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Is hypertriglyceridemia atherogenic?

Fabien Huet^{a,b}, Camille Roubille^{b,c}, and François Roubille^{a,b}

Purpose of review

Hypertriglyceridemia occurs mainly because of metabolic disorders secondary to diabetes, alcohol intake, and/or overweight. Genetic factors have also been clearly identified in most severe cases. Triglycerides are generally considered as 'bystanders' for cardiovascular diseases. However, biological and basic research provides strong data suggesting that triglyceride-rich lipoproteins could be involved in the pathophysiology of cardiovascular diseases.

Recent findings

The REDUCE-IT trial recently showed that icosapent ethyl reduces major cardiovascular events and related death.

Summary

For many years, low-density lipoproteins (LDLs) have been considered the Holy Grail for atherosclerotic cardiovascular disease management. New data from basic research in biology, epidemiology, genetics, and preliminary clinical trials support the hypothesis that triglyceride-rich lipoproteins could be the causal factors for atherosclerotic cardiovascular disease; hence, triglyceride should be taken into consideration in the management of these patients. Omega-3-fatty acids used in the REDUCE-IT trial reduced the residual cardiovascular risk efficiently beyond statins. However, its effect has to be completely understood as it seems to be unrelated to LDLc or triglyceride reduction, but linked to pleiotropic effects involving inflammation, platelet adhesion, and plaque instability reduction, paving the way for trials that will target more specific potential pathophysiologic pathways.

Keywords

cardiovascular risk, cholesterol, low-density lipoproteins, triglycerides

INTRODUCTION

Atherosclerosis is a complex pathophysiologic phenomenon that involves various processes such as dyslipidaemia, oxidative stress, and inflammation [1]. Among all the classes of lipids, cholesterol has been considered as the key factor of atherosclerosis for decades. The discovery of the major role of low-density lipoproteins (LDL) in cardiovascular disease (CVD) risk, based on the observation of patients with familial hypercholesterolemia, high LDL levels, and premature atherosclerotic cardiovascular disease (ASCVD), led to the Nobel Prize award of Brown and Goldstein in 1985; this led to the development of statins [2]. Many large randomized double-blind trials demonstrated that medication-induced reduction of LDL, particularly with statins, led to a decrease in ASCVD and all-cause mortality [3]. Based on these clinical evidences, LDL cholesterol (LDLc) reduction has become the main objective of dyslipidaemia management as a secondary prevention of CVD. International guidelines recommend that the management of dyslipidaemia be dependent on the level of LDL only [4]. However,

a substantial residual cardiovascular risk still remains even though target LDL-C levels are achieved [5].

High cardiovascular risks (including type 2 diabetes mellitus [T2DM] and metabolic syndrome) are related to local and systemic inflammatory conditions, the latter being routinely quantified by high Ultra-Sensitive C-reactive protein (US-CRP). Local inflammation is involved in plaque instability related to cardiovascular events and mortality. In these conditions, hypertriglyceridemia is associated with low high-density lipoproteins (HDLc) and a

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KEY POINTS

- Triglyceride-rich lipoproteins could be causal factors for CVD.
- Mediterranean diet proved to efficiently reduce the risk of CVD.
- The recent REDUCE-IT trial proved that OM3FA is efficient in reducing the residual cardiovascular risk beyond statin action.

high cardiovascular risk. Hyperglycaemia, together with high triglyceride (>150 mg/dl) and low HDLc (<40 mg/dl), has also been shown to promote atherosclerosis through hyperinsulinemia and insulin resistance.

The ‘saga’ of studies supporting the efficacy of anti-inflammatory treatment in the prevention of cardiovascular events, which includes the positive CANTOS trial [6] and the ongoing COLCOT study [NCT02551094], and the benefits of a daily Mediterranean diet [7^{***}] in the prevention of Major Cardiovascular Adverse Events (MACE) in high risk populations constantly argue for a global management in cardiology.

However, the hypothesis that lowering triglyceride-rich lipoproteins could provide clinical benefits is very controversial; hence, several studies on this topic are currently ongoing.

DEFINITIONS

Remnant cholesterol can be estimated as total cholesterol (TC) – LDL cholesterol – HDL cholesterol. When triglycerides are too high (>4 g/l), LDL cholesterol is directly measured. In the fasting state, remnant cholesterol is mainly present as very low-density (VLDL) and intermediate-density lipoproteins; in the non-fasting state, cholesterol in chylomicron remnants is also included. As triglycerides are the main components of chylomicrons and VLDL particles, they are linked to remnant cholesterol, which may explain their involvement in CVD pathophysiology. Non-HDL cholesterol is calculated or estimated as TC – HDL cholesterol and is equivalent to the combination of LDL and remnant cholesterol. Importantly, the use of non-HDL cholesterol for CVD risk prediction has been emphasized.

PRELIMINARY PATHOPHYSIOLOGIC ISSUES

Triglycerides are required for metabolic functions in all the cells as compared to TC. Elevated TC

accumulates, leading to deposits, and is recognized as the well known cause for ASCVD. For decades, TC (but not triglyceride) has been associated with plaque formations. This is one of the main reasons why triglycerides are not suspected in ASCVD. Recent pathophysiology has shown that triglyceride may be a marker of high levels of cholesterol in triglyceride-rich lipoproteins. The question ‘marker or actor?’ remains unanswered.

HIGH TRIGLYCERIDE AND THE RISK OF PANCREATITIS

Figure 1 summarizes the multifactorial causes of hypertriglyceridemia [8]. Although triglyceride levels are known to be highly dependent on genetic factors, several environmental factors may increase hypertriglyceridemia. Alcohol consumption, high fat intake, and diabetes have been identified as possible reversible causes of elevated triglycerides, and lifestyle modification consequently becomes a major issue. Severely elevated triglycerides (>10 mmol/l; >8.80 g/l) [8] increases the risk of pancreatitis and must be addressed because it is potentially life threatening. Despite the lack of randomized trials in this field, guidelines should recommend the reduction of triglycerides to reduce the risk of pancreatitis [8].

Genetic predisposition
Obesity
Type 2 diabetes
Alcohol consumption
Diet high in simple carbohydrates
Renal disease
Hypothyroidism
Pregnancy (physiological triglyceride concentrations double during the third trimester)
Paraproteinaemia and autoimmune disorders such as systemic lupus erythematosus
Multiple medications including: <ul style="list-style-type: none">• Corticosteroids• Oestrogens, especially those taken orally• Tamoxifen• Antihypertensives: adrenergic beta-blocking agents (to a different degree), thiazides• Isotretinoin• Bile acid-binding resins• Ciclosporin• Antiretroviral regimens (protease inhibitors)• Psychotropic medications: phenothiazines, second generation antipsychotics

FIGURE 1. HyperTG is multifactorial. Adapted for the ESC guidelines, with permission. TG, triglyceride. Source: Adapted with permission from Ref. [8].

HISTORICAL POINT OF VIEW

Up until the 1990s, based on postprandial observations, LDL and triglycerides were considered to have major roles in ASCVD. Hence, it was recommended to treat both elevated triglycerides and TC. Thereafter, great interest on elevated LDL has been raised because of the risk of drug tolerance and interactions. The importance of LDL has been largely established, whereas guidelines ignored mild-to-moderately elevated triglycerides.

Randomized, double-blind trials and several publications on triglycerides have provided useful information on epidemiology, genetics, and biology. Taking all these data into account, guidelines were updated and recommend not to neglect triglyceride levels [9–12].

Nevertheless, the clinical management of triglycerides remains unclear, mainly because trials with fibrates generally showed negative results. The increase in HDL levels has been considered as promising in limiting cardiovascular risk. Unfortunately, despite encouraging epidemiological approaches and genetic studies, large clinical trials with cholesteryl ester transfer proteins modulators [13,14] or niacin [15] failed to confirm this enthusiasm. The only trial considered promising with anacetrapib use [16] was also disappointing; hence, drug development ceased. Promising pharmacological and pharmacogenomic studies [17,18] have suggested better patient selection that could show benefits. For this purpose, a large clinical pharmacogenomic dal-gene study (the first in cardiology) was started in 2016, with an estimated completion date in 2020 (NCT02525939). Low HDL levels have been considered as a bystander or a long-term marker of high levels of triglyceride-rich lipoproteins, enhancing the interest in triglycerides further.

Importantly, atherogenesis could prominently take place as a postprandial phenomenon, resulting from high levels of triglyceride-rich lipoproteins in accordance with early hypotheses [19]. A large study including 84 177 individuals (Fig. 2) described the distribution of non-fasting plasma triglycerides and showed that 27% of adults had mild-to-moderately elevated triglycerides (1.76–8.80 g/l), whereas only 0.1% had severely elevated levels (>8.80 g/l) [20].

The primary modifiable causes of elevated triglycerides are diabetes, alcohol consumption, and overweight. It has been recently confirmed that genetic factors play a role in mild-to-moderately elevated triglycerides and are the main cause of severely elevated triglycerides (mutations in *LPL*, *APOC2*, *APOA5*, *LMF1*, *GPIHBP1*, and *GPD1* genes) [12], paving the way to targeted therapeutic approaches for these rare but severe patients.

Similarly, 21% of adults have elevated remnant cholesterol of more than 1 mmol/l (0.4 g/l).

High levels of triglycerides have been shown to be independently correlated with high risk of ASCVD [21] and all-cause mortality [22]. Thus, in the general population, non-fasting triglycerides of more than 4.40 g/l versus less than 0.88 g/l were associated with a 17 and a five-fold risk of myocardial infarction in women and men, respectively. Corresponding risks of all-cause mortality were four and two-fold increase in men and women, respectively (Fig. 3).

PATHOPHYSIOLOGY

Triglycerides are supposedly involved in the various levels of ASCVD pathophysiology (Fig. 4). Triglycerides easily enter the arterial intima, but elevated levels of triglyceride are not sufficient. Patients with chylomicronaemia syndrome caused by lipoprotein lipase deficiency, leading to the accumulation of triglycerides in the blood do not present with ASCVD. This suggests that triglycerides trigger various pathophysiologic pathways. Triglycerides are mainly hydrolyzed by the lipoprotein lipase (LPL), and LPL and the cholesteryl ester transfer proteins hydrolyze its lipolytic products. These contain various molecules including large amounts of oxidized free fatty acids (ox-FFA) responsible for increasing the production of reactive oxygen species, decreasing nitric oxide, and increasing various adherence molecules [intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1)] and other pro-inflammatory ones (NLRP-1). This links them with other pro-inflammatory markers, such as interleukins TNF- α , IL-1 β . Interestingly, the multivariate analysis of a recent retrospective study including HIV-infected patients showed that hypertriglyceridemia was strongly associated with ASCVD when levels were above 1.7 mmol/l (odds ratio [OR] = 1.55 [1.02–2.37], $P = 0.041$) [23]. The inflammatory process associated with hypertriglyceridemia appeared to be the corner stone of hypertriglyceridemia-induced atherosclerosis.

NEW GENETICS DATA

Various genetic approaches provide strong evidence of the causal role of triglycerides in ASCVD [24]. Genetics approaches have been presented by other studies [25]. Indeed, large-scale meta-analyses of cohorts and population-based sequencing studies assessed that some variants in the genes could determine the association between plasma triglyceride and ASCVD. For example, a large Mendelian analysis

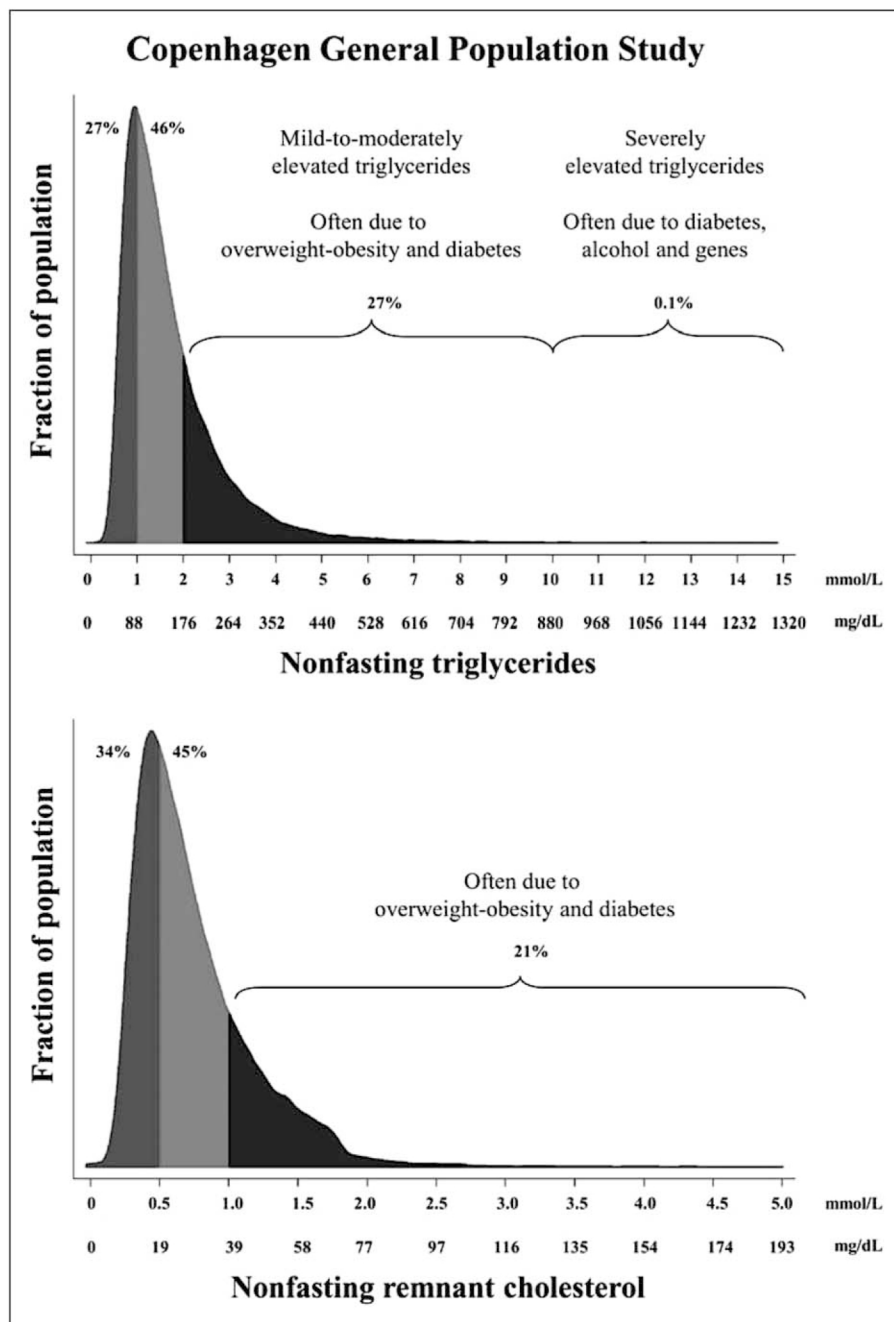


FIGURE 2. Distribution of TG levels in a general population of 84 177 individuals. TG, triglyceride. Source: Adapted with permission from Ref. [20].

comparing 20 000 patients with myocardial infarction to 500 000 control patients found that 1 standard deviation increase in triglyceride levels was associated with a 54% increase in the risk of myocardial infarction [26] (Fig. 5).

Moreover, a Mendelian randomization analysis involving 654 783 participants was performed to evaluate the clinical benefit of lowering plasma triglyceride levels in comparison with lowering LDLc levels [27]. Surprisingly, it appeared that triglyceride-lowering genetic variants in the lipoprotein lipase

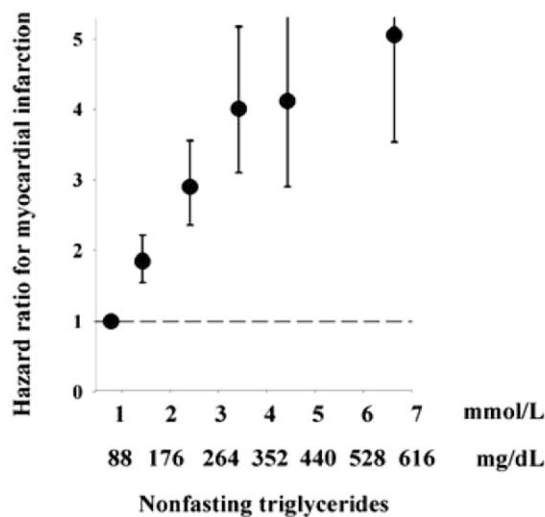
gene and LDLc-lowering genetic variants in the LDL receptor gene were associated with a similar lower risk of coronary heart disease. This recent analysis is strongly paving the way of triglyceride-lowering therapies to reduce ischemic risk.

Among the established pathophysiologic pathways, the best one cited the interactions of lipoprotein lipase with proteins such as apolipoprotein (apo) A-V, apo C-III, and angiopoietin-like proteins 3 and 4. For instance, the loss-of-function mutations in *APOC3* were associated with low levels of triglycerides

Copenhagen City Heart Study and Copenhagen General Population Study

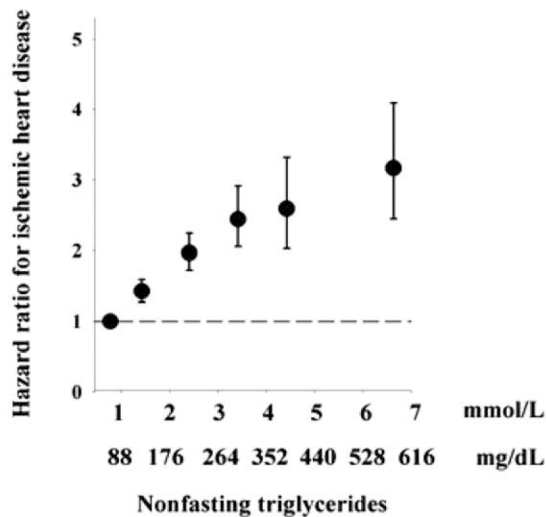
Myocardial infarction

N=96,394 (Events=3,287)
Median follow-up 6 years



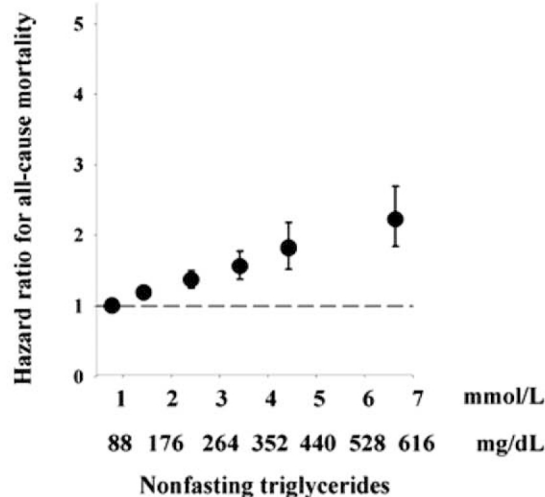
Ischemic (=coronary) heart disease

N=93,410 (Events=7,183)
Median follow-up 6 years



All-cause mortality

N=98,515 (Events=14,547)
Median follow-up 6 years



Ischemic stroke

N=97,442 (Events=2,994)
Median follow-up 6 years

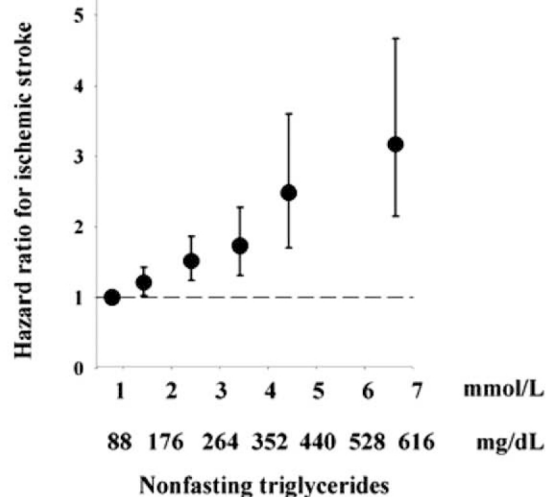


FIGURE 3. Correlations between TG and ASCVD. SCVD: atherosclerotic CVD. TG, triglyceride; ASCVD, atherosclerotic cardiovascular disease. Source: Adapted from [40] with permission.

and a reduced risk of ischemic CVD [28]. More importantly, strong associations with clinical outcomes have been established, establishing a causal link. However, a secondary lipid disturbance, especially a decrease in HDL levels, has been concomitantly established and is a likely synergic action.

CLINICAL TRIALS

The beginning of 2019 was of great interest in the fields of lowering triglyceride in the prevention of atherosclerosis. For many years, the efficacy of statins in various trials has overshadowed the potential interest of strategies targeting triglycerides. Only

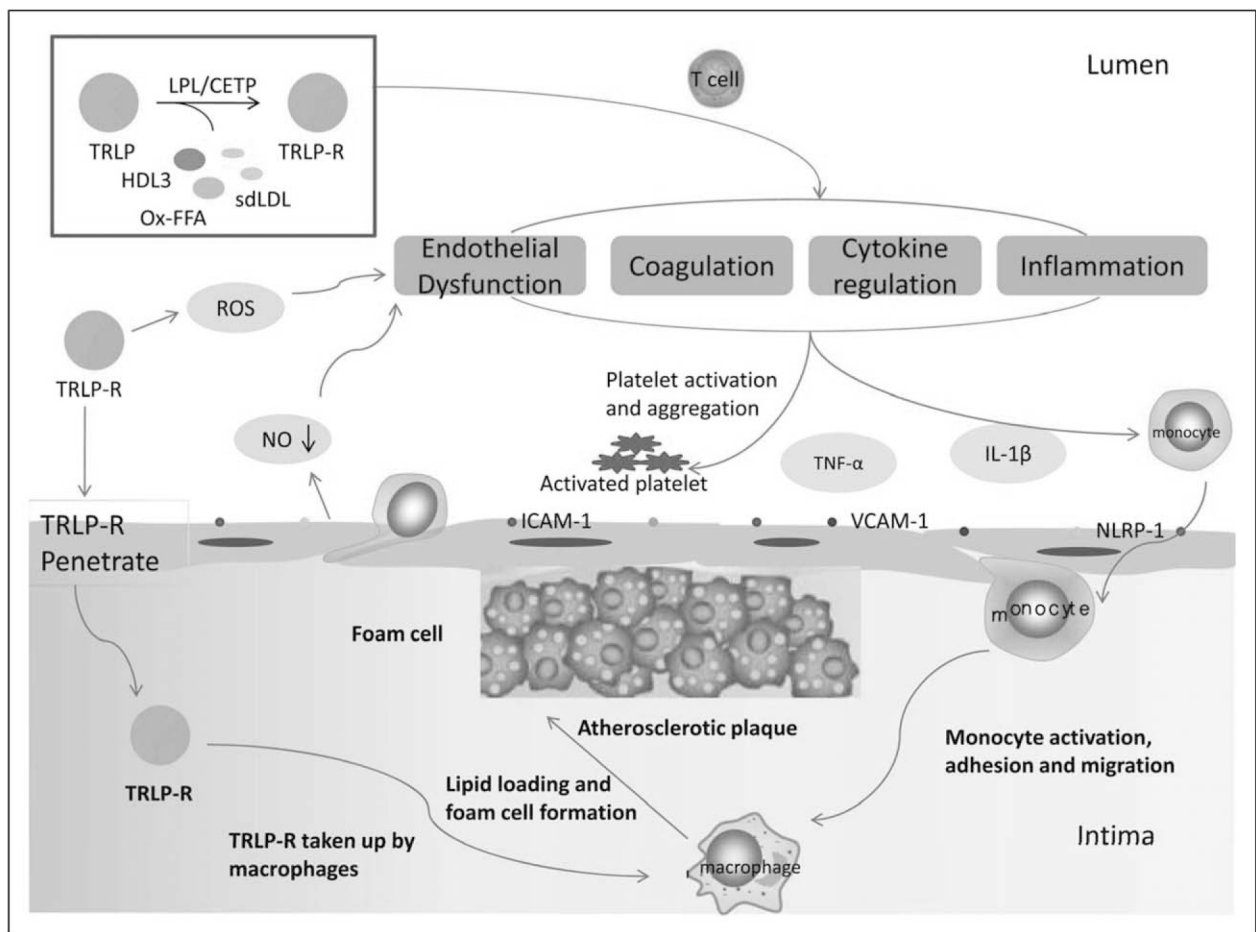


FIGURE 4. Involvement of TG in pathophysiology of atherosclerosis. TG, triglyceride; TRLP, TG rich lipoprotein. Source: Adapted from Ref. [41].

one trial has evaluated the benefits of reducing triglyceride-rich lipoproteins in patients with elevated triglyceride, thus reducing the risks of ASCVD and all-cause mortality (Table 1) [29].

Trials with fibrates provided promising information when considering subgroups. Nevertheless, only studies with historical contexts were available and are not updated. For these reasons, it was mandatory to establish new studies in the same context. Interestingly, small studies have shown that pemafibrate, a selective PPAR- α modulator, significantly decreased plasma triglyceride levels by approximately 45% as compared to the placebo. The effect was associated with a significant increase in HDL-C levels. In patients with T2DM, pemafibrate also reduced insulin resistance score [30,31]. The PROMINENT study (Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides IN patients with diabeteS; NCT03071692) is currently recruiting patients to evaluate cardiovascular outcomes with pemafibrate. The study aims to randomize 10000 patients with T2DM, high triglyceride and low HDL levels, on statin therapy.

For many years, statins and fibrates have proven to be effective in reducing inflammation from atherosclerosis plaques [32]. However, the persisting residual risk for cardiovascular events, despite being on maximal statin therapy, leads to find another therapeutic target. Omega-3 fatty acid (OM3FA), together with statins, has been proven to reduce the inflammatory process (including CRP blood levels that were identified as a significant marker of MACE) and to significantly reduce triglyceride levels [33], without the over-reduction of LDLc levels. OM3FA promotes pro-inflammatory mediators (prostaglandins and leukotrienes) that down regulate plaque formation. At the early stage of the plaque formation, OM3FA reduces endothelial dysfunction, increases nitric oxide availability, reduces the oxidized form of LDLc, and interferes with the migration of cells, such as monocytes, macrophages, and the formation of foam cells [34]. OM3FA significantly reduces inflammatory cytokines (including IL6) and several adhesion molecules (ICAM and VCAM)[35]. At a late stage, OM3FA improves plaque stability by increasing fibrous cap thickness and

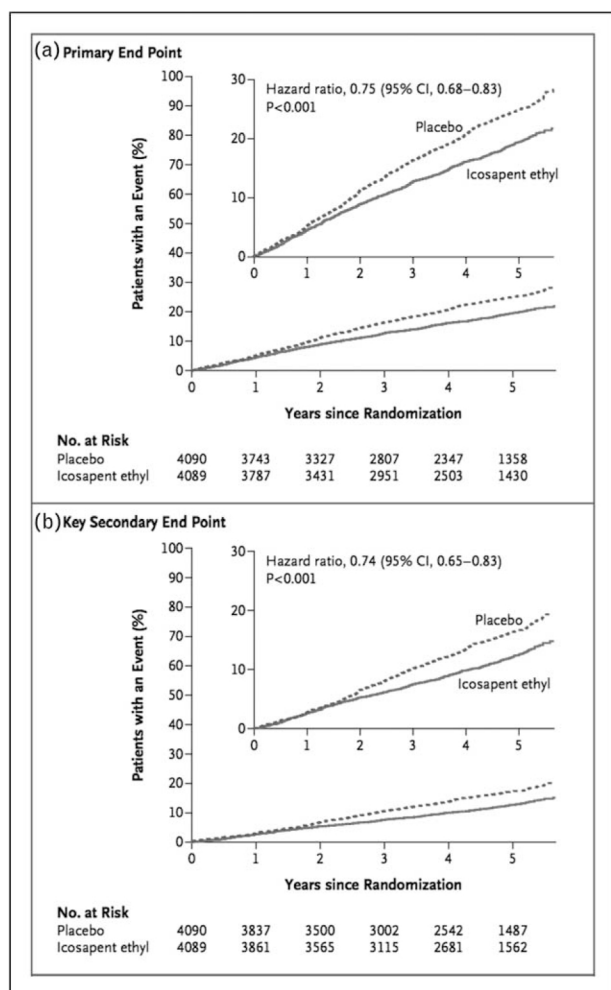


FIGURE 5. survival curves from the REDUCE-IT trial. TG, triglyceride.

reducing thrombosis and platelet adhesion and activation [36[¶]]. Overall, OM3FA reduces the evolution of atherosclerosis plaque and its clinical expression.

The Japan EPA Lipid Intervention Study (JELIS) trial [37] was an open label trial that compared a low dose (1.8 g per day) of eicosapentaenoic acid (EPA)

with a low dose of statin. The study showed a 19% reduction ($P=0.01$) in clinical cardiovascular events defined by a composite endpoint (any major coronary event, including sudden cardiac death, fatal and nonfatal myocardial infarction, and other nonfatal events including unstable angina pectoris, angioplasty, stenting, or coronary artery bypass grafting). However, clinical relevance was unrelated to LDLc or triglyceride reduction. Importantly, major effects were observed in the subgroup of patients with the highest basal triglyceride levels (≥ 150 mg/dl) combined with the lowest HDLc basal levels (<40 mg/dl). In this subgroup of patients, a 53% reduction of clinical events was observed (HR=0.47 [0.23–0.98]; $P=0.04$) [37]. However, it must be noted that EPA was obtained from heterogeneous sources and it was proved that such low doses of OM3FA are not sufficient to promote a significant reduction of triglyceride levels.

The REDUCE-IT trial is a multicentre, randomized, double-blind, placebo-controlled trial, which included 8179 high-risk patients (based on established CVD or with diabetes and other risk factors) who are treated with statins. Biological inclusion criteria included low LDL levels (41 to 100 mg/dl) and high triglyceride levels (135 to 499 mg/dl). The patients were randomly assigned to receive 2g of icosapent ethyl twice daily or a placebo. The primary composite endpoint was cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina. The results showed a major and significant effect on the primary endpoint, with a 25% reduction in clinical events (17.2% vs. 22.0% [Hazard Ratio (HR)=0.75 [0.68–0.83] $P<0.001$], a reduction of cardiovascular death (4.3% vs. 5.2%; HR=0.80 [0.66–0.98] $P=0.03$). Survival curves are presented in Fig. 5. However, the reduction of events was not statistically associated with the triglyceride level reduction; hence, the mechanisms underlying the clinical benefit are not fully understood. Parts of the

Table 1. Currently ongoing trials aiming clinical endpoints. Main ongoing randomized trials. Research keywords were Hypertriglyceridemia and Atherosclerosis on Clinicaltrials.org, Jan 2018. Exception for RESPECT-EPA, coming from the UMIN-CTR Clinical trial website

	Study registration number	Molecule	Number of patients	Endpoint	Date
EVAPORATE	NCT02926027	Vascepa (Omega-3 polyunsaturated fatty acid)	80	Progression rates of low attenuation plaque	September 2019
RESPECT EPA	UMIN000012069	EPA 1800 mg/day	3900	MACE	2021
PROMINENT	NCT03071692	pemafibrate	10 000	MACE, Y4	2022
STRENGTH	NCT02104817	Epanova: omega-3 carboxylic acids	13 000	MACE	2019: end of recruitment

EPA, eicosapentaenoic acid; MACE, major cardiovascular adverse events.

clinical benefits observed may be explained by the membrane stabilizing effects of isosanooid ethyl, and the shape of the Kaplan Meyer curves suggested a delayed effect of the molecule. As mentioned above, OM3FA are involved in plaque stabilization and in the reduction of platelet activation and adhesion, a mechanism that significantly reduces plaque rupture and myocardial infarction or stroke. Importantly, CRP reduction observed in the study is consistent with the anti-inflammatory effects. A safety issue has raised based on a higher rate of hospitalization because of supraventricular arrhythmia ($P=0.004$) and a trend toward a higher rate of serious bleeding events ($P=0.06$) because of the platelet-related effect of the treatment.

The ongoing STRENGTH trial (Statin Residual Risk Reduction with Epanova in High Cardiovascular Risk; NCT02104817) aims to test Epanova against placebo in the reduction of cardiovascular events.

All the new data briefly presented herein take into consideration new approaches evaluating the triglyceride hypothesis. For instance, targeting ApoC-III to reduce ASCVD could be obtained through different approaches [38]. In this respect, some small clinical trials have shown innovative options that offer Triglyceride reduction in patients. Lowering triglyceride levels through selective anti-sense inhibition of APOC3 synthesis [39] in patients with a broad range of baseline levels is possible. Importantly, many trials are currently investigating this strategy. These large PROBE-designed studies are expected to provide major data in the next coming years.

CONCLUSION

LDL status has been considered as the 'holy grail' for ASCVD management (both in primary and secondary prevention settings). New data from biology and basic research, as well as from epidemiology, genetics, and preliminary clinical trials, support the hypothesis that triglyceride-rich lipoproteins could be causal factors for ASCVD; hence, triglycerides should be taken into consideration in the management of these patients. The recent REDUCE-IT trial [42^{***}] proved that OM3FA is efficient in reducing the residual cardiovascular risks beyond statin action. However, its effect has to be completely understood because it seems to be unrelated to LDLc or triglyceride reduction. It is rather linked to its pleiotropic effects involving inflammation, platelet adhesion, and plaque instability reduction, paving the way for trials targeting more specifically potential pathophysiological pathways.

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Conflicts of interest

There are no conflicts of interest.

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