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REVIEW

Triglycerides and risk of atherosclerotic cardiovascular disease: An update

Triglycérides et risque de maladie cardiovasculaire athérosclérotique : une mise à jour

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Summary Low-density lipoprotein cholesterol is a well-known causal factor for atherosclerotic cardiovascular disease, and is the primary target of lipid-lowering therapy. There is, however, still a substantial risk of atherosclerotic cardiovascular disease events despite intensive statin therapy, and data from clinical trials suggest that an elevated concentration of triglycerides is a marker of residual cardiovascular risk on low-density lipoprotein-lowering therapy. Serum triglycerides are a biomarker for triglyceride-rich lipoproteins, and several lines of evidence indicate that triglyceride-rich lipoproteins and their cholesterol-enriched remnant particles are associated with atherogenesis. Moreover, genetic data in humans strongly suggest that the remnants of triglyceride-rich lipoproteins are a causal cardiovascular risk factor. Although lifestyle changes remain the cornerstone of management of hypertriglyceridaemia, a recent trial with high doses of the omega-3 fatty acid icosapent ethyl showed a significant reduction in cardiovascular events that was not explained by the reduction in triglycerides alone.

Abbreviations: Apo, apolipoprotein; ANGPTC, angiopoietin-like protein; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; LPL, lipoprotein lipase; RLP-C, remnant lipoprotein cholesterol; TGRLs, triglyceride-rich lipoproteins; VLDL, very-low-density lipoprotein.

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In patients with elevated triglycerides, several novel drugs are in development to reduce the residual risk on statin therapy linked to an excess of atherogenic triglyceride-rich lipoproteins. In this review, we provide an update on the biology, epidemiology and genetics of triglycerides, and the risk of atherosclerotic cardiovascular disease.

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MOTS CLÉS

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Résumé Le cholestérol des lipoprotéines de basse densité est un facteur causal bien reconnu des maladies cardiovasculaires liées à l'athérosclérose et c'est l'objectif primaire d'un traitement hypolipémiant. Toutefois un risque substantiel persiste malgré un traitement par statine de forte intensité et des données récentes d'essais cliniques suggèrent qu'une élévation des triglycérides est un marqueur du risque cardiovasculaire résiduel sous traitement abaissant les lipoprotéines de basse densité. Les triglycérides sériques sont un biomarqueur des lipoprotéines riches en triglycérides et de nombreuses preuves indiquent que les lipoprotéines riches en triglycérides et leurs résidus d'hydrolyse (ou remnants) enrichis en cholestérol participent à l'athérogénèse. De plus des études génétiques supportent fortement un rôle causal des remnants dans le risque cardiovasculaire. Bien que les mesures hygiéno-diététiques restent la pierre angulaire de la prise en charge d'une hypertriglycémie, une étude clinique récente utilisant de fortes doses d'un acide gras omega-3, l'icosapent ethyl, a montré une réduction significative des événements cardiovasculaires, inexpliquée par la seule baisse des triglycérides. Chez des patients avec élévation des triglycérides sous traitement par statine, plusieurs nouvelles approches thérapeutiques sont en développement pour réduire le risque résiduel lié à l'excès de lipoprotéines riches en triglycérides. Cette revue propose une mise à jour des données biologiques, épidémiologiques et génétiques des relations entre triglycérides et risque de maladies cardiovasculaires liées à l'athérosclérose.

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Background

The existence of an independent association between triglyceride concentrations and risk of atherosclerotic cardiovascular disease (ASCVD) has long been a controversial subject. Although elevated triglyceride concentrations are common in patients with ASCVD, establishing a clear link has been difficult for various reasons. First, triglyceride concentrations have high biological variability, which obscures the strength of any association with ASCVD. Second, although most studies have found a direct association between triglyceride concentrations and ASCVD risk, this association sometimes loses significance after multivariable adjustment including other lipids. Third, patients with high triglyceride concentrations often present other risk factors, such as insulin resistance, visceral obesity or type 2 diabetes, which could also explain their risk of ASCVD. To a certain extent, elevated triglyceride concentrations are considered to be innocent bystanders, and this concept is reinforced by the lack of evidence to suggest that triglyceride-lowering treatment has a beneficial effect. Finally, the lack of an established pathophysiological mechanism linking triglycerides to atherosclerosis has hindered consideration of triglycerides as a cause of atherosclerosis, as opposed to being a marker for other risk factors.

Consequently, the primary target when seeking to reduce the risk of ASCVD is to lower low-density lipoprotein (LDL) cholesterol (LDL-C), a strategy endorsed by all the guidelines

[1,2]. However, despite intensive LDL-lowering therapies, a significant residual risk persists, particularly for patients with elevated triglyceride concentrations. In addition, a number of recent reports have concluded that triglyceride-rich lipoproteins (TGRLs) are independent predictors of ASCVD [3].

Several recent reviews have focused on triglycerides [3–7], and the objective of this article is thus to provide an overview of the biological, epidemiological, genetic and clinical arguments regarding the role of triglycerides in the development of ASCVD.

Biological arguments

Plasma triglycerides are carried in chylomicrons and very-low-density lipoproteins (VLDLs), collectively termed TGRLs. Although chylomicrons and VLDL particles are generally too large to cross the endothelium, triglycerides can influence several specific aspects of atherosclerotic lesion development.

TGRLs contain significant amounts of cholesterol, and are subject to remodelling during intravascular lipolysis, through the action of lipoprotein lipase (LPL). LPL catalyzes clearance of circulating TGRLs, and an inefficient delipidation of VLDL and chylomicrons induces the formation of remnants. A decrease in LPL activity is associated with an excess of remnant particles. These remnants have

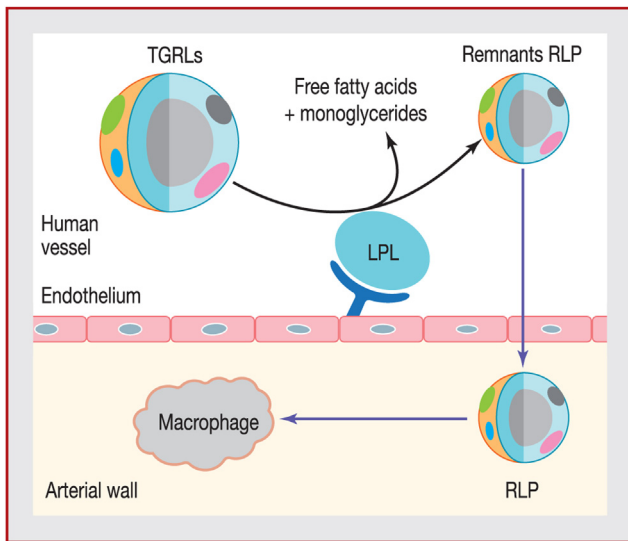


Figure 1. Simplified illustration of the metabolism of triglyceride-rich lipoproteins (TGRLs). LPL: lipoprotein lipase; RLP: remnant lipoprotein.

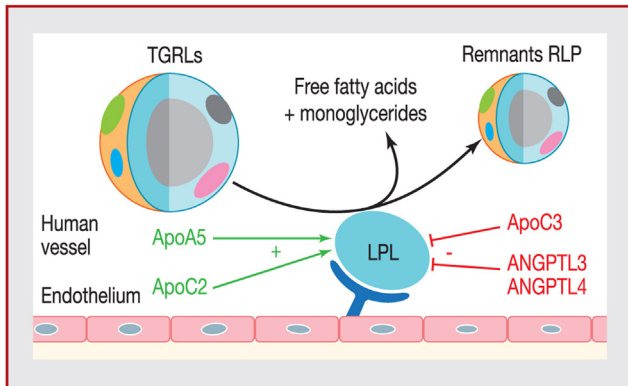


Figure 2. Regulation of lipoprotein lipase activity. Apo: apolipoprotein; ANGPTL: angiopoietin-like protein; TGRLs: triglyceride-rich lipoproteins; RLP: remnant lipoprotein.

an increased percentage of cholesterol, and their smaller size allows them to cross the endothelial layer and to be taken up by macrophages in the arterial wall [8] (Fig. 1). Consequently, the cholesterol content in remnants (remnant lipoprotein cholesterol [RLP-C]) seems to play a more important role than triglycerides in atherogenesis. RLP-C has been described as a causal factor for ischaemic heart disease [9,10].

The activity of LPL is regulated by several factors: lipolysis is reduced by apolipoprotein C3 (ApoC3), which is a component of TGRLs, and by angiopoietin-like proteins 3 and 4 (ANGPTL3 and ANGPTL4), which operate near the endothelium. In contrast, ApoC2 activates LPL, and ApoA5 is a stabilizing cofactor (Fig. 2).

Beyond cholesterol delivery, TGRLs may influence atherosclerosis by other mechanisms: the lipolysis of TGRLs produces free fatty acids and monoglycerides (Fig. 1), inducing a rise in the concentration of cytotoxic free fatty acids, particularly saturated fatty acids. These free fatty acids and remnants can induce production of inflammatory mediators and proatherogenic adhesion molecules. Moreover,

macrophages secrete LPL, and the localized hydrolysis of remnants by macrophages can potentially produce cytotoxic and inflammatory effects [3,6,8].

In addition to their proinflammatory effects, TGRLs and their remnants promote endothelial dysfunction, and activate the coagulation cascade that leads to enhanced platelet aggregation. Patients with elevated triglycerides have increased concentrations of thrombotic factors, such as fibrinogen and plasminogen activator inhibitor [6].

Finally, the rate at which TGRLs are produced is also influenced by metabolic factors—particularly insulin resistance—and many patients with elevated triglycerides have type 2 diabetes, metabolic syndrome or abdominal obesity. The secretion of TGRLs is enhanced with insulin resistance and increased concentrations of free fatty acids [3].

Epidemiological arguments

Numerous epidemiological studies and meta-analyses have demonstrated that high concentrations of triglycerides (fasting and non-fasting) are associated with a high risk of ASCVD [11–13]. In a meta-analysis involving 10,158 incident coronary heart disease (CHD) cases from 262,525 participants in 29 studies, the adjusted odds ratio for CHD was 1.72 (95% confidence interval 1.56–1.90) in a comparison of individuals in the top third with those in the bottom third of triglyceride values [13]. In 2007, two prospective observational studies—the Copenhagen City Heart Study [12] and the Women’s Health Study [11]—provided important insights. In the Copenhagen City Heart Study, increased concentrations of non-fasting triglycerides were associated with an increased risk of myocardial infarction, ischaemic heart disease and death in both men and women [12]. In the Women’s Health Study (involving a cohort of healthy women in the USA), non-fasting triglycerides were associated with an increase in the risk of ASCVD, whereas fasting triglycerides were not [11].

The question of whether triglycerides are an independent risk factor was raised in 2009 by the Emerging Risk Factors Collaboration analysis [14]. In analyses from 68 long-term prospective studies, increased triglyceride concentrations were associated with a 37% increased risk of CHD after adjustment for non-lipid risk factors. This association was weakened after adjustment for high-density lipoprotein cholesterol (HDL-C), and abrogated after adjustment for non-HDL-C, leading to the conclusion that the triglyceride measurement provides no additional information. In fact, this finding is in line with the idea that the causal factor of ASCVD is the cholesterol content in TGRLs rather than the actual raised triglycerides.

More recent epidemiological data have reinforced the role of TGRLs in the risk of ASCVD. In 2014, in studies combining the Copenhagen City Heart Study and the Copenhagen General Population Study, with similar statistical power as the Emerging Risk Factors Collaboration, non-fasting triglycerides were associated with risk of ASCVD and all-cause mortality [15]. In these studies, when compared with individuals with plasma triglyceride concentrations < 89 mg/dL (< 1 mmol/L), the multivariable adjusted hazard ratios for myocardial infarction were 1.6, 2.2, 3.2,

2.8 and 3.4 for individuals with triglyceride concentrations of 1.00–1.99, 2.00–2.99, 3.00–3.99, 4.00–4.99 and ≥ 5.00 mmol/L, respectively [16]. In a complementary analysis from the Copenhagen General Population Study [17], individuals in primary prevention with a triglyceride concentration ≥ 3 mmol/L, but not eligible for statin therapy, had a 10-year risk of myocardial infarction that was around 3-fold higher than those with a triglyceride concentration < 3 mmol/L.

Several studies have also examined the relationship between the cholesterol content of TGRLs and ASCVD risk. In the Copenhagen studies [10,18] elevated non-fasting RLP-C (calculated as total cholesterol minus HDL-C minus LDL-C) was associated with ischaemic heart disease risk, independent of reduced HDL-C [10], and with all-cause mortality in patients with ischaemic heart disease [18]. In Chinese data, RLP-C (measured by nuclear magnetic resonance spectroscopy) was also associated with an increased risk of myocardial infarction and ischaemic stroke [19]. However, in the ARIC study [20], although elevated triglycerides were associated with increased RLP-C, only the triglyceride content in LDL particles predicted ASCVD risk after adjustment for traditional risk factors. A limitation of many of these studies was measurement at only one time point, especially as triglycerides are known to be highly variable. A recent study has evaluated the association between multiple triglyceride measurements over time and future ASCVD, using data from both the ARIC study and the Framingham Offspring Study [21]. The authors found that, compared with a single triglyceride measurement, average triglycerides over time had greater discrimination for ASCVD risk, even after adjustment for factors associated with both ASCVD and high triglycerides, such as diabetes, LDL-C and HDL-C. However, the use of non-HDL-C weakened the association. This suggests that the risk associated with elevated triglycerides may result from elevations in RLP-C. This is also consistent with genetic studies showing that the risk associated with elevated TGRLs can be accounted for through their association with elevated concentrations of ApoB [22].

Finally, most of these observational epidemiological data were obtained in the prestatin era. As statin therapy is recommended as first-line therapy for high-risk patients with elevated triglycerides [2], it is important to examine whether TGRLs and/or RLP-C elevation have an effect in statin-treated patients.

Arguments from statin-treated patients

In the majority of randomized statin trials, patients with triglycerides > 4.5 mmol/L (396 mg/dL) were excluded, and only data from individuals with mildly to moderately elevated triglycerides were examined. However several analyses (mostly post hoc) have demonstrated associations between triglycerides and outcomes in selected populations, including those from 4S [23], PROVE-IT [24], IDEAL [25], TNT [25,26], MIRACL [27] and dal-OUTCOMES [27].

In 4S, patients in the highest triglyceride (> 159 mg/dL) and lowest HDL-C (< 39 mg/dL) quartiles had the highest risk of ASCVD events on placebo, and the greatest event reduction [23]. In PROVE-IT, on-treatment triglyceride concentration ≥ 150 mg/dL was associated with a

higher risk of recurrent events. In addition, the beneficial effect of reducing LDL-C to < 70 mg/dL was the strongest in subjects with triglyceride concentrations < 150 mg/dL [24]. Similarly, a pooled analysis of the TNT and IDEAL trials showed that triglyceride concentrations ≥ 150 mg/dL were associated with a high risk of ASCVD events in statin-treated patients [25]. In the MIRACL and dal-OUTCOMES studies [27], fasting triglyceride concentrations at study entry predicted recurrent ischaemic events in patients with acute coronary syndrome treated with statins.

More information on the role of RLP-C in statin-treated patients has come from the TNT study [26], in which patients with stable CHD received 10 mg of atorvastatin in a run-in phase, and were then randomized to atorvastatin 10 mg or 80 mg. Atorvastatin 80 mg led to an additional 15.4% reduction in RLP-C and significantly reduced risk in patients with the highest concentrations of RLP-C [26]. This post-hoc analysis provides evidence for a cardiovascular benefit of high-intensity statins in patients with high RLP-C.

Furthermore, in an evaluation of coronary atheroma and clinical events in statin-treated patients from 10 intervention trials [28], higher on-treatment RLP-C concentrations were significantly associated with greater progression of coronary atheroma and an increased cumulative incidence of ASCVD events at 24 months. These results are in agreement with another study reporting a relationship between RLP-C and total coronary atherosclerotic plaque burden [29].

Additionally, a meta-analysis of eight studies published between 1994 and 2008 found that in statin-treated patients, non-HDL-C ≥ 130 mg/dL had a stronger association with risk of ASCVD events than LDL-C ≥ 100 mg/dL [30]. Moreover, patients with non-HDL-C ≥ 130 mg/dL and LDL-C < 100 mg/dL on statin therapy had a 32% increase in risk, illustrating the role of RLP-C in residual ASCVD risk.

Beyond data from randomized clinical trials, several recent population-based cohort studies have also observed associations between elevated triglycerides and ASCVD risk [31–33]. These studies have focused on individuals meeting the REDUCE-IT inclusion criteria [34]. In particular, in the CANHEART cohort of patients with ASCVD [31], increasing triglycerides were associated with a graded progressively higher risk of ASCVD events.

Although observational studies cannot demonstrate causality, these studies strongly suggest that elevated triglycerides represent a marker of ASCVD risk. More evidence for potential causality between elevated TGRLs and ASCVD can be provided by genetic data.

Genetic arguments

Genetic evidence of the link between triglycerides or TGRLs and ASCVD risk has been described in several reviews [3,35]. To determine potential causality between triglyceride concentrations and ASCVD, the most critical issue is the association with low HDL-C concentrations on a population level. However, recent data have shown that TGRLs are causally associated with ASCVD, whereas low HDL-C is not [10,36,37]. For instance, the Copenhagen study [10] found that a non-fasting RLP-C increase of 1 mmol/L (39 mg/dL)

was associated with a 2.8-fold causal risk of ischaemic heart disease, independent of reduced HDL-C.

Furthermore, variants in genes involved in TGRL metabolism, namely LPL and those modulating LPL function, are also associated with ASCVD: heterozygous carriers of LPL loss-of-function and missense pathogenic variants had higher triglyceride concentrations and an increased risk of CHD [38]. A genetic variant in ApoA5 that increased triglyceride concentrations by 16% (0.25 mmol/L) was associated with an increased CHD risk (odds ratio 1.18, 95% confidence interval 1.11–1.26) [39]. A doubling in RLP-C concentrations as a result of mutations in ApoA5 was causally associated with a 2.2-fold increase in the risk of myocardial infarction [40]. By comparison, ApoC3, ANGPTL3 and ANGPTL4 loss-of-function genetic variants appear to lead to increased LPL activity and, consequently, a reduction in plasma triglycerides, which translates into a reduction in ASCVD risk [41–47]: in one study, loss-of-function ApoC3 mutations were associated with 39% lower triglyceride concentrations and a 40% lower risk of CHD [46]. Heterozygous carriers of ANGPTL3 loss-of-function mutations had a 17% decrease in triglycerides, a 12% decrease in LDL-C and a 34% reduction in CHD risk [45]. Currently, there are several therapeutic approaches (either monoclonal antibodies or antisense oligonucleotides) targeting ApoC3 and ANGPTL3 in order to reduce triglycerides and ASCVD risk. Loss-of-function variants in ANGPTL4 are also associated with decreased triglyceride concentrations and CHD risk [42]. However, the use of monoclonal antibodies to inhibit ANGPTL4 has induced side effects in animals [42].

As high-risk patients receive LDL-lowering drugs as first-line therapy, it is important to study the effects of the association of both LDL-C-lowering variants and triglyceride-lowering variants. Two genetic analyses have provided concordant results [22,48]: triglyceride-lowering variants in the LPL gene and LDL-C-lowering variants in the LDL receptor gene were associated with a lower risk of CHD, and the carriers of both variants, lowering triglycerides and LDL-C concentrations, had the lowest risk. Moreover, in one study [22], per 10 mg/dL drop in ApoB, carriers of LPL variants

associated with lower triglycerides and carriers of LDL-receptor variants associated with lower LDL-C had a similar lower CHD risk. This suggests that the clinical benefit of lowering triglycerides and LDL-C should be proportional to the absolute change in ApoB [22]. The second study demonstrated that triglyceride-lowering alleles are also associated with a lower risk of type 2 diabetes [48].

Finally, beyond ASCVD risk, recent Mendelian randomization studies suggest that high triglyceride concentrations are associated with the risk of aortic valve stenosis [49,50] and of abdominal aortic aneurysm [51].

Globally, genetic studies show that, in addition to LDL and lipoprotein(a), remnants of TGRLs are directly causal in ASCVD, with a similar increase in the risk of myocardial infarction for the same cholesterol increment (Table 1).

Treatment of hypertriglyceridaemia to reduce ASCVD risk

Lifestyle modifications, including dietary changes, exercise, reduction of alcohol intake and weight loss, are the most important principles for the management of hypertriglyceridaemia. Beyond lifestyle interventions, and despite the association between triglycerides or RLP-C and cardiovascular risk observed in epidemiological and genetic studies, randomized controlled clinical trials focused on treatments that primarily lower triglyceride concentrations have not consistently shown a reduction in ASCVD events. However, with the exception of the recent REDUCE-IT trial [34], these trials were not specifically conducted in patients with high triglyceride concentrations on statin therapy.

Indeed, although the effects of statins on triglyceride concentrations are limited (usually reduction of triglyceride concentrations by 10–20%), guidelines recommend statins as first-line therapy for patients with elevated triglycerides, with the exception of severe hypertriglyceridaemia [2]. For high-risk and very-high-risk patients, the use of a high-intensity statin is supported by recent data from the TNT study, where intensive treatment with atorvastatin (80 mg vs. 10 mg) induced significantly greater ASCVD risk reductions among patients with higher triglyceride or RLP-C concentrations [26].

In addition to the modest triglyceride-lowering effect of statins, if residual triglyceride-associated risk for ASCVD is high, initiation of a specific triglyceride-lowering drug may be justified. In a recent meta-regression analysis of the three classes of triglyceride-lowering therapies (fibrates, niacin and marine-derived omega-3 fatty acids), triglyceride lowering does appear to be associated with a lower risk of major cardiovascular events, but to a lesser extent per absolute amount of reduction than for LDL-C [52]. Given that both the statin-era niacin trials failed to show a cardiovascular benefit, this drug is not currently available in Europe.

Only one trial, ACCORD-Lipid [53], has examined the effect of fenofibrate used in combination with statin therapy in patients with type 2 diabetes. The authors found no further risk reduction, although subgroup analyses indicated that patients with high triglycerides and low HDL-C may benefit from this combination therapy. An ongoing outcome trial, PROMINENT, using a novel selective

Table 1 Comparison of risk of myocardial infarction associated with 1 mmol/L (39 mg/dL) higher concentrations of low-density lipoprotein cholesterol, remnant lipoprotein cholesterol and lipoprotein(a) cholesterol (data from the Copenhagen General Population Study; adapted from Nordestgaard et al. [56]).

	Increased risk of MI associated with 1 mmol/L higher concentration	
	Observational hazard ratio	Causal risk ratio ^a
LDL-C	1.3	2.1
RLP-C	1.4	1.7
Lp(a)-C	1.6	2.0

Lp(a)-C: lipoprotein(a) cholesterol; LDL-C: low-density lipoprotein cholesterol; MI: myocardial infarction; RLP-C: remnant lipoprotein cholesterol.

^a Genetic data.

Table 2 Summary of the evidence for triglycerides as a cardiovascular risk factor.

Epidemiological evidence	Large population-based studies and secondary prevention studies in statin-treated patients identify triglycerides (fasting or non-fasting) as a marker for ASCVD risk
Genetic evidence	Cholesterol transported in TGRLs (RLP-C) is a causal factor for cardiovascular diseases and all-cause mortality Several variants in the genes involved in the metabolism of TGRLs are associated with ASCVD
Therapeutic evidence	Statins are recommended as first-line therapy for high-risk/very-high-risk patients with elevated triglycerides Only one trial (REDUCE-IT) has shown a significant benefit in statin-treated patients with high triglyceride concentrations (benefit unexplained by triglyceride reduction alone) More evidence is needed and should be obtained by novel agents developed to lower triglyceride concentrations

ASCVD: atherosclerotic cardiovascular disease; RLP-C: remnant lipoprotein cholesterol; TGRLs: triglyceride-rich lipoproteins.

peroxisome proliferator-activated receptor alpha modulator called pemafibrate, will provide important insights for patients with type 2 diabetes on statin therapy and with moderate hypertriglyceridaemia and low HDL-C [54].

In a meta-analysis of 10 trials involving more than 77,000 individuals, supplementation with low doses of omega-3 fatty acids was not associated with a cardiovascular benefit [55]. However, the REDUCE-IT trial [34] changed the perception of this class: a high dose (4g/day) of icosapent ethyl, purified eicosapentaenoic acid or placebo was added to background statin therapy in patients with elevated triglycerides (150–499 mg/dL) and either cardiovascular disease or diabetes and an additional risk factor. A dramatic risk reduction was observed for ASCVD over a period of 4.9 years, with a 25% relative risk reduction and a 4.8% absolute benefit, concomitant with a 20% reduction in triglycerides and a 40% reduction in C-reactive protein concentrations [34]. It remains unclear whether the observed benefit relates to the particular omega-3 fatty acid formulation or/and the high daily dose. Of note, another similar study (STRENGTH), with high doses of both eicosapentaenoic acid and docosahexaenoic acid, was stopped recently for futility. In any case, the benefit of high-dose eicosapentaenoic acid appears to exceed what would be expected from the reductions in triglycerides or ApoB [52].

Finally, novel therapeutic approaches targeting either ApoC3 or ANGPTL3, as supported by genetic studies, are under investigation [4,7].

The evidence for a role for TGRLs in the risk of ASCVD is summarized in Table 2.

Conclusions

Despite the reduction in ASCVD events seen with statins and additional LDL-lowering therapies, there is a substantial residual risk of recurrent events. Elevated triglycerides can be used to identify patients with higher residual risk as a result of the presence of potentially atherogenic TGRLs. Indeed, TGRLs have emerged as important contributors to residual risk on statin therapy, and genetic studies strongly

support the hypothesis that remnants of TGRLs are a causal cardiovascular risk factor.

Beyond lifestyle changes and statin therapy, a recent trial with high-dose icosapent ethyl showed a significant cardiovascular benefit in high-risk patients with hypertriglyceridaemia. Moreover, genetic studies have provided novel treatment targets to lower serum triglycerides, and clinical trials will be needed to test their impact on cardiovascular outcomes.

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