TRIGLYCERIDES, ATHEROSCLEROSIS, AND CARDIOVASCULAR OUTCOME STUDIES: FOCUS ON OMEGA-3 FATTY ACIDS

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ABSTRACT

Despite improved atherosclerotic cardiovascular disease (ASCVD) outcomes with statin therapy, residual risk remains. Recent genetic insights provide further compelling evidence that triglycerides are in the causal pathway for the development of atherosclerosis, thereby renewing interest in targeting triglycerides to improve ASCVD outcomes. Fibrates, niacin, and omega-3 fatty acids (OM3FAs) are 3 classes of triglyceride-lowering drugs. Outcome studies with triglyceride-lowering agents have been inconsistent. With regard to OM3FAs, the Japan Eicosapentaenoic Acid (EPA) Lipid Intervention Study (JELIS) showed that EPA significantly reduced major coronary events in statin-treated hypercholesterolemic patients. Regarding other agents, extended-release niacin and fenofibrate are no longer recommended as statin add-on therapy (by some guidelines though not all) because of the lack of convincing evidence from outcome studies. Notably, subgroup analyses from outcome studies have generated the hypothesis that triglyceride lowering may provide benefit in statin-treated patients with persistent hypertriglyceridemia. Two ongoing outcome studies are testing this hypothesis in high-risk, statin-treated patients with triglyceride levels 200–500 mg/dL: the Reduction of Cardiovascular Events with EPA-Intervention Trial (REDUCE-IT) is evaluating EPA (icosapent ethyl) and the Statin Residual Risk Reduction With Epanova in High CV Risk Patients With Hypertriglyceridemia study (STRENGTH) is evaluating omega-3-carboxylic acids (EPA plus docosahexaenoic acid). These studies will determine the role of triglyceride lowering in statin-treated patients with high-dose prescription OM3FAs in terms of improved ASCVD outcomes.

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Abbreviations

AACE = American Association of Clinical Endocrinologists; ACCORD = Action to Control Cardiovascular Risk in Diabetes; AIM-HIGH = Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes; apo = apolipoprotein; ASCEND = A Study of Cardiovascular Events in Diabetes; ASCVD = atherosclerotic cardiovascular disease; BIP = Bezafibrate Infarction Prevention; CHD = coronary heart disease; CHERRY = Combination Therapy of Eicosapentaenoic Acid and Pitavastatin for Coronary Plaque Regression Evaluated by Integrated Backscatter Intravascular Ultrasonography; CI = confidence interval; COMPASS = A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Volanesorsen Administered Subcutaneously to Patients with Hypertriglyceridemia; CV = cardiovascular; CVD = cardiovascular disease; DHA = docosahexaenoic acid; DO-IT = Diet and Omega-3 Intervention Trial; EPA = eicosapentaenoic acid; FDA = Food and Drug Administration; FIELD = Fenofibrate Intervention and Event Lowering in Diabetes; GISSI-HF = GISSI-Heart Failure; GISSI-P = GISSI-Prevenzione; 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; IMPROVE-IT = Reduction of Outcomes: Vytorin Efficacy International Trial; JELIDS = Japan Eicosapentaenoic Acid Lipid Intervention Study; LDL = low-density lipoprotein; LDL-C = low-density lipoprotein cholesterol; MCE = major coronary events; MI = myocardial infarction; NLA = National Lipid Association; Non-HDL-C = non-high-density lipoprotein cholesterol; OM3FAs = omega-3 fatty acids; ORIGIN = Outcome Reduction with an Initial Glargine Intervention study; PROMINENT = Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Diabetic Patients; R&P = Risk & Prevention study; REDUCE-IT = Reduction of Cardiovascular Events with EPA-Intervention Trial; RESPECT-EPA = Randomized Trial for Evaluation in Secondary Prevention Efficacy of Combination Therapy–Statin and Eicosapentaenoic Acid; RR = rate ratio; STRENGTH = Statin Residual Risk Reduction With Epanova in High CV Risk Patients With Hypertriglyceridemia study; SU.FOL.OM3 = Supplementation en Folates et en Oméga 3; VA-HIT = Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial; VITAL = Vitamin D and Omega-3 Trial; VLDL = very-low-density lipoprotein.
INTRODUCTION

The atherogenic potential of triglyceride-rich lipoproteins was postulated nearly 70 years ago by Moreton; Zilversmit later corroborated the concept in a comprehensive review of postprandial lipid effects in atherogenesis (1, 2). Mechanisms by which triglyceride-rich lipoproteins may contribute to atherosclerosis have been recently reviewed and are shown in Figure 1 (3, 4). Epidemiologic studies worldwide in multiple cohorts have consistently demonstrated the direct relationship between serum triglyceride levels and risk of coronary heart disease (CHD), which in many cases was found to be independent of other cardiovascular (CV) risk factors (5-13). Meta-analyses provide supportive evidence for the association between elevated triglyceride levels and CV disease (CVD) risk (14, 15). In a meta-analysis of 29 prospective studies involving more than 260,000 subjects, CHD risk was 72% higher among patients with the highest versus lowest tertile of triglycerides (15). An updated meta-analysis found risk of CV mortality and all-cause mortality increased by 13% and 10%, respectively, for each 88.5 mg/dL increment in triglycerides (16). Fasting triglyceride levels were identified to predict short- and long-term CVD risk after acute coronary syndrome in statin-treated patients (17). Recently, in patients with established CHD, higher triglyceride levels (≥150 mg/dL) were independently associated with increased 22 year mortality (18). Non-fasting triglyceride levels have also been associated with increased risk of ischemic stroke (19).
Although interest in targeting triglycerides for improving CV outcomes has been modest, recent compelling genetic data suggesting that triglycerides are in the causal pathway of atherosclerosis has renewed interest in this topic. Susceptibility loci for CHD identified in genome-wide association studies include genes involved in triglyceride metabolism (20, 21). Linear regression and multivariate analyses of these loci demonstrate that both low-density lipoprotein cholesterol (LDL-C) and triglycerides, but not high-density lipoprotein cholesterol (HDL-C), are significantly, independently, and causally related to CHD risk (22, 23). Mendelian randomization studies also demonstrate that factors involved in triglyceride metabolism are causally related to atherosclerosis and CHD risk (24-27). In a Mendelian randomization meta-analysis of 17 studies, single nucleotide polymorphisms of alleles independently associated with triglycerides increased CHD risk by 61% for each 1-log increment in triglycerides (28). Mutational analyses also demonstrate associations of triglycerides with atherosclerosis and CVD (29, 30). Loss-of-function mutations in APOC3 encode an apolipoprotein that leads to decreases in triglyceride levels and CHD risk (31-33), whereas mutations in APOA5 encode an apolipoprotein that leads to increases in triglyceride levels and CHD risk (34). It has recently been shown that mutations in the gene encoding angiopoietin-like 4, a modulator of triglyceride metabolism, result in lower triglyceride levels and lower risk of coronary artery disease (35, 36).
This increasing body of evidence suggests that targeting hypertriglyceridemia may improve atherosclerotic CVD (ASCVD) outcomes. This article focuses on available and ongoing CV outcome studies testing triglyceride-lowering agents.

TRIGLYCERIDES AND MECHANISMS OF ATHEROSCLEROSIS

Triglycerides are transported from the liver and intestines by very-low-density lipoprotein (VLDL) and chylomicrons, respectively, and delivered to peripheral tissues to meet energy needs (37). Once the triglyceride core of these triglyceride-rich lipoproteins is hydrolyzed, the resulting VLDL and chylomicron become relatively cholesterol enriched. Because triglycerides do not accumulate in foam cells, the association of plasma triglycerides and ASCVD may be due to these remnant lipoproteins. Remnants have the potential to accumulate in the arterial endothelium, where they may be taken up by macrophages, promote foam cell formation, and, ultimately, fatty streak formation and subsequent plaque progression (37, 38). A unique aspect of these remnants compared with LDL particles is that they do not require oxidative modification to be taken up by arterial macrophages; they are also associated with a greater degree of inflammation (26). Hypertriglyceridemia is also associated with higher concentrations of small dense LDL particles (which may be more atherogenic than other LDL particles), reduced HDL particle and apolipoprotein (apo)A-I concentrations, and greater concentrations of apoC-III–containing particles (39). Changes in the structure of these lipoprotein particle subclasses may potentially accelerate atherosclerotic processes. Additionally, lipoprotein particles with higher triglyceride content may be more readily oxidizable.
thereby enhancing their atherogenic potential. Furthermore, triglycerides may have more direct effects on inflammatory responses. Lipoprotein lipase at the endothelial cell surface and within the subendothelial space hydrolyzes remnant triglycerides and generates proinflammatory mediators, including free fatty acids (26, 40).

**TRIGLYCERIDE-LOWERING AGENTS**

After diet and exercise, statins are the main approach to treatment for eligible patients who require ASCVD risk reduction, as reflected in current national guidelines (41-44). While these agents primarily reduce LDL-C levels by inhibiting HMG CoA reductase and by upregulating LDL receptor expression, they can also lower triglyceride levels by approximately 10–40% (depending on statin type, dose, and baseline triglyceride levels) (45-47). Nonetheless, many patients are left with hypertriglyceridemia despite statin therapy. Triglyceride-lowering treatment options include prescription omega-3 fatty acids, fibrates, and niacin. Their place in clinical practice is well established: practically all current guidelines advocate the use of a triglyceride-lowering agent for patients with severe hypertriglyceridemia (triglyceride levels ≥500 mg/dL) to primarily reduce the risk of pancreatitis (41-44, 48). Furthermore, the American Association of Clinical Endocrinologists (AACE) and the National Lipid Association (NLA) both provide recommendations for treating high triglyceride levels (200–499 mg/dL) with a triglyceride-lowering agent, specifically addressing increased non-HDL-C as an approach for managing atherogenic dyslipidemia (43, 44). For those with diabetes, as with others at high ASCVD risk, the AACE recommends considering treatment of
patients to non-HDL-C goals and also suggests reducing triglyceride levels to <150 mg/dL with prescription omega-3 fatty acids, fibrates, niacin, and statins as appropriate (44). While recent updates to product labeling removed the indication for use of niacin or fibrates in combination with statins because of lack of data demonstrating a benefit on CV outcomes of either agent as adjuncts to statin therapy, their roles in clinical practice are still relevant: niacin and fibrates are still recommended for use in combination with statins in AACE guidelines when lipid targets cannot be achieved with a statin alone (44) and by the NLA, particularly in patients with both elevated triglyceride levels and low HDL-C (43, 44, 49, 50). The Endocrine Society recommends fibrates, niacin, and omega-3 fatty acids alone or in combination with statins for patients with moderate to severe triglyceride levels (48). Other patients for whom triglyceride-lowering agents such as niacin, fibrates, and omega-3 fatty acids are used include those with high triglyceride levels and low HDL-C who are unable to take statins and those who continue to have CV events despite high-dose statins and need further lipid and/or lipoprotein level improvements.

Among the various agents that are effective for lowering triglyceride levels, omega-3 fatty acids have a favorable tolerability profile. FDA-approved prescription omega-3 fatty acids are high-purity formulations; most contain a mixture of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (51-53), and one formulation contains only the ethyl ester of EPA (icosapent ethyl) (54). In clinical studies, gastrointestinal adverse events were reported at incidences ≥3% with the DHA-containing products (51-53),
whereas arthralgia (2.3%) was the only adverse event with icosapent ethyl reported more frequently than with placebo (1.0%) (54). Treating high triglycerides with DHA-containing omega-3 fatty acid products has also been associated with increases in LDL-C levels in clinical studies (51-53, 55-58), which have not been observed with the EPA-only product when compared with placebo (54, 59, 60). EPA may also have beneficial effects on mechanisms involved in the development and progression of atherosclerosis that extend beyond triglyceride lowering (61, 62).

**CARDIOVASCULAR OUTCOME STUDIES**

**Fibrates**

Fibrates with and without concomitant statin therapy have been evaluated in several outcome studies (**Table 1**) (63-67). In patients without concomitant statin therapy, the Helsinki Heart Study evaluated primary prevention with gemfibrozil 1200 mg/day in middle-aged men with non-HDL-C levels ≥200 mg/dL (63). Baseline triglyceride levels averaged 176 mg/dL. Gemfibrozil reduced non-HDL-C levels by 14% and triglyceride levels by 43%, and raised HDL-C levels by 10%. After a mean follow-up of 60.4 months, gemfibrozil significantly reduced cardiac endpoints by 34% (95% confidence interval [CI]: 8%–53%; P<0.05). In the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT), gemfibrozil 1200 mg/day was evaluated for secondary prevention of CHD in men with low HDL-C levels (≤40 mg/dL) (64). Eligibility also required LDL-C levels ≤140 mg/dL and triglyceride levels ≤300 mg/dL. At baseline, triglyceride levels averaged 161 mg/dL. Compared with placebo, gemfibrozil raised

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mean HDL-C levels by 6% and lowered triglyceride levels by 31%. After a median follow-up of 5.1 years, gemfibrozil reduced the primary outcome of nonfatal myocardial infarction (MI) or CHD death by 22% compared with placebo (95% CI: 7%–35%; \(P=0.006\)).

The Bezafibrate Infarction Prevention (BIP) study evaluated secondary prevention with bezafibrate 400 mg/day in patients with LDL-C levels \(\leq 180\) mg/dL, HDL-C levels \(\leq 45\) mg/dL, and triglyceride levels \(\leq 300\) mg/dL (65). At baseline, mean triglyceride levels were 145 mg/dL. The most marked changes in lipid levels with bezafibrate were an 18% increase in HDL-C levels and 21% decrease in triglyceride levels. After a mean of 6.2 years, the primary endpoint of MI and sudden death did not differ significantly between bezafibrate and placebo (13.6% vs 15.0%; \(P=0.26\)). However, a hypothesis-generating post hoc analysis of the BIP study demonstrated that bezafibrate significantly reduced the risk of the primary endpoint events of MI and sudden death in the subgroup with high baseline triglyceride levels (\(\geq 200\) mg/dL; rate ratio [RR]: 0.57; 95% CI: 0.35–0.93; \(P=0.02\)) (65). All-cause mortality risk, after 20 years of follow-up from the BIP study, was reduced by 25% in patients with hypertriglyceridemia (\(\geq 200\) mg/dL; hazard ratio [HR]: 0.75; 95% CI: 0.60–0.94; \(P=0.012\)) (68).

In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, micronized fenofibrate 200 mg/day was assessed in patients with type 2 diabetes with or without previous CVD (66). At study entry, subjects were not taking and did not have...
any clear indicated need for lipid-modifying therapy, and had median triglyceride levels of 154 mg/dL. Within 4 months of initiating treatment, fenofibrate lowered LDL-C levels by 12% and triglyceride levels by 29%, and raised HDL-C levels by 5% compared with placebo. By the end of the study, 17% of patients in the placebo group and 8% of those in the fenofibrate group were prescribed additional lipid-lowering therapy, mostly statins. After a median 5-year follow-up, fenofibrate did not significantly reduce the primary endpoint of nonfatal MI and CHD death (HR: 0.89; 95% CI: 0.75–1.05; P=0.16). In a prespecified subgroup analysis from the FIELD study, fenofibrate demonstrated a trend for reducing the primary endpoint of total CVD events compared with placebo in patients with triglyceride levels ≥150.6 mg/dL (P=0.07) (66).

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study was designed to evaluate a fibrate as add-on to statin therapy. ACCORD investigated the effect of intensive blood glucose therapy in combination with either treatment of blood pressure or plasma lipids in type 2 diabetes patients (67). In ACCORD-Lipid, patients were started on open-label simvastatin and then 1 month later initiated blinded treatment with fenofibrate or placebo. Forty percent of the study cohort was naïve to statin therapy at baseline, and therefore baseline lipid levels do not reflect those stabilized by statin therapy (mean LDL-C 100 mg/dL, mean HDL-C 38 mg/dL, median triglycerides 162 mg/dL). During follow-up, the mean daily dose of simvastatin was 22.3 mg. Lipid levels were not re-measured when fenofibrate was initiated. At the first measurement at 4 months, triglyceride levels had declined to approximately 150 mg/dL in the simvastatin...
(+placebo) group and then continued to decline further over time. By the end of the study, the fenofibrate group had a greater decrease in triglyceride levels (26% vs 10%), whereas mean LDL-C and HDL-C levels decreased by similar amounts in both treatment arms. After a mean follow-up of 4.7 years, add-on fenofibrate did not reduce the primary outcome of nonfatal MI, nonfatal stroke, or CV death compared with placebo (HR: 0.92; 95% CI: 0.79–1.08; \( P = 0.32 \)). In a prespecified subgroup analysis of ACCORD-Lipid conducted in patients with high baseline triglyceride levels (≥204 mg/dL) and low HDL-C levels (≤34 mg/dL), the incidence of the primary endpoint of nonfatal MI, nonfatal stroke, or CV death tended to be lower in fenofibrate-treated patients compared with those receiving placebo (12.4% vs 17.3%; \( P = 0.057 \) for interaction) (67, 69). A post-trial follow-up of ACCORD-Lipid participants for approximately 9 years did not alter the original findings of a lack of effect (70). In considering these results, it may be important to recognize that baseline triglyceride levels were measured before statin therapy was initiated in both study arms, and therefore did not represent a true baseline level at the time fenofibrate or placebo was initiated.

A meta-analysis of the major fibrate trials evaluated the impact of fibrate therapy on CV outcomes in patients with dyslipidemia, which was defined as triglyceride levels ≥204 mg/dL and HDL-C levels ≤34 mg/dL (71). Notably, fibrates significantly reduced the odds of CHD by 35% (95% CI: 22%–46%) in patients with dyslipidemia, but non-significantly reduced the odds of CHD by 6% (95% CI: −5%–16%) in those without dyslipidemia (71).
Niacin

Two recent studies evaluated extended-release niacin as add-on to statin therapy (Table 1) (72, 73). The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) study evaluated extended-release niacin 1500 to 2000 mg/day as add-on therapy to statins in patients with established CVD (72). Eligible patients had low HDL-C levels (<40 mg/dL for men and <50 mg/dL for women) and elevated to high triglyceride levels (150–400 mg/dL). Patients received simvastatin 40 mg/day initially, and then the dose was adjusted during the study to maintain LDL-C levels within the range of 40 to 80 mg/dL; ezetimibe 10 mg/day was added if needed to achieve this LDL-C range. Median triglyceride level was 162 mg/dL at baseline, and declined during the study to a greater extent in the niacin group than in the placebo group (31% vs 10% at 3 years). The trial was stopped after a mean follow-up of 3 years due to perceived futility; there was no difference in the primary endpoint of major vascular events between the niacin and placebo groups (HR: 1.02; 95% CI: 0.87–1.21; P=0.79). In a subgroup analysis of AIM-HIGH in patients with high baseline triglyceride levels (≥200 mg/dL) and low HDL-C levels (<32 mg/dL), niacin significantly reduced major vascular events by 36% compared with a statin alone (HR: 0.64; P=0.032) (74).

The Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) evaluated extended-release niacin with the anti-flushing agent...
laropiprant as add-on to statin therapy in patients with a history of MI, cerebrovascular disease, peripheral arterial disease, or diabetes with evidence of symptomatic CHD (73). Notably, the study did not utilize lipid inclusion criteria. During the run-in phase, patients received simvastatin 40 mg/day with added ezetimibe if total cholesterol level was ≥135 mg/dL. After LDL-C was stabilized, patients were randomized to study treatment. Median baseline triglyceride level was 108 mg/dL, markedly lower than in other outcome studies and well within the normal range (75). After a median follow-up of 3.9 years, the study treatment did not reduce the primary endpoint of major vascular events (RR: 0.96; 95% CI: 0.90–1.03; P=0.29) (73).

These negative results of AIM-HIGH and HPS2-THRIVE did not support findings from smaller studies, which had suggested that niacin can improve angiographic endpoints and reduce CV events in statin-treated patients with low HDL-C levels and CHD (76, 77).

**Omega-3 Fatty Acids**

Omega-3 fatty acids have been evaluated in several outcome studies with mixed results (Table 2) (78-86). The GISSI-Prevenzione (GISSI-P) trial used a 2 x 2 factorial design to evaluate omega-3-acid ethyl esters 1 g/day versus vitamin E 300 mg/day, both, or none (control) in patients with recent MI (79). Baseline triglyceride levels averaged 162 mg/dL; treatment with omega-3-acid ethyl esters reduced triglyceride levels compared with control, and yet did not affect LDL-C or HDL-C levels. After a mean follow-up of 3.5 years, the study treatment did not reduce the primary endpoint of major vascular events (RR: 0.96; 95% CI: 0.90–1.03; P=0.29) (73).
years, omega-3-acid ethyl esters significantly reduced risk of the primary endpoint of death, nonfatal MI, and nonfatal stroke by 15% (95% CI: 2%–26%; \( P=0.02 \)) by four-way analysis. Of note, statin use at trial initiation was low, as it was not yet supported by definitive data—statins were used by a mere 5% of patients at baseline, although 46% of patients were using statins at study end.

In the GISSI-Heart Failure (GISSI-HF) study, treatment with omega-3-acid ethyl esters 1 g/day was evaluated in patients with chronic heart failure (80). Approximately 23% of patients were receiving statin therapy. Median baseline triglyceride level was 126 mg/dL and decreased only slightly during treatment. After a median follow-up of 3.9 years, omega-3-acid ethyl esters significantly reduced the co-primary endpoints of all-cause mortality by 9% (\( P=0.041 \)) and all-cause mortality or hospital admission due to CV reasons by 8% (\( P=0.009 \)) compared with placebo.

The JAPAN EPA Lipid Intervention Study (JELIS) compared EPA ethyl ester 1.8 g/day plus low-dose pravastatin or simvastatin versus statin alone in hypercholesterolemic patients (total cholesterol levels \( \geq 250 \text{ mg/dL} \), corresponding to LDL-C levels \( \geq 170 \text{ mg/dL} \)) with or without CHD (78). JELIS enrolled a total of 18,645 patients (primary prevention cohort, 14,981 patients; secondary prevention cohort, 3664 patients). Median triglyceride level at baseline was 153 mg/dL; mean LDL-C level was 181 mg/dL. After a mean follow-up of 4.6 years, EPA significantly reduced the risk of major coronary events (MCE) by 19% compared with statin therapy alone in the entire study population.

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(HR: 0.81; 95% CI: 0.69–0.95; \( P=0.011 \)) and in the secondary prevention cohort (HR: 0.81; 95% CI: 0.657–0.998; \( P=0.048 \)) (78). Although a similar risk reduction was observed in the primary prevention cohort, the effect did not reach statistical significance (\( P=0.132 \)). Overall, both treatment groups had similar reductions in LDL-C levels, whereas triglyceride levels were lowered by an additional 5% with EPA relative to placebo. Additionally, in a subgroup analysis of patients with TG levels ≥150 mg/dL and HDL-C <40 mg/dL, EPA treatment lowered the risk of MCE by 53% (HR: 0.47; 95% CI: 0.23–0.98; \( P=0.043 \)) (87).

Six additional CV outcome studies were conducted with omega-3 fatty acids containing EPA and DHA: they enrolled patients with recent MI (OMEGA) (81), history of MI (Alpha Omega) (82), previous CV or cerebrovascular disease (Supplementation en Folates et en Oméga 3 [SU.FOL.OM3]) (88), or high CV risk due to previous CV events or multiple risk factors (Diet and Omega-3 Intervention Trial [DO-IT] (84, 85), Outcome Reduction with an Initial Glargine Intervention study [ORIGIN] (83), and Risk & Prevention study [R&P] (86)). None of these studies demonstrated a significant improvement in the primary outcome compared with the control group.

When considering these failed omega-3 fatty acid outcome studies, it is important to recognize that most patients in each study were using statins; each study used lower doses of omega-3 fatty acids than those currently recommended to treat very high triglyceride levels (ie, 4 g/day); and each study enrolled study populations with mean or
median baseline triglyceride levels $\leq 150$ mg/dL. Multiple factors have been offered to explain the differences in outcomes results observed across the omega-3 fatty acid trials, including differences in patient populations, disease conditions, background fish intake, contemporary medical CV treatments, and use of composite CV outcomes (89-91).

**ONGOING OUTCOME STUDIES**

Although statins are well recognized to improve CV outcomes for primary and secondary prevention, residual CV risk remains (92). The concept of providing add-on therapy in statin-treated subjects to further reduce risk was further supported by the results of the recent Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), where the addition of ezetimibe to simvastatin significantly reduced major vascular events in patients with recent acute coronary syndromes despite excellent control (reaching the goal of LDL-C levels $<70$ mg/dL) with simvastatin alone (93).

Given the results of the currently available CV outcome studies with fibrates, niacin, and omega-3 fatty acids, the hypothesis that lowering triglyceride levels in patients with hypertriglyceridemia ($\geq 200$ mg/dL) can reduce CV risk has not yet been proven, though not tested adequately, particularly in statin-treated patients. Two large ongoing outcome studies are testing the triglyceride-lowering hypothesis in high-risk statin-treated patients with persistently high triglyceride levels (200–500 mg/dL). The Reduction of
Cardiovascular Events with EPA-Intervention Trial (REDUCE-IT; NCT01492361) is evaluating a highly purified EPA-only prescription product (icosapent ethyl). The Statin Residual Risk Reduction With Epanova in High CV Risk Patients With Hypertriglyceridemia study (STRENGTH; NCT02104817) is evaluating omega-3-carboxylic acids (EPA plus DHA). Both studies are using prescription drugs that have been approved by the US FDA at a dose of 4 g/day for use in a different hypertriglyceridemic patient population than is being studied in these CV outcome studies. The primary endpoint for both studies is a composite including CV death, MI, stroke, coronary revascularization, and hospitalization for unstable angina. Data from these trials will help to define whether lowering high triglyceride levels in statin-treated patients with high-dose prescription omega-3 fatty acid products can improve CV outcomes. The Randomized Trial for Evaluation in Secondary Prevention Efficacy of Combination Therapy–Statin and Eicosapentaenoic Acid (RESPECT-EPA) is another ongoing outcome study and is being conducted in Japan (UMIN000012069). RESPECT-EPA aims to confirm the benefits of high-purity EPA as an adjunct to statin therapy that were observed in JELIS, but in a secondary-only prevention population. Additional large omega-3 outcome studies underway include the Vitamin D and Omega-3 Trial (VITAL; NCT01169259) and A Study of Cardiovascular Events in Diabetes (ASCEND; NCT00135226). VITAL and ASCEND will provide results in 2016 to 2017. However, the omega-3 agents under investigation are low dose (below prescription dosing and more in line with omega-3 dietary supplements), contain both EPA and DHA, and are being administered concomitantly with either vitamin D (VITAL) or aspirin.
Another large outcome study, Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Diabetic Patients (PROMINENT), has been proposed in order to evaluate whether lowering triglycerides and increasing functional HDL with the novel and potent fibrate agent, pemafibrate, can reduce elevated CV risk in high-risk, statin-treated patients with diabetes mellitus.

The CV benefits of omega-3 fatty acids, particularly EPA, may extend beyond only triglyceride-lowering effects (61, 62). This may help explain why positive effects on CV outcomes were demonstrated in the JELIS study on top of statin therapy despite relatively small lipid changes (78). To this end, EPA has recently been shown to significantly reduce coronary plaque volume and increase plaque regression in the Combination Therapy of Eicosapentaenoic Acid and Pitavastatin for Coronary Plaque Regression Evaluated by Integrated Backscatter Intravascular Ultrasonography (CHERRY) study of approximately 200 CHD patients (94). Similar results on coronary plaque characteristics were also seen in a small study with EPA as an adjunct to statin therapy (95). Thus, differences between triglyceride-lowering agents in effects beyond triglyceride lowering may be reflected in the results of CV outcome studies.

Novel triglyceride-lowering agents are already appearing on the horizon. Recently, volanesorsen, a second-generation antisense APOC3 mRNA specifically designed to reduce levels of APOC3 mRNA, was evaluated in a phase 2 randomized trial of 57 patients with triglyceride levels 350 to 2000 mg/dL (mean, 581 mg/dL) (96).
administration once weekly for 13 weeks as monotherapy, volanesorsen dose-dependently reduced plasma apoC-III levels, with concomitant dose-dependent decreases in triglyceride levels and increases in HDL-C levels. Similar findings were reported in a second cohort on stable background fibrate therapy. Volanesorsen is currently being evaluated in a phase 3 trial (A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Volanesorsen Administered Subcutaneously to Patients with Hypertriglyceridemia [COMPASS]) enrolling participants with triglyceride levels >500 mg/dL. It may be worth noting that omega-3 fatty acid agents have also been shown to reduce plasma apoC-III levels, including levels in statin-treated patients (57, 97-101).

SUMMARY AND CONCLUSIONS

Residual CV risk may remain despite statin therapy. Thus, there is a need for add-on treatment options to help reduce this risk in appropriate high-risk patients (92). There is consistent epidemiologic data and compelling genetic evidence that triglyceride-rich lipoproteins are in the causal pathway of atherosclerosis and are associated with increased risk; treatment options that reduce triglyceride levels in addition to statin therapy may be warranted. The evidence from CV outcome studies of triglyceride-lowering agents has been mixed. Given the general lack of evidence for benefit with regard to CV outcomes, extended-release niacin and fenofibrate products are no longer recommended in product prescribing information for use as statin add-on therapy (49, 50). JELIS demonstrated that EPA provides benefit when added to statin therapy; the
relatively small lipid changes seen in the study suggest that EPA may have cardioprotective benefits independent of triglyceride lowering (78). Beyond JELIS, the data to date have not directly proven the hypothesis that lowering triglyceride levels in statin-treated patients with high triglyceride levels can reduce CV risk. The ongoing REDUCE-IT and STRENGTH outcome studies are the first trials to study high-dose prescription omega-3 fatty acid treatment in an at-risk patient population with high triglyceride levels; results should help clarify the potential role of high-dose prescription omega-3 fatty acid therapies as add-on options to statin therapy for reduction of residual CV risk in patients with persistent hypertriglyceridemia.

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79. GISSI-Prevenzione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the


integrated backscatter intravascular ultrasonography: a randomized controlled trial


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Figure 1. Proposed mechanisms of triglyceride-rich lipoproteins in atherosclerosis. Lipolysis of triglyceride-rich lipoproteins releases triglyceride-rich remnants, which increase inflammation, coagulation, and endothelial dysfunction in the vessel lumen and also cross the endothelium, leading to foam cell formation and plaque formation and progression. Adapted by permission from Macmillan Publishers Ltd: [Nature Reviews Cardiology] Watts GF, Ooi EM, Chan DC. Demystifying the management of hypertriglyceridaemia. Nat Rev Cardiol. 2013;10(11):648–661 (3).

Copyright © 2013. LPL, lipoprotein lipase; TRL, triglyceride-rich lipoproteins; TRL-R, triglyceride-rich lipoprotein remnants.
Table 1. Fibrate and Niacin Outcome Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>CV Risk Profile</th>
<th>N</th>
<th>Daily Intervention</th>
<th>Statin Use</th>
<th>Baseline TG Level</th>
<th>Effect on TG Level</th>
<th>Primary Outcome</th>
<th>Primary Outcome Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>HHS (63)</td>
<td>Men aged 40–55 years with non-HDL-C levels ≥200 mg/dL</td>
<td>4081</td>
<td>Gemfibrozil 600 mg BID</td>
<td>None</td>
<td>176 mg/dL (mean)</td>
<td>−43%</td>
<td>Fatal or nonfatal MI or cardiac death; mean f/u: 60.4 months</td>
<td>Decrease in frequency: 34.0% (95% CI: 8.2%–52.6%); P&lt;0.05; ARR: 1.4% (2.7% with gemfibrozil vs 4.1% with placebo)</td>
</tr>
<tr>
<td>VA-HIT (64)</td>
<td>Men aged &lt;74 years with CHD and HDL-C levels ≤40 mg/dL and TG levels ≤300 mg/dL</td>
<td>2531</td>
<td>Gemfibrozil 1200 mg/day</td>
<td>None</td>
<td>161 mg/dL (mean)</td>
<td>−31% at 1 year</td>
<td>Nonfatal MI or CHD death; median f/u: 5.1 years</td>
<td>Decrease in frequency: 22% (95% CI: 7%–35%); P=0.006; ARR: 4.4% (17.3% with gemfibrozil vs 21.7% with placebo)</td>
</tr>
<tr>
<td>BIP (65)</td>
<td>Age 45–74 years with prior MI and/or stable angina and HDL-C levels ≤45 mg/dL and TG levels ≤300 mg/dL</td>
<td>3090</td>
<td>Bezafibrate 400 mg/day</td>
<td>None</td>
<td>145 mg/dL (mean)</td>
<td>−21%</td>
<td>Fatal or nonfatal MI or sudden death; mean f/u: 6.2 years</td>
<td>Reduction in cumulative probability of endpoint at 6.2 years: 7.3%; P=0.24; ARR: NC° (13.6% with bezafibrate vs 15.0% with placebo)</td>
</tr>
<tr>
<td>FIELD (66)</td>
<td>Age 50–75 years with T2DM</td>
<td>9795</td>
<td>Micronized fenofibrate 200 mg QD</td>
<td>Added during study in 2547 patients</td>
<td>154 mg/dL (median)</td>
<td>−30% at 1 year</td>
<td>Nonfatal MI or CHD death; median f/u: 5 years</td>
<td>HR: 0.89 (95% CI: 0.75–1.05); P=0.16; ARR: 1.4%</td>
</tr>
<tr>
<td>ACCORD (67)</td>
<td>T2DM; age 40–79 years with CVD or age 55–79 y with ≥2 CV risk factors</td>
<td>5518</td>
<td>Fenofibrateb</td>
<td>Open-label simvastatin (mean dose: 22 mg)</td>
<td>162 mg/dL (median)</td>
<td>−26%</td>
<td>Nonfatal MI or stroke or CV death; mean f/u: 4.7 years</td>
<td>HR: 0.92 (95% CI: 0.79–1.08); P=0.32; ARR: NC° (2.2% with fenofibrate vs 2.4% with placebo)</td>
</tr>
<tr>
<td>AIM-HIGH (72)</td>
<td>Age ≥45 years</td>
<td>3414</td>
<td>Niacin ER</td>
<td>Simvastatin</td>
<td>162 mg/dL</td>
<td>−28%</td>
<td>Nonfatal MI or stroke or CV death or CV death; mean f/u: 4.7 years</td>
<td>HR: 1.02 (95% CI: 0.75–1.38)</td>
</tr>
</tbody>
</table>
with CVD, low HDL-C levels, and high TG levels (150–400 mg/dL)

<table>
<thead>
<tr>
<th>Study</th>
<th>Age/Duration</th>
<th>N/A</th>
<th>Dose of Niacin and/or Simvastatin</th>
<th>LDL-C Reduction</th>
<th>Outcome Measures</th>
<th>RR/ARR</th>
<th>Notes</th>
</tr>
</thead>
</table>
| HPS2-THRIVE (73)      | Age 50–80 years with CVD    | 25,673 | Niacin ER 2000 mg/day + laropiprant 40 mg/day | 108 mg/dL (median) | Nonfatal MI, coronary death, stroke, or revascularization; median f/u: 3.9 years | RR: 0.96 (95% CI: 0.90–1.03); P=0.29; ARR: NC (13.2% with niacin vs 13.7% with placebo) | HPS2-THRIVE = Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events; RD = rate ratio; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; NC = not calculated; QD = once daily; RR = rate ratio; T2DM = type 2 diabetes mellitus; TG = triglyceride; VA-HIT = Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial.  

ARR was calculated based on reported values for treatment groups and control/placebo groups for studies that reached statistical significance but was not calculated for studies that did not reach statistical significance for the primary endpoint.  

Dose of fenofibrate was 160 mg/day at start of trial, but starting in 2004, dose was adjusted according to glomerular filtration rate.

ACCORD = Action to Control Cardiovascular Risk in Diabetes study; ACS = acute coronary syndrome; AIM-HIGH = Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes study; ARR = absolute risk reduction; BID = twice daily; BIP = Bezafibrate Infarction Prevention study; CHD = coronary heart disease; CI = confidence interval; CV = cardiovascular; CVD = cardiovascular disease; ER = extended release; FIELD = Fenofibrate Intervention and Event Lowering in Diabetes study; f/u = follow-up; HDL-C = high-density lipoprotein cholesterol; HHS = Helsinki Heart Study; 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; NC = not calculated; QD = once daily; RR = rate ratio; T2DM = type 2 diabetes mellitus; TG = triglyceride; VA-HIT = Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial.
<table>
<thead>
<tr>
<th>Study</th>
<th>CV Risk Profile</th>
<th>N</th>
<th>OM3FA Intervention; Dose</th>
<th>Statin Use</th>
<th>Baseline TG Level</th>
<th>Effect on TG Level</th>
<th>Primary Outcome</th>
<th>Primary Outcome Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>JELIS (78)</td>
<td>Men or postmenopausal women age &lt;75 years with total cholesterol levels ≥250 mg/dL with or without CHD</td>
<td>18,645</td>
<td>EPA ethyl ester 1.8 g/day</td>
<td>Simvastatin 5 mg/day or pravastatin 10 mg/day</td>
<td>153 mg/dL (median)</td>
<td>~9% with OM3FA; ~4% in control</td>
<td>Major coronary eventa; mean f/u: 4.6 years</td>
<td>HR: 0.81 (95% CI: −0.69–0.95); P=0.011; ARR: 0.7%b (2.8% with EPA vs 3.5% with control)</td>
</tr>
<tr>
<td>GISSI-P (79)</td>
<td>Recent MI (≤3 months); no age limits</td>
<td>11,324</td>
<td>Omega-3-acid ethyl esters, 1 g/day (± vitamin E)</td>
<td>None; use of cholesterol-lowering drugs increased during study</td>
<td>162 mg/dL (mean)</td>
<td>~3.4% with OM3FA; +1.4% in control</td>
<td>Nonfatal MI or stroke or all-cause death; mean f/u: 3.5 years</td>
<td>RR: 0.85 (95% CI: 0.74–0.98); P=0.023; ARR: 2.3%c (12.3% with omega-3-acid ethyl esters vs 14.6% with control)</td>
</tr>
<tr>
<td>GISSI-HF (80)</td>
<td>Age ≥18 years with heart failure</td>
<td>7046</td>
<td>Omega-3-acid ethyl esters, 1 g/day</td>
<td>Statin use in ~23%</td>
<td>126 mg/dL (median)</td>
<td>Decreased to 119 mg/dL with OM3FA; no change with placebo</td>
<td>Co-primary endpoints: death; death or hospital admission for CV reason; median f/u: 3.9 years</td>
<td>HR: 0.91 (95% CI: 0.833–0.998); P=0.041; ARR: 2% (27% with omega-3-acid ethyl esters vs 29% with placebo)</td>
</tr>
<tr>
<td>OMEGA (81)</td>
<td>Age ≥18 years</td>
<td>3851</td>
<td>Omega-3-acid Statin use by NR</td>
<td>Statin use by NR</td>
<td>121 mg/dL with</td>
<td>Sudden cardiac</td>
<td>OR: 0.95</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Omega-3 Fatty Acid Outcome Studies
<table>
<thead>
<tr>
<th>Trial</th>
<th>Age</th>
<th>Intervention</th>
<th>Study Population</th>
<th>Statistical Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-Omega (82)</td>
<td>Age 60–80 years with prior MI (within 10 years)</td>
<td>OM3FA; 1 g/day</td>
<td>Lipid-modifying agents (mostly statins) used by 86%</td>
<td>127 mg/dL in control</td>
</tr>
<tr>
<td>SU.FOL.OM3 (88)</td>
<td>Age 45–80 years with recent acute coronary or cerebral ischemic event (1–12 months)</td>
<td>OM3FA, 0.4 g/day (± alpha-linolenic acid 2 g/day)</td>
<td>Lipid-modifying agents (mostly statins) used by 86%</td>
<td>144 mg/dL (median)</td>
</tr>
<tr>
<td>DO-IT (84, 85)</td>
<td>Men age 64–76 years with high cholesterol</td>
<td>OM3FA, 0.6 g/day (± folates)</td>
<td>Lipid-modifying agents (mostly statins) used by 86%</td>
<td>108 mg/dL (no coronary event); 125 mg/dL (coronary event)</td>
</tr>
<tr>
<td>ORIGIN (83)</td>
<td>Age ≥50 years at high CVD risk</td>
<td>Omega-3-acid ethyl esters, 1 g/day</td>
<td>Lipid-modifying agents (mostly statins) used by 86%</td>
<td>141 mg/dL (median)</td>
</tr>
<tr>
<td>R&amp;P (86)</td>
<td>High CVD risk</td>
<td>Omega-3-acid ethyl esters, 1 g/day</td>
<td>Lipid-modifying agents (mostly statins) used by 86%</td>
<td>150 mg/dL (median)</td>
</tr>
</tbody>
</table>
ARR = absolute risk reduction; CABG = coronary artery bypass grafting; CHD = coronary heart disease; CI = confidence interval; CV = cardiovascular; CVD = cardiovascular disease; DO-IT = Diet and Omega-3 Intervention Trial; EPA = eicosapentaenoic acid; f/u = follow-up; GISSI-HF = GISSI-Heart Failure study; GISSI-P = GISSI-Prevenzione study; HR = hazard ratio; JELIS = JAPAN EPA Lipid Intervention Study; MI = myocardial infarction; NC = not calculated; NR = not reported; OM3FA = omega-3 fatty acid; OR = odds ratio; ORIGIN = Outcome Reduction with an Initial Glargine Intervention; PCI = percutaneous coronary intervention; R&P = Risk & Prevention study; RR = relative risk; SU.FOL.OM3 = Supplementation en Folates et en Oméga 3 study; TG = triglyceride.

aDefined as sudden cardiac death, fatal and nonfatal MI, and other nonfatal events including unstable angina pectoris, angioplasty, stenting, or coronary artery bypass grafting.

bARR was calculated based on reported values for treatment groups and control/placebo groups for studies that reached statistical significance but was not calculated for studies that did not reach statistical significance for the primary endpoint.

cARR information not available.

dDiagnosis of diabetes; history of MI, stroke, or revascularization; angina with documented ischemia; ratio of urinary albumin to creatinine >30 mg/g; left ventricular hypertrophy; ≥50% stenosis of a coronary, carotid, or lower-limb artery on angiography, or ankle-brachial index <0.9.

eMultiple CV risk factors, clinical evidence of atherosclerotic vascular disease, or any other condition putting the patient at high CV risk in the opinion of the patient’s general practitioner.
Lumen

Lypolytic products

TRL-R taken up by macrophages

Macrophage

Monocyte

Activated platelets

Platelet activation and aggregation

Monocyte

Platelet activation and aggregation

Activated platelets

Endothelial dysfunction

Inflammation

Coagulation

TRL-R penetrated intim a

Cholesterol loading and foam cell formation

Foam cell

Plaque formation and progression

Monocyte adhesion and activation

Monocyte

Monocyte adhesion and activation

Intima

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