15 Management of Hypertriglyceridemia (Including Fibrates and n-3 Fatty Acids)

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Introduction

Historically, lifestyle and pharmacological interventions aimed at decreasing cardiovascular disease risk have focused on reducing low-density lipoprotein cholesterol (LDL-C), particularly through the beneficial effects of statins, or 3-hydroxy-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors. However, multiple large, randomized controlled trials have demonstrated that despite achieving large reductions in cardiovascular disease risk by obtaining what are considered optimal levels of LDL-C, the incidence of major adverse cardiovascular events in these patients remains considerably elevated. Over the last several years, compelling evidence suggests a significant association between hypertriglyceridemia and cardiovascular disease, and more recent data demonstrates further reduction in adverse cardiovascular outcomes after treatment of hypertriglyceridemia with the use of omega-3 fatty acids in these patients.

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Residual Cardiovascular Disease Risk Despite LDL-C Lowering Therapy

Throughout the last 20 years, statins have become a mainstay of therapy in the primary and secondary prevention of cardiovascular disease events as demonstrated in several randomized controlled trials (Scandinavian Simvastatin Survival Study (4S) [1], Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) [2], Cholesterol and Recurrent Events (CARE) [3], Heart Protection Study (HPS) [4], West of Scotland Coronary Prevention Study (WOSCOPS) [5], Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) [6], Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) [7]). However, these trials have also demonstrated that even with LDL-C lowering, significant residual cardiovascular disease risk remains. For example, patients treated with statin therapy in the 4S trial experienced cardiovascular disease event rates approximating 20% (compared to 28% with placebo) over the 5-year study period.

Over the next several years, further analyses evaluated the effects of high-dose statin treatment for more intensive LDL-C lowering. Specifically, in the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 Investigators (PROVE IT-TIMI 22) [8], Incremental Decrease in Events through

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Aggressive Lipid Lowering (IDEAL) [9], and Treat to New Targets (TNT) [10] trials, high-intensity (80 mg atorvastatin daily) therapy demonstrated greater cardiovascular disease risk reduction when compared to moderate intensity statin therapy, but residual risk in the high-intensity treatment arms was still noteworthy at 22.4%, 12%, and 8.7% over a median follow-up period of 4.9 years, respectively, despite mean LDL-C levels that were not elevated (62, 81, and 77 mg/dL, respectively).

Recognition of this persistently elevated cardiovascular disease risk despite high-intensity statin therapy has prompted investigation into non-statin therapies as a means for further risk reduction. In the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) trial, patients receiving ezetimibe in addition to moderate-intensity simvastatin experienced event rates of 32.7% compared with 34.7% with simvastatin alone over a 7-year period, despite mean LDL-C levels of 53.2 mg/dL [11].

In the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial, patients with elevated LDL-C (>70 mg/dL) despite moderate- or high-intensity statin therapy who received evolocumab, a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, were found to have statistically significant risk reduction relative to placebo. Yet, they still experienced adverse cardiac events at a rate of 9.8% with median follow-up of 2.2 years, despite a median LDL-C approximating 30 mg/dL [12]. Similarly, in the Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (ODYSSEY OUTCOMES) trial, which examined the effects of another PCSK9 inhibitor, alirocumab, in patients with a recent acute coronary syndrome (ACS) event within the previous 12 months, treated patients experienced cardiovascular events at a rate of 9.5% over median follow-up period of 2.8 years (compared to 11.1% with placebo) [13].

Accordingly, despite LDL-C optimization attained with both statin and non-statin therapies, cardiovascular disease risk remains elevated, thereby prompting investigators to search for other potential targets aimed at further risk reduction. Among the most well-established yet unexplored targets is hypertriglyceridemia.

Evidence for Hypertriglyceridemia as an Independent Risk Factor for Cardiovascular Disease

Isolating the direct contribution of hypertriglyceridemia on cardiovascular disease risk can be challenging because these patients frequently present with other comorbid conditions, which increase the risk of cardiovascular disease. They include type 2 diabetes mellitus, hypertension, hypercholesterolemia, and metabolic syndrome. In addition, the precise mechanisms linking triglyceride elevation and atherosclerosis are incompletely understood. That in part is due to the inability of large triglyceride-rich remnant particles to penetrate the vessel wall. However, because triglycerides are hydrolyzed from triglyceride-rich particles, their cholesteryl ester-enriched by-products (chylomicron and very-low-density lipoprotein remnants) can promote atherogenesis via multiple mechanisms, including direct infiltration of remnants into the vessel wall and activation of pro-inflammatory and prothrombotic signaling pathways (Fig.15.1) [14–17].

From an epidemiological standpoint, a large meta-analysis of 29 prospective studies encompassing 262,525 patients identified serum triglyceride concentration as a strong independent risk factor for cardiovascular disease events that was independent of gender and the concomitant conditions listed above [18]. Moreover, the Cholesterol Treatment Trialists' (CTT) meta-analysis encompassing 14 statin trials demonstrated that among 18,000 patients with diabetes, patients in the highest triglyceride tertile experienced cardiovascular disease events at a 26% higher rate compared to the lowest tertile; these differences persisted in the stain-treated group [19]. Finally, in the Action to Control Cardiovascular Risk in Diabetes (ACCORD)-Lipid trial, event rates in patients in the highest

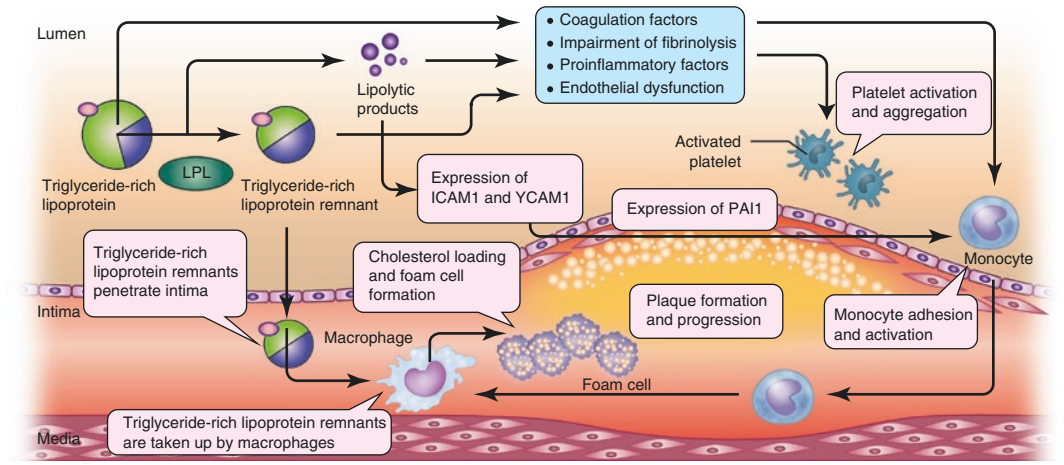


Fig. 15.1 Elevated triglyceride-rich lipoproteins and atherogenic factors driving cardiovascular disease risk. Adapted from Reiner [17]

triglyceride tertile were 21.9% higher than those taking statins alone compared with those receiving statins and fenofibrate [20].

As mentioned, post hoc analyses of several of the landmark statin trials have also demonstrated a correlation between hypertriglyceridemia and cardiovascular disease risk. In the 4S trial, patients in the highest triglyceride subgroup (> 159 mg/dL) had the highest risk for cardiovascular disease events on placebo and experienced significantly greater event reduction (52%) than either the isolated LDL-C elevation subgroup (14%) or the total study population (34%), again suggestive of hypertriglyceridemia as an important contributor to cardiovascular disease risk beyond elevations in LDL-C [21].

A similar subgroup analysis of the PROVE IT-TIMI 22 trial showed that triglyceride levels <150 mg/dL were associated with reduced cardiovascular disease risk; each 10 mg/dL decrement in serum triglyceride conferred a 1.5% reduction in the incidence of death, MI, and recurrent ACS. In addition, the combination of low LDL-C and low triglyceride levels (less than 70 and 150 mg/dL, respectively) coincided with the lowest risk of recurrent cardiovascular events [22]. In both the Myocardial Ischemia Reduction with Acute Cholesterol Lowering (MIRACL) and (dalcetrapib) dal-OUTCOMES trials, two short- and long-term post-ACS studies, elevated fasting triglyceride levels were associated with subsequent primary outcomes after adjusting for LDL-C and high-density lipoprotein cholesterol (HDL-C) [23].

In addition, a Mendelian randomization study of individuals enrolled in the Copenhagen City Heart Study (CCHS) revealed that patients with lower concentrations of non-fasting plasma triglyceride experienced lower rates of all-cause mortality [24]. Similarly, there was a causal association between elevated levels of non-fasting triglyceride and increased risk of myocardial infarction (MI) among CCHS patients with genetic variation in the apolipoprotein A5 (APOA5) gene, which codes for a protein that serves as an important determinant of plasma triglyceride levels [25]. Along with patients enrolled in the Copenhagen General Population Study (CGPS), patients with very high non-fasting triglyceride levels (e.g., >500 md/dL) were found to have a higher risk of cardiovascular disease and all-cause mortality [14].

Lifestyle Modification

For patients with borderline and high triglyceride levels (150–499 mg/dL), first-line therapy consists of adjustments to nutrition and physical activity levels (Fig.15.2). Triglyceride reduction

Diet / Lifestyle Change	TG Reduction
Weight loss (5-10% of body weight)	20%
Implement Mediterranean-style diet vs high-carb diet	10-15%
Exercise of moderate intensity (e.g. brisk walking 4-5 mph, 30 m/d)	10-20%

Fig. 15.2 Effect of lifestyle practices on triglyceride reduction. Adapted from the American Heart Association scientific statement on triglycerides and cardiovascular disease [37]

is the first and most notable effect of increased physical exercise on the lipid profile, and weight loss is the most effective non-pharmacological means of lowering serum triglycerides; a 5–10% reduction in body weight is noted to confer a 20% decrease in triglycerides [26]. Other studies have indicated for every kilogram of weight loss, one can reasonably expect a 2% reduction in serum triglyceride levels [27]. This observed reduction is mediated via upregulation of lipoprotein lipase (LPL) activity and increased utilization of triglycerides by exercising muscles, and decreases in serum triglycerides in response to aerobic exercise appear to be dose dependent [28]. In a study of middle-aged men, participants who ran 7–14 miles weekly at a mild to moderate pace experienced 20% lower fasting triglyceride levels compared to no activity, and those in the highest activity level (>20 miles weekly) experienced a 31% decline in triglycerides and the lowest observed fasting triglyceride levels [29].

Changes in dietary macronutrient composition can also contribute to further reductions in serum triglyceride levels. A Mediterranean-style diet, consisting of foods rich in monounsaturated fatty acids (MUFAs), polyunsaturated fatty acids (PUFAs), and dietary fiber primarily through incorporation of whole grains, vegetables, fruits, nuts, and olive oil, may result in a 10–15% lowering of triglycerides compared to a low-fat diet [30]. In the Framingham Heart Study Offspring Cohort, patients in the highest quintile of the Mediterranean-style dietary pattern were noted to have the lowest triglyceride levels (103 vs 114 mg/dL, $p < 0.001$) over a 7-year follow-up period [31].

Marine-derived omega-3 (OM3) PUFAs, primarily eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), concentrated in marine-derived fish including anchovies, herring, salmon, and mackerel (Fig.15.3), lower triglyceride levels in part by reducing hepatic output of very-low-density lipoprotein (VLDL) [32]. PUFAs also induce peroxisome proliferator-activated receptors (PPARs), transcription factors involved in the metabolic regulation of lipid metabolism [33]. Prior studies have demonstrated a 20–30% reduction in serum triglyceride levels with incorporation of approximately 4 g of marine-derived PUFAs to the diet each day [34]; it has been estimated there is an approximate 5–10% reduction in serum triglycerides for each gram of OM3 incorporated into daily food intake [35].

Pharmacological Management

Given the robust evidence regarding reductions in cardiovascular disease risk observed with statin therapy, the American College of Cardiology/American Heart Association (ACC/AHA) cholesterol guidelines recommend statins as first-line therapy in patients with hypertriglyceridemia characterized as moderate (TG 175 to 499 mg/dL) or severe (TG ≥500 mg/dL or greater) if the atherosclerotic cardiovascular disease (ASCVD) risk score is 7.5% or higher [36]. A meta-analysis of 91 randomized clinical trials showed among patients with an average baseline triglyceride level of 177 mg/dL statins reduced mean triglyceride levels 15–20% with greater reductions (40–45%) obtained with higher baseline levels (i.e., >273 mg/dL) [37]. If triglyceride levels remain elevated despite lifestyle modifications and the maximally tolerated statin dose, some professional society recommendations advocate the use of additional triglyceride-lowering agents such as fibrates, niacin, and OM3 fatty acids [38, 39].

	EPA+DHA (mg/100 g)
Anchovy	2055
Herring, Atlantic	2014
Salmon, farmed	1966
Salmon, wild	1840
Mackerel, Atlantic	1203
Bluefish	988
Sardines, Atlantic	982
Trout	936
Goldenbass (tilefish)	905
Swordfish	899
Tuna, white (albacore)	862
Mussels	782
Striped bass	754
Shark	689
Pollock, Atlantic	542

Fig. 15.3 Selected marine sources enriched in EPA and DHA. Adapted from Bays [32]

Niacin

Niacin has been found to effectively decrease levels of small, dense LDL-C particles and increase levels of HDL-C and to inhibit the activity of hepatic microsomal diacylglycerol acyltransferase-2 (DGAT2), a key enzyme that catalyzes the final reaction in triglyceride synthesis [40].

A number of randomized studies have demonstrated that niacin monotherapy substantially reduces triglyceride levels, and a meta-analysis of 30 such trials showed that niacin was associated with an average reduction of as much as 20% [41]. Yet, despite these appreciable reductions, clinical outcomes trials of niacin-statin combination therapy have failed to demonstrate clinical benefit beyond statin monotherapy. In the AIM-HIGH trial, 3414 participants treated with simvastatin +/− ezetimibe were randomized to extended-release niacin (1.5–2 g daily) or placebo. The incidence of the primary outcome, a composite of cardiovascular death, nonfatal MI, ischemic stroke, hospitalization for an acute coronary syndrome, or symptom-driven coronary or cerebral revascularization, occurred in 16.4% in the niacin group versus 16.2% in the placebo group (p = 0.79) [42]. The trial was terminated

early after a mean follow-up of 3 years to a lack of efficacy. Similarly, in the HPS2-THRIVE study, 25,673 statin-treated patients with vascular disease were randomized to either 2 g of extended-release niacin or placebo. Once again, there was no statistically significant difference ($p = 0.29$) in major adverse cardiovascular events (MACE) defined as nonfatal MI, cardiovascular death, stroke, or arterial revascularization. In addition, the rate of adverse effects (namely diarrhea, dyspepsia, and myopathy) was significantly higher in the niacin group [43]. Consequently and not surprisingly, niacin use for treating hyperlipidemia has waned in recent years.

Fibrates

Fibrates attenuate hepatic secretion of very-low-density lipoprotein (VLDL) particles and serve as peroxisome proliferator-activated receptor alpha (PPAR-α) agonists to modulate the metabolism of triglyceride-rich lipoproteins, resulting in shifts in LDL and HDL particle size, believed to contribute to reduced cardiovascular risk [38, 44, 45].

Several randomized, placebo-controlled trials have demonstrated the triglyceride-lowering efficacy of fibrate monotherapy, in particular gemfibrozil and bezafibrate [46–48]. In addition, a meta-analysis of 53 clinical trials demonstrated that fibrate therapy lowered triglyceride levels by approximately 36% [38, 41]. However, clinical outcomes trials for fibrates have had inconsistent results with more favorable results obtained with gemfibrozil compared to bezafibrate or fenofibrate.

Specifically, in the Helsinki Heart Study, 4081 asymptomatic patients with primary dyslipidemia (non-HDL cholesterol >200 mg/dL) were randomized to receive either 600 mg of gemfibrozil twice daily or placebo. Patients receiving gemfibrozil experienced a 34% reduction in the incidence of ischemic events compared to placebo ($p < 0.02$) [46]. These findings were supported by those in the VA-HIT trial, in which 2531 men with established coronary artery disease were again randomized to 1200 mg of gemfibrozil daily compared to placebo. Patients in the gemfibrozil group experienced a primary event (defined as a composite of nonfatal MI or cardiovascular death) 22% less often compared to those in the placebo group ($p = 0.006$) [47].

In contrast, however, the BIP study randomized 3090 patients with prior MI or stable angina to either 400 mg of bezafibrate daily or placebo; after a mean follow-up of 6.2 years, there was no statistically significant reduction in the primary endpoint of fatal or nonfatal MI or sudden death ($p = 0.26$) [48]. Similarly, in the FIELD study, 9795 patients with type 2 diabetes mellitus were randomized to receive either 200 mg daily of fenofibrate or placebo. There was no statistically significant difference in the primary outcome (coronary heart disease death or nonfatal MI) between the two groups ($p = 0.16$) [49]. In both studies, there was a statistically significant increase in the use of statin therapy in the placebo groups than in the fibrate groups; this may be a confounding factor, which attenuated the treatment effects relative to previous studies [38].

Interestingly, post hoc analyses of the clinical benefit of fibrate therapy in patients with elevated triglyceride levels (>200 mg/dL) suggested a trend toward greater cardiovascular event reduction compared to those with triglyceride levels less than 200 mg/dL [41]. In the ACCORD study, 5518 patients with type 2 diabetes treated with simvastatin were randomized to receive either fenofibrate or placebo, and no statistically significant reduction in the primary outcome of nonfatal MI, nonfatal stroke, or cardiovascular death was observed during the trial period of 5 years ($p = 0.32$). However, the trial did show benefit in the subgroup with elevated triglyceride levels (>204 mg/dL) and low HDL cholesterol (<34 mg/dL) [20]. These findings suggest that fibrate therapy may be beneficial in patients with high triglyceride levels and reduced HDL cholesterol [39]. A randomized clinical outcomes trial is currently testing the selective PPAR-α agonist, pemafibrate, in diabetic patients with hypertriglyceridemia and low HDL-C [50].

Potential adverse effects associated with fibrate therapy include myopathy, cholelithiasis, and elevations in serum creatinine levels. In FIELD, creatinine levels were reversibly increased by an average of 12% [49]; although elevations have been reported in a number of clinical trials, decreases in creatinine clearance and glomerular filtration rate were not observed [51]. The incidence of myopathy is reportedly 5.5-fold greater with the use of fibrates compared with statin monotherapy and has been shown to increase further with statin-fibrate combination therapy. The incidence of muscle symptoms is reportedly greater with the use of gemfibrozil compared with fenofibrate [51]. Even when considering these adverse effects, however, in the previously mentioned meta-analysis of 53 clinical trials, the rate of discontinuation of fibrate therapy (15%) was comparable between the fibrate and placebo groups [41].

Omega-3 Fatty Acids

The cardioprotective benefits of OM3 PUFAs have been well described, as mentioned above. In addition to reducing serum triglyceride levels, EPA and DHA may attenuate atherosclerotic plaques, lower systolic and diastolic blood pressure, and improve endothelial function [52]. OM3 fatty acids serve as precursors for bioactive lipid mediators that regulate inflammation, including eicosanoids, prostaglandins, leukotrienes, protectins, and resolvins. EPA interferes with lipid oxidation by various signal transduction pathways linked to inflammation, endothelial dysfunction, and plaque instability via incorporation into cellular membranes. Due to differences in their structure, EPA and DHA associate with distinct regions of biological membranes and differential modulate membrane structure-function relationships. In particular, the lipophilic structure and space dimensions of EPA allow it to insert efficiently into lipoprotein particles and cell membranes where it scavenges free radicals [15, 53].

There are three FDA-approved omega-3 fatty acid agents available: omega-3 fatty acid ethyl esters (OM3 A EE) (marketed as Lovaza®), icosapent ethyl (IPE) (marketed as Vascepa®), and omega-3 carboxylic acids (marketed as Epanova®). In the COMBOS trial, addition of OM3 A EE to simvastatin resulted in significantly reduced non-HDL-C. In addition, treatment when compared to placebo resulted in significantly reduced triglyceride levels (27.5% vs 7.2%) [54]. The efficacy of IPE was assessed in the MARINE and ANCHOR trials, where patients experienced statistically significantly reductions in serum triglyceride levels. In MARINE, patients were randomized to receive either 4 g/daily, 2 g/daily, or placebo and experienced reductions in serum triglyceride level of 33.1% and 19.7%, respectively [55]. In ANCHOR, reductions of 21.5% and 10.2% were demonstrated with the same dosages [56].

Despite clear evidence that these products lead to statistically significant reductions in serum triglyceride levels, there has until recently been conflicting data as to whether these reductions lead to clinically significant improvements in cardiovascular outcomes.

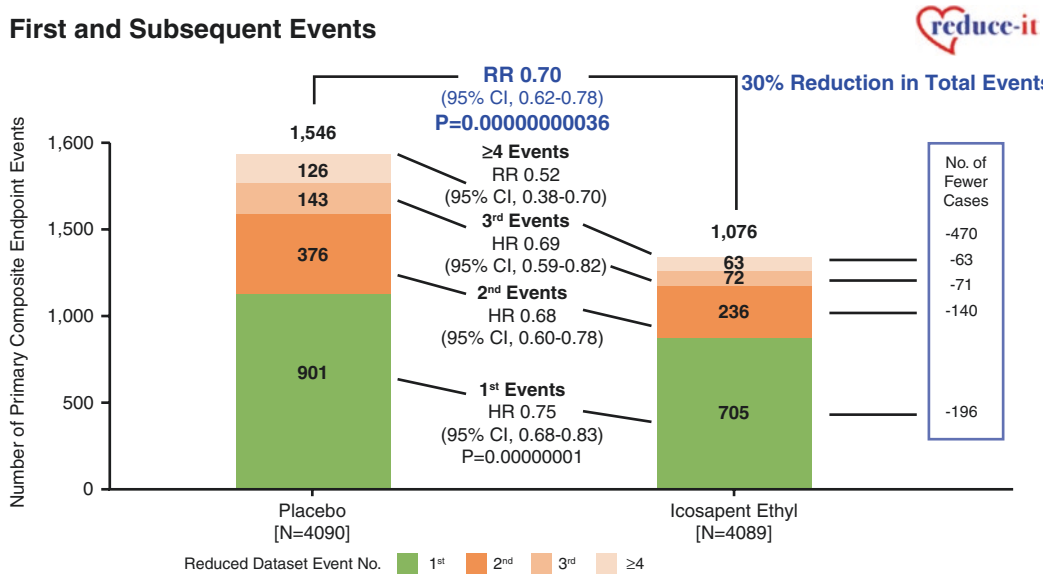
The Gruppo Italiano per lo Studio della Sopravvivenza (GISSI)-Prevenzione trial was an open-label prospective study of 11,324 patients post-MI randomly assigned to receive either OM3 fatty acid supplementation (1 g of EPA plus DHA), vitamin E (0.3 g daily), both, or none, for 3.5 years. Patients in the EPA/DHA group had a 15% reduction in the primary outcome of death, nonfatal MI, and stroke [57]. It is important to note that statins were not commonly used during the study period, and therefore, this study has minimal generalizability to current treatment paradigms. Subsequently, the Japan EPA Lipid Intervention Study (JELIS) trial randomized 18,645 Japanese patients with hyperlipidemia to receive low-dose statin (pravastatin or simvastatin) monotherapy or combination therapy with a statin and 1.8 g of EPA – patients in the EPA group experienced a 19% relative reduction in major coronary events [58].

Over the next several years, other large studies (Omega-3 Fatty Acids on the Reduction of Sudden Cardiac Death After Myocardial

Infarction (OMEGA), ALPHA OMEGA, and Outcome Reduction With Initial Glargine Intervention (ORIGIN)) failed to reproduce the results of GISSI and JELIS. However, the investigational doses in all three trials were less than the 1 g/day of OM3 fatty acids recommended by the American Heart Association (AHA) for patients with established coronary artery disease (0.84, 0.40, and 0.90 g/day, respectively) and significantly less than the doses demonstrated to be efficacious in ANCHOR and MARINE (2–4 g/d) [59–61].

The Reduction of Cardiovascular Events With EPA–Intervention Trial (REDUCE-IT) trial enrolled 8,179 patients from 11 countries with either established cardiovascular disease or diabetes and other risk factors to receive either 2 g of IPE twice daily or placebo. The primary endpoint was a composite of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina. The risk of the primary composite endpoint was 25% lower in the icosapent ethyl (IPE) group than in the placebo group ($P < 0.0001$), corresponding to a number needed to treat 21 patients [62]. The reduction in risk of myocardial infarction, stroke, and cardiovascular death (secondary endpoint) was also significantly reduced (24%; $P < 0.0001$) as was the prespecified evaluation of endpoints that was reduced by 30% ($P < 0.0001$) [63] (Fig.15.4).

The most likely explanation for the lack of benefit seen in other contemporary OM3 fatty acid trials may be attributable to the low doses used (generally <1 g/d) or the low ratio of EPA to DHA [64]. Although the dose of EPA administered in JELIS was lower than the EPA-equivalent dose in REDUCE-IT, it resulted in a plasma EPA level (170 μg per milliliter in a Japanese population) similar to that attained in a previous 12-week lipid study, in which a total daily dose of 4 g of IPE was used in a Western population and similar to that attained in REDUCE-IT. Unlike REDUCE-IT, JELIS was an open-label design without a placebo group, used only a low-intensity stain, and was conducted in a country where fish consumption is high compared to that in the USA. In addition, at baseline, patients in JELIS had higher levels of LDL cholesterol and lower baseline triglyceride values than the patients in REDUCE-IT [62]. While the magnitude of TG reduction achieved in REDUCE-IT (~20%) is unlikely to fully account for the cardio-



Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol.* 2019.

Fig. 15.4 REDUCE-IT study primary and recurrent events. Adapted from Bhatt et al. [63]

vascular benefits observed, further analyses and future studies are needed to evaluate the mechanisms underlying the benefits observed. They may include reduction of inflammation, oxidation, platelet aggregation, and restoration of endothelial function [65, 66].

It is also unclear to what extent the highly concentrated EPA compound, IPE, might be clinically superior to DHA vis-à-vis cardiovascular disease events. The soon to be completed secondary prevention STatin Residual Risk Reduction With EpaNova in HiGh CV Risk PatienTs With Hypertriglyceridemia (STRENGTH) study testing the combination of EPA/DHA carboxylic acids in patients with hypertriglyceridemia and low HDL-C will undoubtedly provide further insight regarding the use of OM3 for cardiovascular disease protection [67].

Gastrointestinal side effects (nausea and diarrhea/loose stools) appear to be the most common adverse events, occurring in up to 27% of patients at doses of 4 g daily [68]. In a meta-analysis of 29 clinical trials of OM3 fatty acid therapies, the risk of treatment discontinuation was again similar between treatment and placebo groups [69].

Summary

Despite maximally tolerated therapy targeting LDL-C reduction, a considerable amount of residual cardiovascular disease risk remains in most patients. Several genetic, observation, and post hoc analyses have provided evidence for hypertriglyceridemia as a potential target for further minimizing this risk. First-line therapy for patients with mild to moderate hypertriglyceridemia includes lifestyle modification in the form of carbohydrate reduction, weight loss, and implementation of a Mediterranean-style diet rich in unsaturated fatty acids. For patients with elevated triglyceride levels, despite these modifications, pharmacotherapy including statins, fibrates, and omega-3 fatty acids may be indicated. Ongoing randomized controlled trials continue to assess the effects of these classes on clinical cardiovascular outcomes.

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