



Genetics of Triglyceride-Rich Lipoproteins Guide Identification of Pharmacotherapy for Cardiovascular Risk Reduction

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Abstract

Objective: Despite aggressive reduction of low-density lipoprotein cholesterol (LDL-C), there is a residual risk of cardiovascular disease (CVD). Hypertriglyceridemia is known to be associated with increased CVD risk, independently of LDL-C. Triglycerides are one component of the heterogeneous class of triglyceride-rich lipoproteins (TGRLs). **Methods/Results:** Growing evidence from biology, epidemiology, and genetics supports the contribution of TGRLs to the development of CVD via a number of mechanisms, including through proinflammatory, proapoptotic, and procoagulant pathways. **Conclusion:** New genetics-guided pharmacotherapies to reduce levels of triglycerides and TGRLs and thus reduce risk of CVD have been developed and will be discussed here.

Keywords Hypertriglyceridemia, · Triglyceride-rich lipoproteins, · Pharmacotherapy, · Cardiovascular disease, · Triglycerides, · Genetics

Introduction

Cardiovascular disease (CVD) remains the leading cause of death in the world, causing nearly 860,000 deaths in the USA alone and 17.8 million globally in 2017 [1]. As a result of significant clinical evidence, low-density lipoprotein cholesterol (LDL-C) reduction via statin therapy has long been a mainstay of primary and secondary prevention of atherosclerotic CVD [2]. However, there appears to be a residual cardiovascular risk even with the use of therapies that aggressively reduce LDL-C levels [3, 4]. This residual risk remains even after multivariate adjustment for other risk factors, including lifestyle factors and comorbidities. Systematic reviews of lipid-lowering therapies that reduce triglyceride (TG) levels more than LDL-C levels demonstrate that

lower TG levels are associated with a lower risk of major vascular events, even after adjusting for LDL-C reductions [5].

A growing body of evidence derived from Mendelian randomization (MR) indicates that triglyceride-rich lipoproteins (TGRLs) contribute to the development of atherosclerotic coronary artery disease. TGRLs constitute a heterogeneous class of particles, synthesized from exogenous (chylomicrons) and endogenous (very low-density lipoprotein [VLDL] and intermediate density lipoprotein [IDL]) pathways [6]. Insights from biology, epidemiology, and genetics suggest a causal association between elevated TGRLs, CVD, and mortality [7–9].

This review aims to discuss the association between TGRLs and risk of atherosclerotic CVD, as well as the latest genetics-guided pharmacotherapies for TG reduction.

Metabolism of TGRLs

TGRLs are composed of a neutral core of TG and cholesterol esters and a surface monolayer of phospholipids, free cholesterol, and apolipoproteins [10, 11]. TGRLs are synthesized through an exogenous, enterocyte-based pathway and an endogenous hepatocyte-based pathway (Figure 1). Chylomicrons are predominantly formed in the jejunum through the exogenous pathway, and VLDL is synthesized by the liver [12].

After consumption of a meal, gastric lipase in the stomach and then pancreatic lipase in the proximal small intestine hydrolyze

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dietary TG to form fatty acids and 2-monoacylglycerol (MG) [13]. These lipid products are emulsified by bile salts to produce micelles, which facilitate their absorption by enterocytes through either passive diffusion or with assistance from transporter proteins. Once in the enterocyte, monoacylglycerol:acyl CoA transferase (MGAT) at the smooth endoplasmic reticulum (ER) membrane combines fatty acids and MG into diacylglycerol acids. The enzyme diacylglycerol:acyl CoA transferase (DGAT) subsequently converts these into TG [14]. The TG, along with some cholesteryl esters, are released into the cytosol in transient lipid droplets.

Chylomicron assembly continues through the two-step secretory pathway: the major chylomicron protein, apoB-48, is synthesized in the rough ER and then fuses with lipid droplets to create the primordial chylomicron—both steps require assistance from the microsomal transfer protein (MTP). Pre-chylomicron transport vesicles carry these particles from the ER to the Golgi apparatus where the chylomicrons mature further. As the chylomicron travels between ER and Golgi compartments, various apolipoproteins, such as apoC-III, apoA-I, and apoA-IV, are added to the phospholipid monolayer, creating a diverse array of chylomicron particles [15].

Of note, the size and composition of chylomicrons is dependent on the amount and type of dietary fat ingested and absorbed. They are predominantly composed of TG molecules. Since each chylomicron only has one apoB-48, the variation in size is due to intestinal lipid flux [16, 17].

Mature chylomicrons are ultimately secreted from the basal pole of the enterocyte to the peri-mesenteric lymphatics, which drain into the circulation via the thoracic duct, where they contribute to the postprandial TG concentrations [18]. In the circulation, chylomicrons further acquire apoC-II, apoC-III, and apoE lipoproteins from HDL molecules often via intravascular exchange for apoA-I and apoA-IV. ApoC-III is secreted by both the small intestine and the liver and is exchanged between circulating TGRLs [19]. In addition, the plasma cholesteryl ester transfer protein (CETP) facilitates the intravascular exchange of cholesteryl ester in HDL molecules for TG in the apoB-containing lipoproteins. Thus, chylomicrons that are present longer in the circulation become more enriched in cholesteryl ester. (Unfortunately, several CETP-inhibiting drugs have failed to show meaningful clinical improvement despite increasing HDL levels.) [20]

Lipoprotein lipase (LPL) is an endothelium-localized enzyme that is activated by apoC-II. Hydrolysis of core triglyceride from chylomicrons elaborates free fatty acids and results in the formation of chylomicron remnants. Free fatty acids are oxidized into adenosine triphosphate (ATP) as an energy source by skeletal muscle cells and cardiomyocytes. Excess fatty acids are acquired by adipocytes through diffusion and protein-mediated uptake to be stored [21]. Meanwhile, chylomicron remnants, which are now enriched in cholesteryl esters and contain apoE, bind to LDL receptors (LDLR) on hepatocytes via the apoE ligand or

the LDL receptor-related protein 1 (LRP1) through the heparan sulfate proteoglycan pathway and are ultimately removed from the circulation [22]. A third mechanism of clearance via the syndecan-1 receptor and an independent heparan sulfate proteoglycan pathway in hepatocytes also exists [23].

LPL is synthesized by myocytes and adipocytes, which utilize fatty acids for energy and TG storage, respectively [24]. The endothelial glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein-1 (GPIHBP1) binds LPL at its hydrolase domain, preventing its denaturation and translocates it to the luminal side of capillaries where it can hydrolyze chylomicrons [25–27]. LPL is activated by apoC-II and is further tightly regulated at the transcriptional, posttranscriptional, translational, and posttranslational levels [28].

One such regulatory protein is angiopoietin-like protein 4 (ANGPTL4), secreted by adipocytes during fasting states, which inhibits LPL activity, thus increasing plasma TG levels [29, 30]. ANGPTL4 catalyzes the unfolding of the hydrolase domain in LPL, leading to the dissociation of the catalytically active dimer into inactive, unstable monomers [31]. Similarly, angiopoietin-like protein 3 (ANGPTL3) also raises plasma TG levels by inhibiting LPL and HDL-C levels by inhibiting endothelial lipase activity [32]. ANGPTL3 loss-of-function variants result in lower levels of plasma lipoproteins, as seen in conditions like familial hypolipidemia [33].

Meanwhile, increased expression of the *APOC3* gene results in hypertriglyceridemia in mice and a null mutation in the gene decreases TG levels, but the mechanism by which apoC-III reduces TG catabolism is less certain [34, 35]. While it was initially believed that apoC-III inhibits LPL via direct competition with apoC-II, this has only been found to be the case when the ratio of apoC-III to apoC-II molecules is higher than what is typically physiologically seen [36]. Further challenging the physiological impact of apoC-III on LPL inhibition, a study in familial chylomicronemia syndrome (FCS) patients, in whom significantly reduced LPL activity results in extremely high plasma TG levels, found that antisense oligonucleotides targeting hepatic *APOC3* expression led to reductions in plasma TG levels, suggesting that apoC-III acts independently of LPL as well [37]. Subsequent research demonstrated that apoC-III in fact prevents LDLR and LRP1-mediated remnant TGRL clearance, though the exact mechanism is still under investigation [38]. Another potential mechanism is that the coexistence of apoC-III on VLDL particles reduces apoE binding to LDLR, LRP1, and the syndecan-1 receptor, opposing the role of apoE in metabolism [39]. Conversely, a higher apoE content of VLDL was associated with a lower risk of CVD [40].

The endogenous pathway of TGRL metabolism results in VLDL synthesis in hepatocytes. First, the apoB-100 lipoprotein is made by the rough ER in hepatocytes. Then, similar to the production of chylomicrons, once triglycerides are synthesized from free fatty acids and glycerol, they are subsequently incorporated into the core of the apoB-100 VLDL particles, with

help from MTP. VLDL transport vesicles then facilitate movement to the Golgi for further maturation and acquisition of apoE [41, 42]. Upon being secreted into the circulation, VLDL particles gain additional apolipoproteins. LPL again mediates the hydrolysis of VLDLs, resulting in progressively smaller and denser VLDLs and then IDLs, with progressively diminishing amounts of TG (Table 1 and Fig. 1).

Key pathways regulating intestinal and hepatic synthesis and metabolism of triglyceride-rich lipoproteins (TGRLs) are illustrated (see the text for details of these pathways and their genetic regulation).

ANGPTL3 = angiopoietin-like protein 3; Apo = apolipoprotein; CE = cholesterol ester; CETP = cholesteryl ester transfer protein; DGAT = diglyceride acyltransferase; ER = endoplasmic reticulum; FA = fatty acid; HSPG = heparin sulfate proteoglycan; GHIHBP1 = glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1; HDL = high-density lipoprotein; HMG-CoA = hydroxymethylglutaryl-coenzyme A; IDL = intermediate-density lipoprotein; LDL = low-density lipoprotein; LDL-R = low-density lipoprotein receptor; LPL = lipoprotein lipase; LRP1 = low-density lipoprotein receptor-related protein; MG = monoglyceride; MGAT = monoglyceride acyl transferase; MTP = microsomal transfer protein; NPLC1L1 = Niemann-Pick C1 like; PCSK9 = proprotein convertase subtilisin/kexin type 9; PPAR- α = peroxisome proliferator-activated receptor; SERBP-2, sterol regulatory element-binding protein 2; TG = triglyceride; VLDL = very low-density lipoprotein

Pathophysiology of TGRL-Mediated Atherosclerosis


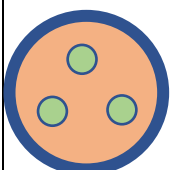
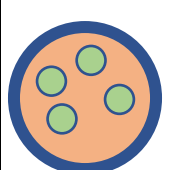
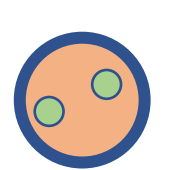
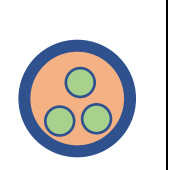
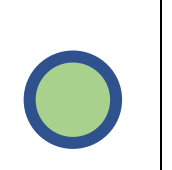
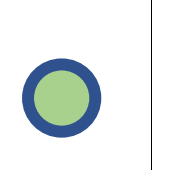
There are several proposed mechanisms by which TGRLs both directly and indirectly promote atherosclerosis. The

products of LPL-mediated TGRL lipolysis contribute to atherosclerosis via proinflammatory, procoagulant, and proapoptotic gene activation mechanisms. Similar to LDL, TGRLs and their remnants, which are now cholesterol-rich and TG-depleted, can penetrate the arterial wall and can be bound within the connective tissue matrix. From the subendothelial space, they are then scavenged by arterial wall macrophages, contributing to the formation of macrophage foam cells and plaque progression as the cholesterol cannot be metabolized [43–45]. Remnant cholesterol levels can be estimated by non-HDL-C minus LDL-C. Unlike LDL, which must undergo oxidative modification in order to be taken up by macrophages, TGRLs need no further modification [46–48]. Additionally, their larger size allows them to carry more cholesterol per particle than LDL, making them equally as or more atherogenic than LDL. VLDL receptors on the macrophage surface selectively recognize apoE ligands rather than apoB, allowing them to bind TGRLs and not LDL [49]. The apoE4 isoform specifically has been found to increase the risk of atherosclerosis in part due to its increased association with VLDL and its subsequent enhanced interaction with LDLR in macrophages [50, 51].

Furthermore, endothelial dysfunction occurs as TGRL lipolysis releases oxidized and neutral free fatty acids that stimulate endothelial inflammation, vascular apoptosis, and reactive oxygen species (ROS) production in endothelial cells. ROS can increase the permeability of vascular endothelium, promote leukocyte adhesion, and even lead to cell injury and death [52]. The increased secretion of proapoptotic cytokines, tumor necrosis factor alpha (TNF- α) and interleukin 1 beta (IL-1 β), impair endothelium-dependent vasodilation, increase arterial inflammation, and induce endothelial apoptosis [53].

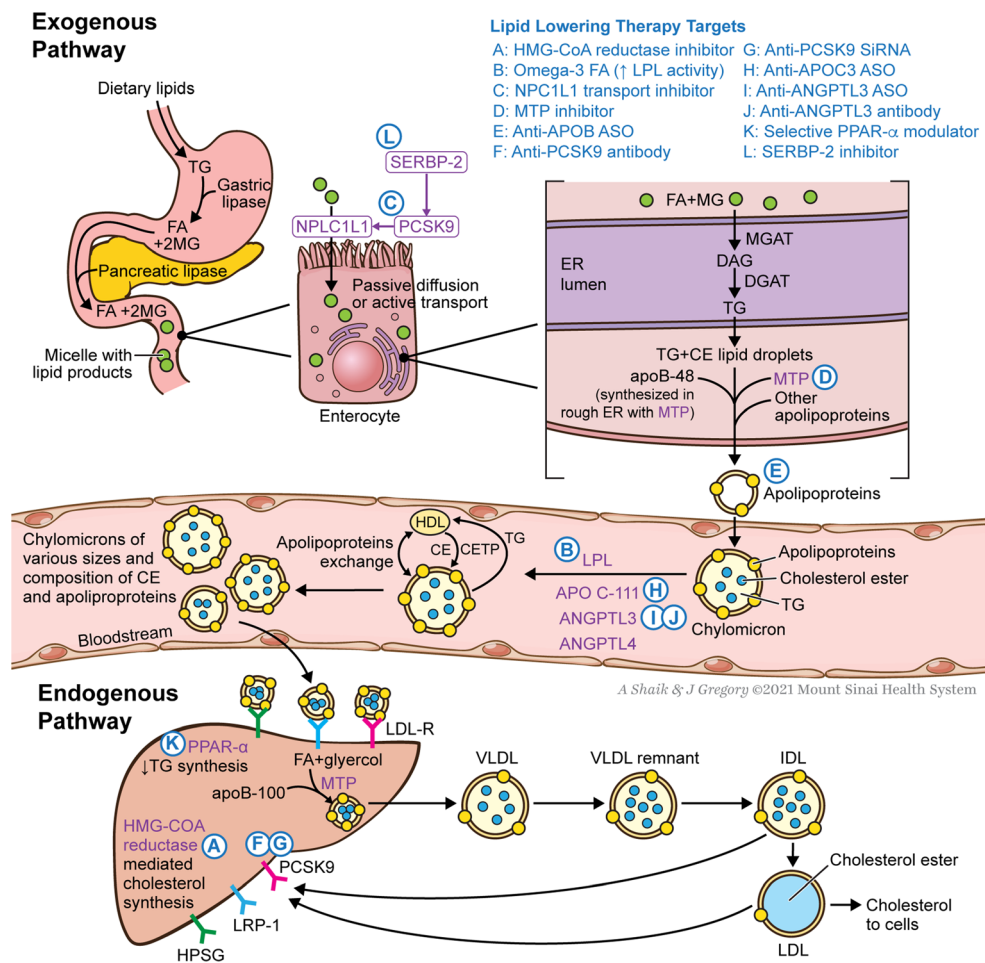
Finally, inflammation activation occurs as the oxidized free fatty acids released from TGRL hydrolysis induce the expression of inflammatory cytokines (TNF-a) and interleukins (IL-

Table 1 Lipoprotein classes and composition

	Chylomicron	Chylomicron Remnant	VLDL	IDL	LDL	HDL
						
Density	<0.93	0.93-1.006	0.93-1.006	1.006-1.019	1.019-1.063	1.063-1.210
Major Lipids	Triglycerides	Triglycerides Cholesterol	Triglycerides	Triglycerides Cholesterol	Cholesterol	Cholesterol Phospholipids
Major Apolipoproteins	ApoB-48, ApoC, ApoE, ApoA-I, ApoA-IV	ApoB-48, ApoE	ApoB-100, ApoE, ApoC	ApoB-100, ApoE, ApoC	ApoB-100	ApoA-I, ApoA-II, ApoC, ApoE

PL, phospholipid bilayer; CE, cholesteryl ester; TG, triglyceride; VLDL, very low-density lipoprotein; IDL, intermediate density lipoprotein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; apo, apolipoprotein

Fig. 1 Synthesis and metabolism of TGRLs



1, IL-6, IL-8). TGRL remnants upregulate the expression of proatherogenic adhesion molecules (intracellular adhesion molecule-1 and vascular cell adhesion molecule-1 [VCAM-1]), which facilitate leukocyte migration to areas of inflammation [54]. They also promote the early activation of monocytes and neutrophils. As a result, inflammatory response is enhanced. TGRLs with lower levels of TG have an atheroprotective effect due to decreased VCAM-1 expression and monocyte recruitment [54–56].

TGRLs and remnants also have a procoagulant effect as they enhance platelet aggregation and clot formation by promoting prothrombinase complex assembly and upregulating plasminogen activator inhibitor-1 and plasminogen activator inhibitor-1 antigen expression [57].

Data from computed tomography coronary angiography in patients with suspected CVD has shown that remnant cholesterol levels are associated with significant coronary atherosclerotic plaque burden, even when LDL-C were optimal [58]. There is limited data analyzing more invasive measurements of plaque burden in relation to lipid levels. Challenges with such a study include the multifactorial nature of plaque development and the polygenic causes of hypertriglyceridemia.

Support from Genetic Studies

Human genetic studies over the past several decades have supported the hypothesis that TGs causally influence the development of ASCVD (Table 2). A large Mendelian randomization study utilizing the data from over 10,000 Copenhagen City Heart Study subjects found that decreased concentrations of non-fasting TG as a result of genetic variants in LPL were associated with reduced all-cause mortality [59].

Another multivariable Mendelian randomization meta-analysis examined 185 single nucleotide polymorphisms (SNPs) mapped for lipids in 188,578 people and found a strong correlation between the strength of a particular SNP's effect on TG levels and the magnitude of its effect on CAD risk. These findings were consistent even with adjustment for effects on LDL-C and HDL-C, supporting the causal influence of TGRLs on CAD risk [60]. Similarly, sequence variants in genes encoding LPL and its regulatory proteins demonstrated a strong association between TGRL metabolism and CAD risk in targeted and exome-wide analyses [61–63].

As mentioned previously, loss-of-function studies show that apoC-III overexpression results in hypertriglyceridemia and thus with worsening cardiovascular risk [64]. In one such

study, an analysis of 75,725 individuals found that when compared to wildtype individuals, those with heterozygous loss-of-function mutations in the *APOC3* gene had a 44% reduction in non-fasting TG levels, which corresponded with a 41% reduction in incidence of CVD [65]. Another study identified four loss-of-function mutations in the *APOC3* gene in 3734 individuals. Compared to noncarriers, those who were heterozygous carriers for any of these mutations had a 46% lower concentration of circulating apoC-III, resulting in a 39% lower plasma TG levels and corresponding with a 40% lower risk of CAD [66].

Similar conclusions were drawn from studies of loss-of-function variants in the *ANGPTL4* and *ANGPTL3* genes. When compared to noncarriers, carriers of the *ANGPTL4* variant had lower TG levels and a lower incidence of CAD events [67]. Patients with heterozygous loss-of-function variants in *ANGPTL3* in the DiscovEHR human genetics study also had significantly lower levels of TG, HDL-C, and LDL-C than noncarriers. These variants were associated with a decreased odds (adjusted odds ratio 0.59, $p=0.004$) of ASCVD [68].

Meanwhile, contrasting effects were noted in studies with loss-of-function mutations in the *APOA5* gene, which encodes for ApoA-V, an LPL activator. Heterozygous carriers of *APOA5* mutations have higher TG levels and were at a 2.2-fold higher risk of myocardial infarction (MI) than noncarriers [69]. In addition, a polymorphism in the promoter region of *APOA5* demonstrated an elevated risk of genetically increased TG levels and a resultant increase in CAD [70].

Furthermore, individuals with hyperlipoproteinemia type 3, a monogenic disorder of TG metabolism, are known to be predisposed to CAD, suggesting that the accumulation of TG and remnant cholesterol molecules are significant in their contributions to CVD risk [71].

With regards to the role of HDL-C, classic studies, including the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT), indicated an inverse association between HDL-C levels and CAD risk [72–74]. The Heart Institute of Japan-Prospective level of lipid lowering with Pitavastatin and Ezetimibe in acute coronary syndrome (HIJ-PROPER) study presented an association between lower

levels of HDL-C and higher incidence of cardiovascular events in patients with acute coronary syndrome (ACS) [75]. However, per more recent mendelian randomization studies, this relationship does not appear to be causal [76]. This was also demonstrated in the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes (AIM-HIGH) trial as the addition of niacin did not result in significant clinical benefit despite raising HDL-C levels [77] (Table 2).

Classic Triglyceride-Lowering Therapies

The foundation of hyperlipidemia management is lifestyle modifications. When secondary factors, unhealthy diets, and poor exercise are addressed, a plasma TG level reduction of up to 60% can be seen [78]. In addition to primarily LDL-lowering therapies, such as statins and ezetimibe, there are currently three classes of drugs available for hypertriglyceridemia management: fibrates, niacin, and omega-3 fatty acids.

Fibrates

Fibrates activate peroxisome proliferator-activated receptor alpha (PPAR- α), a nuclear receptor protein that increases the expression and activity of LPL, apoA-I, and other such genes, while reducing the production of apoB, apoC-III, and VLDL, ultimately having a hypotriglyceridemic effect [79]. PPAR- α promotes fatty acid oxidation and ketogenesis during fasting states [80]. In the VA-HIT and the Helsinki Heart Study, gemfibrozil was found to reduce the risk of ASCVD, but no statistically significant improvement in mortality was noted [73]. In the Helsinki Heart Study, gemfibrozil was noted to have a 34% reduction in the incidence of CAD [81]. Of note, gemfibrozil was found to inhibit the glucuronidation of statins and thus reduce their renal clearance, possibly resulting in serious adverse effects, including rhabdomyolysis [82, 83].

In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, fenofibrate resulted in a 24%

Table 2 DNA sequence variants in lipoprotein lipase-regulating genes effects on triglyceride levels (TG) and cardiovascular disease (CVD) risk

Gene	Protein	Effect of variant on protein function	Effect of mutation on LPL activity	Effect on TG	Effect on CVD risk
<i>LPL</i>	LPL	Loss	Decrease	↑	↑
		Gain	Increase	↓	↓
<i>APOA5</i>	ApoA-V	Loss	Decrease	↑	↑
<i>APOC3</i>	ApoC-III	Loss	Increase	↓	↓
<i>ANGPTL3</i>	ANGPTL3	Loss	Increase	↓	↓
<i>ANGPTL4</i>	ANGPTL4	Loss	Increase	↓	↓

reduction in nonfatal myocardial infarctions and a significant reduction in total cardiovascular events. However, there was no significant reduction in the primary outcome of coronary events [84]. Furthermore, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study demonstrated that the combination of fenofibrate and simvastatin did not significantly improve CVD risk when compared to simvastatin alone in patients with type 2 diabetes who were at high risk for CVD [85]. However, post hoc analyses of subgroups with high TG and low HDL-C in each of the aforementioned studies suggested that patients with TG levels greater than 200 mg/dL may benefit. Fenofibrate monotherapy reduced TG levels by 25–50% and LDL-C levels, depending on baseline TG and LDL-C levels, and also raises HDL-C levels by 5–15% [86]. In men with hypertriglyceridemia with low HDL-C, treatment with micronized fenofibrate resulted in a 7% decrease in apoB levels [87]. Potential fibrate-related adverse effects to consider include creatinine level elevations, myopathy, rhabdomyolysis, and increased risk of hepatic steatosis.

Niacin

Niacin inhibits lipolysis in adipocytes, thus reducing the production of fatty acids, which further leads to a decrease in VLDL synthesis in the liver. In addition, niacin reduces concentrations of apoB by accelerating its clearance, notably in hepatic cells [88, 89]. Despite the reduction in TG levels, the Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) and the AIM-HIGH studies did not find adding extended-release niacin (ER-niacin) to statin monotherapy to have a significant impact on risk for cardiovascular events [77, 90]. In patients with type 2 diabetes mellitus, dose-related TG level reductions were noted. Those receiving 1000-mg ER-niacin did not have a statistically significant reduction in TG compared to placebo. Those receiving ER-niacin 1500 mg had a median reduction in TG levels of 28–36%. However, worsening of glycemic status was noted in 27% of individuals in the latter group, potentially diminishing the TG-lowering effect of this agent [91]. With ER-niacin, there was a mild 13% decrease in apoB levels at 1 year in the AIM-HIGH trial, but lipoprotein concentration changes did not significantly affect CVD risk [92]. Additionally, niacin use is associated with a high incidence of side effects, including chemical hepatitis, hyperglycemia, myopathy, and, most commonly, flushing due to cutaneous vasodilation.

Omega-3 Fatty Acids

Omega-3 fatty acids are essential in the formation and stability of cell membranes. They also act as precursors for inflammatory mediators, like prostaglandins, eicosanoids, and

leukotrienes. They lower TG levels by reducing TG and apoB secretion from the liver and increasing LPL activity and the rate of TG clearance from the circulation [93]. The most common side effects of omega-3 fatty acids are gastrointestinal. Unfortunately, studies examining the cardiovascular outcomes of omega-3 fatty acids have produced inconsistent results.

There are three major omega-3 fatty acids, each of which has overlapping but unique activities: eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and docosapentaenoic acid (DPA). EPA and DHA both downregulate transcription factor SREBP-1c, which controls lipogenesis. However, EPA is a more potent PPAR- α agonist than DHA. Meanwhile, DHA is more involved in the regulation of hepatic nuclear factor-4 α , forkhead box O transcription factor O1, and carbohydrate response element-binding protein [94]. Formulations of these omega-3 fatty acids have been shown to reduce plasma TG levels by 25–45% in patients with severe hypertriglyceridemia [95–97].

The EpanoVa fOr Lowering Very high triglyceridEs (EVOLVE) trial demonstrated the effectiveness of omega-3 fatty acids in postprandial, exogenous metabolism, reducing TG and non-HDL-C levels [98]. Furthermore, the Japan EPA Lipid Intervention Study (JELIS) showed a significant reduction in major coronary events when EPA was used in addition to a statin compared to statin monotherapy in patients with a history of CAD [99]. When used in high-risk patients in the Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT), high-dose icosapent ethyl, a highly purified formulation of only EPA, resulted in a significant reduction in major adverse cardiovascular events by 25% and other secondary CVD endpoints by 20–35%. TG levels were reduced by a net of 15% and apoB levels by 9.7%. However, there were no significant differences in the clinical impact of icosapent ethyl in patients with lower or higher baseline TG levels or whether posttreatment TG levels were reduced, suggesting that EPA affects ASCVD risk via non-TG-lowering mechanisms, likely through a multitude of ways [100, 101]. Early results of the Effect of Vascepa on Improving Coronary Atherosclerosis in People with High Triglycerides Taking Statin Therapy trial (EVAPORATE; NCT02926027) demonstrated a statistically significant reduction in low-attenuation coronary plaque volume by coronary computed tomographic angiography in patients treated with high-dose icosapent ethyl after 18 months [102]. Meanwhile, the Phase III Statin Residual Risk Reduction with Epanova in High CV Risk Patients with Hypertriglyceridemia (STRENGTH) trial was discontinued in early 2020 after initial data suggested that Epanova, a combination of EPA and DHA, had a low likelihood of clinical benefit [66, 103].

LDL Therapies with Triglyceride-Lowering Efficacy

While not primarily TG-lowering agents, *statins* can reduce TG levels by 22–45% in those with baseline TG levels >250mg/dL, with more modest reductions for those with lower baseline TG levels [104]. Atorvastatin has been shown to have dose-dependent reduction effects on total serum TG levels when compared to placebo and lowers TGs in all lipoprotein fractions [105]. In patients with TG levels between 300 and 800 mg/dL, high doses of high-potency statins (i.e., atorvastatin 40 and 80 mg daily and rosuvastatin 20 and 40 mg daily) can reduce TG levels by 37 to 43% [106]. These data support the role of statins in lowering VLDL. However, when the fasting TG concentration is greater than 850–880 mg/dL, statins have limited efficacy as chylomicrons are the predominant plasma lipoproteins. Statins also reduce apoB-containing lipoprotein levels by decreasing hepatic VLDL production, and thus apoB secretion, and increasing LDL receptor-mediated clearance [107]. In the Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin (STELLAR) trial, rosuvastatin was noted to lower apoB levels by 36.7 to 45.3% [108].

Ezetimibe inhibits the Niemann-Pick C1 Like 1 (NPC1L1) transporter protein, which is responsible for absorbing cholesterol in the small intestine. Inhibition of the transporter channels in hepatocytes also results in decreased reabsorption of cholesterol from the intestines, so that there is an increase in cholesterol excretion from the body and decreased production of apoB lipoprotein [109]. Furthermore, there is a resultant increase in hepatic uptake and degradation of apoB-containing lipoproteins [110]. The Efficacy and Safety of Ezetimibe for Japanese Patients with Dyslipidemia (ESSENTIAL) study demonstrated the efficacy of ezetimibe in reducing LDL-C levels when used both as monotherapy and with a statin after 12 weeks in Japanese patients with dyslipidemia [111]. In the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), ezetimibe-simvastatin combination therapy (32.7% Kaplan-Meier event rate) resulted in a statistically significant absolute risk reduction of 2% compared to simvastatin monotherapy (34.7% event rate), where the primary endpoint was cardiovascular death, nonfatal MI, nonfatal stroke, and unstable angina needing rehospitalization and revascularization more than 30 days after randomization in the study. Rates of adverse effects were similar in both groups [112]. There was a 13% reduction in apoB levels with ezetimibe alone and a 48% reduction with simvastatin-ezetimibe combination therapy [113].

Lomitapide inhibits MTP, thus interfering with the assembly of apoB-containing lipoproteins and resulting in decreased secretion of both VLDL and chylomicron secretion. Lomitapide 40mg daily was shown to significantly reduce

LDL-C levels by 50% in patients with homozygous familial hypercholesterolemia. TG, apoB, and total cholesterol levels were also lower in lomitapide-treated patients compared to placebo, with reductions by 45, 49, and 46%, respectively. However, it was also noted to have reduced HDL-C and apoA-1 levels by 12 and 14%, respectively [114]. Additionally, it is associated with adverse effects including severe gastrointestinal disturbances (such as nausea, vomiting, and diarrhea) and hepatotoxicity as transaminitis and steatosis progressed to fibrosis. Lomitapide also has numerous CYP3A4 interactions. Two case studies have demonstrated the utility of lomitapide in patients with familial chylomicronemia. In the first, the patient had a significant history of recurrent near-fatal pancreatitis as a result of severe hypertriglyceridemia. On starting lomitapide, her fasting TG concentration was reduced from greater than 3000 to 525mg/dL and she did not have further episodes of pancreatitis. However, after 12 to 13 years, her pre-treatment fatty liver progressed to steatohepatitis and fibrosis [115]. Recently, another case study of a patient with recurrent pancreatitis in the setting of familial chylomicronemia demonstrated a 67% reduction in TG levels from baseline, though again with persistent liver steatosis [116]. Given the unclear overall effect on lipids and concern for adverse effects, lomitapide is currently only FDA-approved for the treatment of homozygous familial hypercholesterolemia.

Mipomersen is a second-generation antisense oligonucleotide. It binds to apoB mRNA in hepatocytes, causing its degradation and thus reducing apoB production. As a result of decreased levels of apoB, there is also a decrease in production of chylomicrons, VLDL, and LDL particles. Unlike with lomitapide, a meta-analysis demonstrated that mipomersen significantly reduces non-HDL-C, LDL-C, and apoA-I without reducing HDL-C levels. It was found to decrease apoB levels by 38% and lipoprotein(a) levels by 24% [117]. Adverse effects of concern with mipomersen include transaminitis, hepatic steatosis, and injection site reactions. Like lomitapide, it is currently only FDA-approved for the treatment of homozygous familial hypercholesterolemia in the USA, but manufacturing of mipomersen was discontinued in 2018.

Evolocumab is a monoclonal antibody that inhibits the enzyme proprotein convertase subtilisin/kexin type 9 (PCSK9), which normally recycles LDL receptors on the cell surface, decreasing LDL particle ingestion and increasing plasma LDL-C levels. In the large-scale randomized Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial, evolocumab reduced LDL-C levels by 59% and reduced the risk of cardiovascular endpoints (9.8% vs 11.3%, $P<0.001$) when compared to placebo. Injection site reactions were more common with evolocumab, but otherwise, there were no significant differences in rates of adverse events, like new-onset diabetes

and neurocognitive events [118]. A secondary ad hoc analysis of the FOURIER trial demonstrated the comparable efficacy of evolocumab in reducing cardiovascular events irrespective of baseline LDL-C levels (less than 70 mg/dL vs at least 70 mg/dL) and whether the background statin was one of maximum potency [119]. In a study of patients with mixed hyperlipidemia and type 2 diabetes, evolocumab lowered fasting and postprandial chylomicrons suggesting that an increase in LDL (apoB/E) receptor facilitates clearance of remnant particles [120]. A pooled analysis of evolocumab phase 2 and 3 trials demonstrated that it results in comparable significant reductions in LDL-C, non-HDL-C, and apolipoprotein B levels both in patients with and without mixed hyperlipidemia. A modest reduction in TG levels and increase in HDL-C were also noted [121].

Alirocumab is another subcutaneously administered monoclonal antibody against PCSK9. The Evaluation of Cardiovascular Outcomes after an Acute Coronary Syndrome During Treatment with Alirocumab (ODYSSEY Outcomes) trial demonstrated that among patients with prior ACS, the addition of alirocumab to a high intensity statin was associated with a lower risk of recurrent ischemic CVD events than among those who received placebo. The absolute benefit was greater in patients with a baseline LDL-C level greater than 100mg/dL when compared to those with lower baseline levels. The incidence of adverse events was similar in the two groups with a slightly higher incidence of injection site reactions with alirocumab [122]. A pooled analysis of eight controlled phase 3 ODYSSEY trials showed similar significant reductions in LDL-C, non-HDL-C, and apolipoprotein B levels regardless of revascularization status. There was no statistically significant change in TG levels [123]. However, in the Long-term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with their Lipid Modifying Therapy (ODYSSEY LONG TERM) trial, a mean reduction of 15.6% in TG levels was noted among patients at high risk for cardiovascular events being treated with alirocumab compared to a mean increase of 1.8% in the placebo group [124]. PCSK9 inhibition also results in reduction of the pro-atherogenic lipoprotein(a), which is an LDL particle with apo(a) and apoB-100 moieties. A recent post hoc analysis of the ODYSSEY trial determined that reduction in lipoprotein(a) by alirocumab was an independent contributor to the reduction of major adverse cardiovascular events, suggesting that lipoprotein(a) could be a treatment target in post-ACS patients. The baseline levels of lipoprotein(a) predicted the total risk of cardiovascular events and the alirocumab-induced risk reduction [125].

Inclisiran is another PCSK9 inhibitor, but unlike evolocumab and alirocumab, it is a small interfering RNA molecule that binds to the PCSK9 mRNA and promotes its degradation. Inclisiran thus leads to reduced PCSK9,

increased LDL receptor, and reduced plasma LDL-C levels. The Inclisiran or Participants with Atherosclerotic Cardiovascular Disease and Elevated Low-Density Lipoprotein Cholesterol ORION 10 and ORION 11 trial demonstrated a 52.3 and 49.9% reduction in LDL-C, respectively, in the inclisiran group compared to the placebo group after 18 months in patients with increased ASCVD risk and elevated LDL-C levels despite maximal statin therapy. Inclisiran also resulted in apoB level reductions of 44.8 and 38.2% in ORION 10 and ORION 11, respectively. A median reduction of 14.9 and 12% in TG levels was noted in the two trials [126]. The ORION 9 trial similarly showed a reduction of 39.7% in LDL-C levels with inclisiran in patients with heterozygous familial hypercholesterolemia [127]. Unlike typical PCSK9 inhibitors which require monthly or bimonthly injections, inclisiran need only be administered biannually. The ongoing ORION 4 trial is examining the long-term cardiovascular outcomes inclisiran use has in patients being treated with statins as well.

Novel Triglyceride-Lowering Therapies

As more is learned from genetic studies about the mechanisms by which TGRLs promote atherosclerosis, new approaches for therapeutic drug targeting are emerging (Table 3). These novel agents differ with respect to mechanisms of triglyceride lowering and reducing apoB concentrations that may impact the effectiveness of these agents in lowering ASCVD events.

Selective Inhibition of apoC-III

Volanesorsen, previously ISIS-APOCIII_{RX}, is a second-generation antisense oligonucleotide that binds hepatic apoC3 mRNA, prompting its degradation, and resulting in decreased plasma apoC-III and TG levels. The APPROACH phase 3 trial demonstrated that patients with familial chylomicronemia syndrome who received volanesorsen had a 77% reduction in TG levels compared to an 18% increase in the placebo group, $P < 0.001$. It additionally led to decreases of 76% in apoB-48 levels, 46% in non-HDL-C, and 58% in VLDL-C. Volanesorsen resulted in increases of 46% in HDL-C, 136% in LDL-C, and 20% in total apoB levels [128]. Major adverse effect concerns include thrombocytopenia and injection site reactions [129]. Volanesorsen has been approved for use in the European Union for patients with familial chylomicronemia syndrome at high risk of pancreatitis who did not have adequate response to traditional medications.

There are also promising ongoing phase 1/2a studies of a hepatocyte-targeted APOC3 small interfering RNA (ARO-APOC3) directed against *APOC3* mRNA, which can potentially be dosed quarterly or semi-annually, in healthy adults

and in patients with severe hypertriglyceridemia and familial chylomicronemia syndrome (NCT03783377).

Selective Inhibition of ANGPTL3

Vupanorsen is an N-acetyl galactosamine-conjugated antisense oligonucleotide targeting hepatic ANGPTL3 synthesis. A phase 2 double-blind, placebo-controlled, dose-ranging study examined the efficacy of vupanorsen in lowering TG and atherogenic lipoproteins in patients with type 2 diabetes, hepatic steatosis, and hypertriglyceridemia. Vupanorsen at a dose of 80mg every 4 weeks resulted in 53% reduction in fasting TG levels and a 59% reduction in ANGPTL3 concentrations at 6 months compared to 16% TG reduction and 8% increase in ANGPTL3 in the placebo group. It was also associated with reductions of 9% in apoB levels, 58% in apoC-III, and 18% in non-HDL-C [130]. Unlike volanesorsen, there were no significant changes noted in platelet counts with vupanorsen. The most common side effect was a mild injection site reaction. The efficacy of antisense oligonucleotides targeting *Angptl3* mRNA was also demonstrated in patients with TG levels greater than 90 mg/dL receiving various doses of the treatment. After 6 weeks, those receiving multiple doses per week had reductions from baseline of 46.6 to 84.5% in ANGPTL3 levels, 33.2 to 63.1% in TG levels, 1.3 to 32.9% in LDL levels, 27.9 to 60% in VLDL levels, and 10 to 36.6% in non-HDL levels [131].

Evinacumab, a monoclonal antibody against ANGPTL3, has been shown to have potential benefit in those with homozygous familial hypercholesterolemia. The ELIPSE phase 3 trial found that patients with homozygous familial hypercholesterolemia receiving evinacumab had a 47.1% relative reduction in LDL-C levels compared to an increase of 1.9% in the placebo group, $P < 0.001$. There was also a 41.4% decrease in apoB levels from baseline, as well as a significant reduction in TG levels [132]. Additionally, in patients with TG levels between 150 and 450mg/dL and LDL-C levels more than 100mg/dL, a significant dose-dependent reduction was noted in TG levels [133]. A recent phase 2 trial in patients with refractory hypercholesterolemia demonstrated a significant reduction in LDL-C levels by more than 50% with the maximum dose of weekly evinacumab [134]. There is an ongoing phase 2 trial in patients with severe hypertriglyceridemia (≥ 500 mg/dL) with prior hospitalization for acute pancreatitis (NCT03452228).

Like ARO-APOC3, there are similar ongoing phase 1/2a studies in healthy patients and those with familial hypercholesterolemia and severe hypertriglyceridemia to evaluate the novel RNA-interference-based agent ARO-ANG3 targeting *ANGPTL3* mRNA (NCT03747224).

SPPARMs

Pemafibrate is a selective PPAR- α modulator (SPPARM) that results in the reduction of TG levels and increasing HDL-C levels. It also has nonlipid effects as it appears to play a role in increasing hepatic uptake of glucose and improving insulin sensitivity [135]. Pemafibrate monotherapy demonstrated a 30% mean reduction in TG levels and a 10–15% mean increase in HDL-C after 12 weeks when compared to placebo. When pemafibrate was used in conjunction with statin therapy, there was a 50% reduction in TG. However, there was also an increase in medium and large-sized LDL-C fractions, the impact of which on ASCVD is unclear. Pemafibrate also results in a significant dose-dependent reduction in total apoB and apoB-48 levels [136]. Additionally, one study reported a minor elevation in homocysteine levels, also of uncertain long-term impact. Pemafibrate has been shown to be effective and safe in reducing TG levels in patients with chronic kidney disease, regardless of estimated glomerular filtration rate (eGFR), with similar incidences of adverse events across eGFR groups [137]. It is currently approved in Japan for use in patients with dyslipidemia. Phase 3 trials are ongoing in the USA and Europe. The large-scale Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes trial (PROMINENT; NCT03071692) is underway, evaluating cardiovascular outcomes with the use of pemafibrate as adjunctive therapy to statins in patients with hypertriglyceridemia and type 2 diabetes [138].

FGF21

Fibroblast growth factor 21 (FGF21) plays an important role in angiogenesis and metabolism, in addition to other cell functions. It is expressed in higher levels in the liver, adipose, skeletal muscle, and pancreatic tissue, all of which are involved in metabolism. FGF21 leads to increased hepatic gluconeogenesis and fatty acid oxidation. By inhibiting the lipogenic gene encoding sterol regulatory element-binding protein 2 (*SERBP-2*), a PCSK9 activator, it results in decreased hepatic cholesterol production and reduces serum TG levels [139]. In mice, FGF21 was shown to reduce plasma non-esterified fatty acid levels and hepatic VLDL lipidation, as well as to increase the catabolism of TGRLs in white and brown adipose tissues, ultimately resulting in lower plasma TG levels [140]. Thus, FGF21 has significant therapeutic implications for TG reduction in humans. A study of LY2405319 (NCT01869959), an FGF21 analog, examined its effect on the lipid profile of obese patients with type 2 diabetes. At a dose of 10 mg per day of the subcutaneously injected molecule, there was a significant reduction of 29.5% in LDL-C, 46.2% in TG levels, and 25.1% in apoB levels from baseline. Further work needs to be done to identify the effects on endogenous FGF21 levels. Injection site reactions

Table 3 Summary of existing and emerging triglyceride-lowering therapies: mechanism of action and lipid-lowering effects

	Agent	Mechanism of action	HDL-C	Non-HDL-C	TG	LDL-C	VLDL-C	apoB
Existing therapies	Fibrates	Activates PPAR- α	↑		↓	↓	↓	↓
	Niacin	Inhibits lipolysis and accelerates apoB clearance	↑		↓		↓	↓
	Omega-3 fatty acids	Reduce hepatic TG and apoB secretion, increase LPL activity			↓			↓
	Statins	Inhibits HMG-CoA reductase			↓	↓	↓	↓
	Ezetimibe	Inhibits NPC1L1 transporter protein				↓		↓
	Lomitapide	Inhibits MTP	↓		↓			↓
	Mipomersen	Second-generation anti- <i>APOB</i> ASO		↓		↓	↓	↓
	Evolocumab	Anti-PCSK9 antibody		↓		↓		↓
	Alirocumab	Anti-PCSK9 antibody		↓		↓		↓
Emerging therapies	Inclisiran	Anti-PCSK9 siRNA			↓	↓		↓
	Volanesorsen	Second-generation anti- <i>APOC3</i> ASO	↑	↓	↓	↑	↓	↑
	Vupanorsen	N-acetyl galactosamine-conjugated anti- <i>ANGPTL3</i> ASO		↓	↓	↓	↓	↓
	Evinacumab	Anti- <i>ANGPTL3</i> antibody			↓	↓		↓
	Pemafibrate	Selective PPAR- α modulator		↑	↓	↑		↓
	FGF21	Inhibits <i>SERBP-2</i>			↓	↓		↓

HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; VLDL-C, very lipoprotein cholesterol; apoB, apolipoprotein B; PPAR- α , peroxisome proliferator-activated receptor; LPL, lipoprotein lipase; HMG-CoA, hydroxymethylglutaryl-coenzyme A; NPC1L1, Niemann-Pick C1 Like 1; MTP, microsomal transfer protein; ASO, anti-sense oligonucleotide; PCSK9, proprotein convertase subtilisin/kexin type 9; siRNA: small interfering ribonucleic acid; apoC, apolipoprotein C; ANGPTL3, angiopoietin-like protein 3; SERBP-2, sterol regulatory element-binding protein 2

and hypersensitivity were the most common adverse effects [141].

Conclusion

Statin therapy continues to be the mainstay of primary and secondary prevention of ASCVD given its powerful ability to reduce LDL-C levels and, to a lesser extent, TGs transported by VLDL and IDL particles. However, significant residual cardiovascular risk remains despite maximally tolerated statin doses. New insights from genetics strongly support a causal association between TGRLs and ASCVD. A number of direct and indirect mechanisms, including proinflammatory, proapoptotic, and procoagulant pathways, allow TGRLs to contribute to ASCVD progression. Therefore, guidelines now recommend the use of TG-lowering therapies in patients with persistently elevated TG or non-HDL-C levels following lifestyle modifications and statin therapies. As specific targets in the causal pathway are identified through genetic studies, novel TGRL-lowering therapies are emerging as new agents to reduce the risk of cardiovascular disease (Table 3).

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Declarations

Conflicts of Interest/Competing Interests Dr. Rosenson reports research funding to the institution from Amgen, Astra Zeneca Medicines Company, National Institutes of Health, Novartis, Regeneron, consulting fees from Amgen, Medicines Company, Novartis, Regeneron and 89 Bio, honoraria for non-promotional speaking fees from Amgen, Kowa and Regeneron, royalties from Wolters Kluwer (UpToDate) and stock holdings in MediMergent, LLC.

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