 9-month interim analysis of EVAPORATE showed that icosapent ethyl at 4 g/day did not reduce progression of low attenuation plaque volume (74% vs 94%; P = 0.47) or fibrofatty plaque volume (87% vs 25%; P = 0.65) versus placebo, respectively (n = 30, icosapent ethyl; n = 37, placebo) [74]. However, icosapent ethyl did reduce progression of total plaque versus placebo (15% vs 26%; P < 0.001). The study is designed to conclude after 18 months of therapy [74].

6. Pleiotropic effects of EPA

Putative pleiotropic effects of EPA beyond TG lowering include reduction of inflammatory markers (e.g., high-sensitivity C-reactive protein) and inflammatory cytokines [46,47,75]. In addition, EPA has been shown to have beneficial effects on endothelial function, oxidative stress, foam cell formation, plaque formation/progression, cholesterol crystal formation and plaque rupture, platelet aggregation, and thrombus formation (Fig. 3) [75,76]. These collective effects may attenuate development and progression of atherosclerotic plaque.

The possible mechanism underlying these effects may involve EPA acting as a competitive inhibitor of arachidonic acid (AA) for cyclooxygenase and lipoxigenase enzymes [77]. This competitive inhibition results in EPA-derived compounds with slightly different structures than AA-derived compounds and, importantly, less potent inflammatory effects (Fig. 4) [78]. Resolvins are a family of molecules that function as an “off switch” for inflammation, and AA and EPA both give rise to different specialized pro-resolvin mediators: AA is a precursor for lipoxins LxA4 and LXB4, whereas EPA is a precursor for E-series resolvins, RvE1 and RvE2 [79,80]. EPA can also compete with AA for incorporation into membrane phospholipids [81]. Thus, increasing plasma content of EPA may play a role in creating a less inflammatory environment, potentially impacting development and severity of inflammatory diseases, including atherosclerosis and other CVDs [75,77,81]. In addition, whereas AA has been shown to promote activity of genes in the pro-inflammatory NF-κB pathway [82], EPA downregulates expression of inflammatory cytokines and the NF-κB pathway [77,83]. EPA has a more potent effect on this gene expression than DHA, a precursor of D-series resolvins, protectins, and maresins [80], or combinations of DHA+EPA [83]. Consistent with data supporting the potential pleiotropic effects of EPA, a recent meta-analysis of 24 TG-lowering clinical trials (including 13 omega-3 fatty acid trials) noted that the magnitude of lipid profile reduction did not fully account for the CV benefit of EPA therapy [67].

The anti-inflammatory effects of EPA and other omega-3 fatty acids may have potential for mitigating the symptoms of the novel 2019 coronavirus (COVID-19) infection. The production of resolvins and protectins by omega-3 fatty acids, as well as reducing reactive oxygen species and pro-inflammatory cytokines, such as tumor-necrosis factor-α and interleukin-1β, –6, and –8, have been shown to have a role in ameliorating outcomes in lung infection [84,85]. At least three clinical trials designed to investigate the effects of icosapent ethyl on inflammatory markers in patients with COVID-19 infection and the potential for prevention in high-risk individuals are ongoing (NCT04505098 [86], NCT04412018 [67], and NCT04460651 [88]). In addition, the efficacy of EPA free fatty acid gastro-resistant capsules is being evaluated in hospitalized patients with confirmed SARS-CoV-2 viral pneumonia (NCT04335032 [89]).

7. Discussion and conclusions

TG biochemistry and observational data support elevated TG levels as an ASCVD risk marker, and suggest a potentially causative role. Despite
this, many studies of TG-lowering modalities including niacin, fibrates, and DHA+EPA combination omega-3 fatty acids failed to demonstrate CV event risk reduction. Among factors that may have impacted CV outcomes trial results are lack of enrollment of hypertriglyceridemic patients and lack of focus on persistent TG-related CV event risk. Nonetheless, subgroup analyses from several of these studies have been hypothesis-generating, suggesting potential benefit to TG level reduction in patients with hypertriglyceridemia and providing clinical support for targeting this population, as in REDUCE-IT. In fact, a meta-analysis of 24 TG-lowering clinical trials, which included REDUCE-IT, concluded that lowering TG levels was associated with a lower risk of major vascular events, even after adjusting for lowering LDL-C [67]. The effect of this meta-analysis was mostly powered by the REDUCE-IT trial. Another recent meta-analysis including REDUCE-IT concluded that data support routine dietary supplementation with omega-3 fatty acids to prevent vascular events and mortality and improve cardiometabolic risk factors.
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