Published in final edited form as:

Prog Cardiovasc Dis. 2016 ; 59(2): 107–118. doi:10.1016/j.pcad.2016.08.003.

Triglyceride Treatment in the Age of Cholesterol Reduction

Nidhi Agrawal, Patricia Freitas Corradi¹, Namrata Gumaste², and Ira J. Goldberg*

Division of Endocrinology, Diabetes and Metabolism, New York University School of Medicine, New York, NY

Abstract

Cholesterol reduction has markedly reduced major cardiovascular disease (CVD) events and shown regression of atherosclerosis in some studies. However, CVD has for decades also been associated with increased levels of circulating triglyceride (TG)-rich lipoproteins. Whether this is due to a direct toxic effect of these lipoproteins on arteries or whether this is merely an association is unresolved. More recent genetic analyses have linked genes that modulate TG metabolism with CVD. Moreover, analyses of subgroups of hypertriglyceridemic (HTG) subjects in clinical trials using fibric acid drugs have been interpreted as evidence that TG reduction reduces CVD events. This review will focus on how HTG might cause CVD, whether TG reduction makes a difference, what pathophysiological defects cause HTG, and what options are available for treatment.

Keywords

Triglyceride; Hypertriglyceridemia; Hyperlipidemia; Cardiovascular disease

In all mammals the major transport system for energetic substrates is via movement of triglycerides (TGs). This occurs via incorporation of dietary TGs into chylomicrons and assembly of liver fatty acids into very low density lipoproteins (VLDLs); together these particles are referred to as TG-rich lipoproteins (TGRLs). Three fatty acids of varying length and degree of saturation (number of double bonds) are covalently attached to a glycerol backbone. Each mole of TG converts to 386 mol of ATP; full oxidation of each mole of glucose yields 30 mmol of ATP. Therefore, 10 mol of glucose are required to substitute for each mole of TG. Most human blood has ~1 mmol/Lt of TG and ~5 mmol/Lt of glucose. Thus, TG is the major pathway for energy transport.

A transport system is required to shuttle this non-water-soluble molecule between organs. TG metabolism involves what appears to be a futile cycle of esterification to glycerol and lipolysis to regenerate glycerol and non-esterified (or “free”) fatty acids. Dietary TG meets bile salts and pancreatic lipases in the small intestine. The newly absorbed fatty acids and a truncated form of apolipoprotein B (apoB-48) are then assembled into chylomicrons (CMs)

*Address reprint requests to Ira J. Goldberg, M.D., NYU-Langone Medical Center, 522 First Avenue, Smilow 901, New York, NY, 10016. Ira.Goldberg@NYUMC.org (I.J. Goldberg).

¹Current address: Division of Endocrinology, Department of Diabetes, Hospital Mater Dei, Belo Horizonte, Brazil.

²Current address: Robert Wood Johnson Medical School, Rutgers University, New Brunswick, NJ.

Statement of conflict of interest

None of the authors have any conflicts of interests with regard to this publication.

with the assistance of the microsomal TG transport protein (MTTP); CMs also contain the smaller apoCs, apoE and apoA-I; apoA-I is the major protein of high density lipoprotein (HDL). Unlike glucose and protein, dietary TGs do not directly enter the circulation.¹ Rather, chylomicrons are transported within the lymphatic system until the thoracic duct empties into the left subclavian vein (Fig 1). Within the circulation there is an exchange of the surface apoproteins with a loss of apoA-IV from the CMs and an increase in apoCs, including apoC-II and apoE.

TG lipolysis requires interaction between the CM and lipoprotein lipase (LpL), a dimeric enzyme associated with heparan sulfate proteoglycans and a novel accessory protein, glycosylphosphatidyl-inositol anchored HDL binding protein 1 (GPIHBP1) associated with the luminal surface of capillary endothelial cells. A number of steps regulate LpL activity, including its folding within cells via lipase maturation factor 1 (LMF1), dimerization, movement to the capillary lumen, activation by apoC-II,² and inhibition by angiopoietin-like proteins (Angptl) 3, 4, and 8.³ The first organ that chylomicrons see after entry into the circulation is the right side of the heart. But the first capillary network is within the lung. Whether a significant amount of lipolysis occurs during the transit through the pulmonary circulation is unclear.

Several steps are required for delivery of circulating TGs into tissues. The interaction of TGRLs with capillary LpL is likely modulated by the size of the particle and its margination within the bloodstream (Fig 2). ApoA-V and perhaps apoE might increase TGRL–capillary interaction and propel the lipolysis reaction. Chronically activated muscles such as the heart and diaphragm have the most robust LpL expression. Chronic exercise increases LpL in skeletal muscle and adipose tissue, especially brown adipose, which uses LpL to acquire fatty acids for energy and storage.⁴ Human molecular defects in LpL, GPIHBP1, and LMF1 cause fasting hyperchylomicronemia and pancreatitis. Defects in apoA-V lead to less severe hypertriglyceridemia (HTG),⁵ while those in Angptl3 and Angptl4 are associated with reduced circulating TG levels.⁶

The liver is a site of TG delivery and also a source of additional TG production; CM–TG that is not delivered to peripheral tissues arrives within the liver via CM remnants. This step is incompletely defined but appears to involve hepatic TG lipase (HTGL), cell surface syndecan (a proteoglycan), the low-density lipoprotein (LDL) receptor (LDLR) and LDLR related protein 1 (LRP1).

TG is also assembled within the liver from fatty acids in the blood that during fasting predominately are derived from adipose tissue; the liver is by far the most active organ that clears fatty acids from the blood. In addition, with calorie excess, TGs are synthesized from glucose and some amino acids, i.e. de novo synthesis. It is likely that these sources of TG are compartmentalized, as not all liver lipids equally affect liver metabolism and the propensity to develop non-alcoholic fatty liver disease (NAFLD). For example, from studies done decades ago,⁷ we know that the last TG to arrive in the liver is the first to be re-secreted and therefore it does not mix with TG within hepatic lipid droplets.

VLDL assembly, secretion and catabolism are similar to those processes that occur for CMs. VLDL contains full length apoB (apoB100), apoCs and apoE and requires MTTP. Within the circulation, VLDL loses TG and surface apoproteins via the LpL reaction and then appears to require a final step via HTGL to complete the conversion to LDL. VLDL turnover in the bloodstream is much slower than that of CMs; this is explained by the geometry of the interaction with LpL (Fig 2), the shape of the lipoprotein surface, or associated apoproteins. With very high levels of VLDL (probably with TG over 1 mmol, ~880 mg/dL), VLDL blocks CM metabolism.⁸

Are TG levels a risk factor for CVD?

In a cohort of 500 hyperlipidemic survivors of myocardial infarction (MI), Goldstein and collaborators found that elevated TG levels with or without an associated elevation in cholesterol levels were more prevalent in cardiovascular disease (CVD) patients than high cholesterol levels alone. These results raised the possibility that HTG is as important a risk factor for coronary atherosclerosis as hypercholesterolemia.⁹ Patients with HTG caused by LpL deficiency can present with premature atherosclerosis, meaning that they are not entirely immune to vascular disease¹⁰ and heterozygous LpL deficiency is associated with CVD risk.^{11,12} Conversely, some human observational studies led to uncertainty regarding the relationship between CVD risk and genetic hypertriglyceridemic syndromes. Patients with familial HTG (FHTG) appear to develop less CVD than those with familial combined hyperlipidemia (FCHL).¹³

The TG-atherogenesis hypothesis has gained support via recent human genetic studies. A number of loci primarily associated with TGs also increased CVD risk. These included single nucleotide polymorphisms in genes encoding LpL, tribbles 1 (*TRIB1*), N-acetyltransferase 2 (*NAT2*) and the *ZNF259/APOA5/APOA4/APOC3/APOA1* gene cluster. Some of these genes/gene clusters are associated with multiple lipid traits. The gene product of *TRIB1* regulates hepatic TG synthesis and, although most strongly associated with TGs, also associates with HDL and LDL levels.¹⁴ The 11q23 locus encompassing *ZNF259*, *APOA5*, *APOA4*, *APOC3* and *APOA1* is most strongly linked to TGs but has multiple effects on other lipoproteins. Studies in genetic isolates also support a role for regulators of the TG lipolytic pathway in atherosclerosis. Several *LpL* variants have systematically been identified as determinants of plasma TG concentration and CVD risk and are associated with increased plasma TG and decreased HDL concentration. Moreover, these effects seemed to be magnified in obese individuals. Other genetic variants of the *LpL* gene have a more favorable lipid profile, since they lead to enhanced LpL activity.¹⁵

The *APOC3* gene is part of the *APOA5-APOA4-APOC3-APOA1* gene cluster on chromosome 11.¹⁶ ApoC-III has been thought to inhibit TG lipolysis but is more likely to function by blocking hepatic lipoprotein receptors.¹⁷ Rare mutations that disrupt APOC3 function were associated with lower levels of plasma TGs; carriers of these mutations have a reduced risk of coronary heart disease (CHD).¹⁸ Furthermore, increases in apo-CIII-containing lipoproteins may confer an additional risk of CVD.¹⁹

ANGPTL4 inhibits LpL, most likely by disrupting LpL dimers. Recent studies have found a low-frequency missense variant of *ANGPTL4*, p.E40K, which is associated with protection against CHD. Since no significant association between this variant of *ANGPTL4* and LDL cholesterol or blood pressure levels was found, the protective effect likely occurs by TG reduction. This finding raises the likelihood that complete loss-of-function variants in *ANGPTL4* may play an even more dramatic role in reducing TG concentration and, therefore, CVD risk.⁶

How might TGs cause vascular disease?

In the 1970's, Zilversmit hypothesized that atherogenesis occurs in the postprandial state, and that raised concentrations of TGs and remnant lipoproteins were the main cause of atherosclerosis.²⁰ This process correlated with greater LpL activity in the artery associated with macrophage infiltration.²¹ Furthermore, CM remnants and also VLDL can deposit in the wall of the perfused artery, especially in the presence of LpL.²² Unlike cholesterol, TGs can be degraded by most cells. This may imply that the cholesterol content of TGRLs (remnant cholesterol) is more likely to be the cause of atherosclerosis and CVD than raised TGs per se. Indeed, rather than TGs, cholesterol is the accumulated lipid found in foam cells within the atherosclerotic plaque.

The generation of lipolysis products, the lipids formed by the LpL reaction, is another possible cause of toxicity due to interaction between TGRLs and the vascular wall. LpL activity either at the vascular endothelium or within the intima leads to liberation of free fatty acids, monoacylglycerols, lysolecithin and other molecules²³ that could cause local injury and inflammation, thus fueling the atherogenesis process. Like most enzymatic reactions, lipolysis is primarily regulated by the availability of substrates, i.e. the TG levels in the blood.

Why is HDL cholesterol (HDL-C) the hemoglobin A1C of TGs?

High levels of TG and low HDL are commonly found in the same patients. The exception is if increased HDL is due to alcohol or estrogen, both of which stimulate TG and HDL production simultaneously. HDL formation is complex and discussed in detail in other chapters. Of importance for the relationship with TG, circulating HDL levels are dependent on the lipolysis pathway (Fig 3). During lipolysis of TGRLs surface lipids including phospholipids, cholesterol, and proteins are transferred to HDL to reduce cell surface area as the spherical particles decrease in size. For this reason patients with LpL deficiency have very low levels of HDL.²⁴ In fact the genetic marker in young people for heterozygous LpL deficiency is low HDL and not HTG.²⁵ Moreover, acute LpL inhibition in animal models leads to a rapid >50% reduction in HDL within hours.²⁶ A second cause of HDL reduction in humans but not rodents is due to transfer of HDL cholesteryl ester to TGRLs via the actions of the cholesteryl ester transfer protein (CETP). TG-enrichment of HDL accelerates its catabolism via the actions of HTGL,^{27,28} leading to increased clearance of small HDL by the kidney.

Elevated HDL is associated with reduced risk of CHD in epidemiological studies within western populations. Although TGs are measured more precisely than HDL-C, TG concentrations vary more on a daily basis than HDL-C; this may be one reason that HDL is more strongly associated with CVD than TGs. Nevertheless, even after adjustment for HDL concentrations, several meta-analyses showed an association between high fasting and non-fasting concentrations of TGs and increased risk of CHD (see below). Publications from Hokanson et al.,²⁹ Abdel-Maksoud et al.³⁰ and Sarwar et al.³¹ all assign TG levels as an independent risk factor for CVD. Stalenhoef et al. also suggested that an elevated concentration of TG-rich remnant lipoproteins is associated with CVD risk.³² Elevated plasma TG levels are frequently observed with insulin resistance, including type 2 diabetes mellitus (T2DM), metabolic syndrome (MetS) and FCHL.

Post-prandial lipemia is the excursion of TG levels after a meal.³³ Increased postprandial lipemia, which occurs as a result of impaired metabolism of postprandial TGRLs, is a risk factor for CVD and occurs due to overproduction^{34,35} and/or decreased catabolism of TGRLs. In 1984, Patsch and his colleagues described the effect of post-prandial lipemia on HDL particles in 15 patients with normal TG levels. He described the transfer of TGs from CMs into HDL-2 particles in exchange for cholesteryl esters. HDL-2 particles are a subfraction of HDL that is inversely related to the risk of CVD. HDL-2 particles are subsequently converted to HDL-3 by the action of HTGL. The magnitude of HTG showed a negative correlation with the plasma levels of HDL-2.³⁶

Is HTG associated with small dense LDL (sdLDL) and is sdLDL worth measuring?

Many clinicians obtain measurements of LDL particle size and apoB particle number as an additional measurement of CVD risk.³⁷ Several studies have confirmed that the presence of sdLDL particles is associated with increased CVD risk. The possible reasons for this include a greater oxidation potential of small particles, reduced affinity of sdLDL for the LDL receptor, and the correlation between sdLDL and high levels of TG and low HDL. This cluster of metabolic abnormalities associated with sdLDL is found with insulin resistance and MetS and also T2DM.³⁸

There are two possible routes to sdLDL production, and both are increased with HTG. LDL, like HDL, can become more TG enriched by CETP exchange. The TG enriched LDL is a substrate for HTGL; HTGL deficiency increases circulating levels of large LDL and reduces sdLDL.³⁹ Another option suggested by kinetic analysis is that a subgroup of smaller VLDL that is destined to become sdLDL is secreted from the liver.⁴⁰

Although LDL size correlates with CVD risk, a causal relationship is unclear. The Multi-Ethnic Study of Atherosclerosis (MESA) revealed that both small and large LDLs were significantly associated with subclinical atherosclerosis independent of each other with no association between LDL size and atherosclerosis after accounting for the concentrations of the two subclasses.^{41,42} The landmark Québec Cardiovascular Study suggested that sdLDL may be an independent risk factor for CVD.⁴² The study indicated that the risk attributed to variations in the LDL size phenotype was largely related to markers of a preferential

accumulation of sdLDL particles leading to increased atherogenic risk in patients with elevated plasma apoB and sdLDL.⁴³

Could sdLDL be more atherogenic because it indicates the presence of more apoB?

Atherosclerosis is thought to initiate with the binding of apoB-containing particles in the arterial intima leading to an inflammatory state. It is generally believed that atherosclerosis is due to the deposition of cholesterol within the artery; if this is the case, then larger LDL particles that contain more cholesterol per particle should be more atherogenic. This conclusion is consistent with the accelerated CVD found in patients with familial hypercholesterolemia who predominantly have large LDL. However, recent studies describe an important role of the adaptive immune system in atherosclerosis and CVD. Vaccination with atherosclerosis-related antigenic proteins such as oxidized LDL, apoB-100, and heat shock protein, may reduce the risk of atherosclerosis and CVD.⁴⁴ Therefore, greatly increased concentrations of apoB, not just apoB-containing cholesterol, could prove atherogenic.

What are the causes of HTG?

Common and rare variants in multiple genes, together with environmental influences, collectively determine a patient's plasma TG concentration. To date, the majority of genetic susceptibility in people with HTG remains unclear. Two major genetic forms of HTG are FCHL and FHTG. Although originally described as a monogenic form of HTG,⁴⁵ FCHL more likely is a complex genetic disorder in which the interaction of multiple susceptible genes along with environmental components, contributes to the phenotype of mixed dyslipidemia, ranging from mild to moderate HTG. Linkage to several FCHL traits has been observed, including high levels of apoB, plasma TG and cholesterol.⁴⁶ The apolipoprotein *A1/C3/A4/A5* gene cluster, which is associated with TG levels and LDL particle size, is an important modifier gene locus that has been linked with FCHL and its related traits in several (but not all) studies.⁴⁷

Conversely, little has been unraveled about the genetics of FHTG, which often is not expressed until adulthood and likely is influenced by dietary, environmental and other factors. Accumulation of common and rare genetic variants that increase an individual's susceptibility may result in FHTG.⁴⁸

GWAS have identified SNPs associated with regions containing both classically established genes and previously unknown genomic regions as determinants of plasma TG concentration.⁴⁹ A case-control study comparing 462 HTG patients with 1197 normotriglyceridemic population-based controls revealed that common variants in *APOA5*, *GCKR*, *LpL* and *APOB* genes were associated with the HTG phenotype at genome-wide significance. Furthermore, another three loci were replicated at a corrected significance threshold of $P < 0.005$ (*MLXIPL*, *TRIB1*, *ANGPTL3*).⁵⁰

Diabetes

Low HDL in insulin resistance results from decreased HDL production as well as increased HDL catabolism. Insulin resistance leads to decreased LpL activity, thus reducing the breakdown of TGRLs and decreasing the availability of apolipoproteins needed for HDL synthesis. The increased catabolism of HDL results from an increased exchange of cholesteryl ester for TG by CETP. The resultant TG-rich HDL is a good substrate for hydrolysis by HTGL, which has increased activity in insulin resistance, and the smaller HDL is cleared more rapidly from the circulation.

HTG and reduced plasma levels of HDL are the most frequent forms of dyslipidemia observed in insulin-resistant states, such as obesity, impaired fasting glucose, T2DM and MetS and are thought to be atherogenic in these settings.⁵¹ It is postulated that increased free fatty acid transport in plasma, which is commonly seen in insulin resistant states, may be the underlying driving force for HTG in patients with T2DM. Increased fatty acid flux to the liver stimulates the assembly and secretion of apoB-containing lipoproteins leading to increased rates of VLDL secretion into the plasma. Fatty liver, which occurs as a component of MetS, is strongly correlated with hepatic overproduction of large TGRLs. This in turn triggers a sequence of events resulting in the classic T2DM dyslipidemia triad of elevated TG and, sdLDL, and low HDL.⁵²

Lipodystrophy

Lipoatrophy leads to T2DM and sometimes marked HTG. In part, this results from a defect in fat storage leading to greater hepatic uptake of fatty acids and their incorporation into VLDL. In addition, adipose loss also reduces total LpL; genetic deletion of LpL only in adipose is sufficient to cause HTG in mice.⁵³ Leptin deficiency that accompanies lipoatrophy prevents normal appetite control. Joseph et al. treated lipodystrophy patients with the synthetic analog of leptin, metreleptin, and found that these patients had reduced TG levels⁵⁴; the failure to also increase HDL may be explained by the continued defect in LpL.⁵⁵ Premature and accelerated atherosclerosis has been reported in Dunningan-type familial partial lipodystrophy.⁵⁶

Estrogen and glucocorticoids and TG

The mechanism behind estrogen-induced HTG is unclear. Estrogen-induced HTG likely results from an increase in hepatic VLDL synthesis, and decreased LpL activity. Murase et al. proposed that estrogens inhibit LpL promoter activity, causing LpL deficiency⁵⁷; estrogens also cause a reduction in hepatic lipase activity,⁵⁸ which is thought to be one of the reasons for the increase in HDL. The effects of estrogen on TG are thought to be more pronounced in patients with genetic deficiencies of LpL. Estrogen also promotes TG synthesis in the liver, which leads to greater VLDL secretion into the circulation.⁵⁹ Glucocorticoids also often increase TG and like estrogen also increase HDL.

Alcohol induced HTG

Alcohol elevates TG levels due to a combination of three major mechanisms: increased VLDL secretion, impaired lipolysis and increased free fatty acid influx from adipose tissue to the liver. In addition, alcohol reduces fatty acid oxidation in the liver, so more fatty acids are re-secreted as TG. It may cause both fasting and postprandial elevations in TG levels and can lead to pancreatitis when associated with extremely high TG levels.^{60,61}

Anti-hypertensive medications

Several antihypertensive agents influence serum lipid profiles. Angiotensin-converting enzyme inhibitors, calcium channel antagonists, dual alpha- and beta-blockers are lipid neutral⁶²; however, thiazide diuretics and beta blockers increase TG levels,⁶³ but with little effect on total cholesterol and LDL.⁶⁴ Cardioselective beta-blocker monotherapy usually increases serum TGs and decreases the concentration of HDL, especially HDL2 cholesterol.⁶⁵ This is likely a drug class-related effect, since non-specific beta-blockers with intrinsic sympathomimetic activity, such as oxprenolol and pindolol, appear to produce qualitatively similar but less pronounced changes in circulating lipids.⁶⁶ In combination, a tendency for increased TG and lower HDL was also apparent during thiazide-type diuretic-beta-blocker therapy.⁶⁷ A reasonable approach to minimize the lipid problems often associated with hypertension is to select drugs that alone or in combination do not adversely affect lipid profiles.

Chronic kidney disease

Common initial abnormalities in patients with renal failure include HTG and low HDL due to abnormal removal of TGRLs associated with diminished LpL activity.⁶⁸ In part this might be associated with greater circulating Angptl4 levels.⁶⁹ Moreover, apoB-containing lipoproteins are elevated in various animal models due to reduced expression and activity of HTGL, and VLDL, LDL and LRP receptors.^{70–72} Decreased apoA-I production leads to low HDL levels in advanced renal failure.⁷³ In addition, decreased production and activity of lecithin-cholesterol acyltransferase further decrease HDL levels and maturation of HDL-C.⁷³

HIV and hypertriglyceridemia

HIV positive patients have several metabolic abnormalities, including insulin resistance, diabetes-altered fat distribution and dyslipidemia, which put them at increased risk of CVD.^{74–77} The two major components of dyslipidemia in patients with HIV are HTG and reduced HDL. There are several proposed mechanisms to explain HTG in patients with HIV. These include a systemic inflammatory response against persistent viral infection with elevated TNF levels,⁷⁸ decreased LpL and HTGL activity, and increased lipogenesis.^{79,80} There is an unexplained elevated level of CETP activity, which may explain why HDL levels are lower in this population.⁸¹ Combination antiretroviral therapy, particularly protease inhibitors, has long been associated with HIV related dyslipidemia as well.

Does TG reduction reduce CVD?

Clinical trials studying the effects of TG reduction on CVD events have not been designed to focus on subjects with only HTG. Table 1 summarizes the relevant trials and the effect of anti-hyperlipidemic medications on hypertriglyceridemia. The Bezafibrate Infarction Prevention (BIP) study⁸² and the Lower Extremity Arterial Disease Event Reduction (LEADER) study⁸³ showed a non-significant reduction in CVD events except for non-fatal MI. Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) was a secondary prevention multicenter, randomized trial including 2531 men from 20 VA centers conducted from 1991 to 1998. The subjects had a history of CVD, with low HDL (mean 32 mg/dL) and low LDL (mean 111 mg/dL). Unlike the large statin trials, where lowering LDL levels was the target, increasing HDL was the aim of treatment in the VA-HIT study, which enrolled patients with both low HDL and low LDL and randomized them to gemfibrozil or placebo. Gemfibrozil significantly reduced major CVD events. The findings suggest that the rate of CHD events is reduced by gemfibrozil, perhaps because it reduces levels of fasting and postprandial TGs, without lowering LDL levels.⁸⁴

The Fenofibrate Intervention and Endpoint Lowering in Diabetes (FIELD) Trial was a randomized controlled study with 9795 participants with T2DM aged 50–75 years, who were not on lipid lowering therapy. Patients were randomized to receive fibrates or placebo. Fenofibrate therapy was associated with a significant reduction in albuminuria and retinopathy in patients with T2DM. After 4 months of treatment, fenofibrate reduced TGs by 29% and raised HDL-cholesterol by 5%; however, the 5% increase in HDL seen at the start of the trial in the fenofibrate group was attenuated during the study period. A significant reduction in events was seen with the fenofibrate group with no prior CVD, but not in patients with underlying CVD.⁸⁵

The Action to Control Cardiovascular Risk in Diabetes (ACCORD)-lipid trial tested the hypothesis that combination therapy with a fibrate and statin would more effectively prevent major CVD events in a high-risk population of patients with T2DM compared with statin monotherapy. In this study, 5518 patients were randomized to fibrate or placebo in addition to a statin. Fenofibrate was not associated with risk improvement of CHD events compared to placebo, however a subgroup analysis revealed that fenofibrate was beneficial in patients with high TG (>204 mg/dL) and low HDL (<34 mg/dL).⁸⁶ This trial and others have been used in a meta-analysis that showed a consistent reduction in CVD in fibric acid trials when only subgroups with TG > 200 and low HDL were considered.⁸⁷

Very-long-chain omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), lower TG levels but CVD-reducing benefits are not established. **GISSI-Prevenzione** was an Italian secondary outcomes study in which patients with an acute CHD event were randomly assigned to receive EPA plus DHA or placebo.⁸⁸ The treated groups had a 30% decrease in CVD mortality. However, in a similar double blinded study on more than 12,000 patients with impaired glucose tolerance or T2DM, daily supplementation of omega-3 fatty acids did not reduce the rate of CVD events over a follow-up period of 6 years.⁸⁸ These data conflicted with the GISSI-Prevenzione study, making the effect of TG

reduction on CVD mortality inconclusive and being the reason that several additional trials are in progress.

The EVOLVE (EpanoVa fOr Lowering Very High TGs) trial showed a significant reduction in TG (26%) and non-HDL-C levels (8%) along with reduced markers of atherogenicity.⁸⁹ In the EVOLVE study, responses in high-sensitivity C-reactive protein (hs-CRP) to any dose of Epanova did not differ significantly from responses to placebo. Two large outcome trials are using different omega 3 fatty acid preparations. REDUCE-IT is an ongoing CVD event study started in 2011 with Vascepa as an add-on to statin therapy. Outcomes Study to Assess STatin Residual Risk Reduction With EpaNova in HiGh CV Risk PatienTs With Hypertriglyceridemia (STRENGTH) trial is an ongoing randomized controlled trial with more than 13,000 patients enrolled with HTG, low HDL and high risk for CVD. They will be randomized to corn oil plus statin or Epanova plus statin, once daily, to determine the risk of major CVD events.

How do you treat chronic HTG?

A number of societies have published guidelines on TG treatments, although the only clear Federal Drug Administration (FDA) accepted indication for these therapies is for pancreatitis prevention. The Endocrine Society guidelines classify TG levels in four HTG categories. The two lowest categories, which span from 150 to 500 mg/dL and 500 to 999 mg/dL, are considered mild and moderate HTG, respectively.⁹⁰ Because risk for pancreatitis is greatest in patients with TG levels ≥ 2000 mg/dL, this is termed very severe HTG. TG levels of 1000–1999 mg/dL are classified as severe HTG.^{91,92} The AHA/NCEP ATP III and the American Association of Clinical Endocrinologists (AACE)⁹³ defined very high TG levels as any TG level above 500 mg/dL. Recently published 2013 ACC–AHA cholesterol guidelines also support this TG cutoff level to start treatment.⁹⁴ When TG levels are above 500 mg/dL, most guidelines recommend lifestyle changes and treatment with fibrate, omega 3 fatty acids, or nicotinic acid to lower TG levels in order to prevent pancreatitis. When TG levels are between 150 and 500 mg/dL, the treatment aim is to reach target LDL levels. If TGs are ≥ 200 mg/dL after the LDL goal is reached, the secondary goal for non-HDL-C (total – HDL) should be set to 30 mg/dL higher than the LDL goal, with additional drugs if necessary.

Lifestyle therapy, including appropriate diet composition, physical activity and a program to achieve weight reduction is the foundation of treatment for mild-to-moderate HTG.⁹⁵ A diet with reduced dietary fat and reduced simple carbohydrate intake, particularly reduced intake of fructose-rich foods is recommended.⁹⁶ Exercise effectively lowers post-prandial lipemia,⁹⁷ and helps to achieve weight loss due to increased caloric expenditure. Patients with severe HTG who are treated with drugs or lifestyle often do not return to a “normal” baseline TG level.⁹⁸ This suggests that they have an underlying lipid disorder, which is exacerbated by dietary factors.

What treatments are effective in patients with HTG and pancreatitis?

There are no randomized clinical trials of interventions in the setting of acute HTG pancreatitis. In most patients, their disease resolves with fluids and fasting. Often these patients are given glucose and insulin to block adipose lipolysis, lower circulating free fatty acid levels, and decrease hepatic assembly of TG. Very low amounts of insulin, much less than often used for diabetic ketoacidosis, should be sufficient, e.g. 1 unit per hour along with glucose if needed. Heparin –which releases LpL from the capillary endothelial surface, stabilizes the LpL dimer, and prevents LpL removal by the liver – may reduce TG levels more rapidly but is usually not a reasonable option during acute pancreatitis. Although plasmapheresis has been employed and will reduce TG levels more rapidly, it is rarely needed and not routinely employed in most centers that see many of these patients. Plasmapheresis increases hospital costs and has side effects such as increased risk of sepsis. When TG levels are below 1000 mg/dL, they are likely to no longer pose a risk for pancreatitis, and because CM levels are low, plasmapheresis is ineffective. Plasmapheresis may be indicated with extremely high TG levels or in pregnancy-associated pancreatitis where fasting might not lead to rapid TG reduction; however, TGs are likely to re-accumulate in 2–3 days.

What are the current medications?

To date, three drug classes are clinically available for treatment of HTG: fibrates, niacin and n-3 fatty acids.

Large amounts of clinical trial data have been obtained for fibrates, making them the first line of therapy. Fibrates work through several mechanisms, including increased fatty acid oxidation, increased LpL synthesis, and reduced apoC-III expression. The net effect is a decrease in VLDL TG production and an increase in catabolism of TGRLs.⁹⁵ Fibrates generally decrease TG levels by 30%–50% and sometimes increase HDL-C.⁹⁹ In patients with TG-induced pancreatitis, treatment of underlying causes and concomitant fibrate therapy are thought to be beneficial to prevent recurrent disease. Due to a large excursion of TG levels in the setting of severe and very severe HTG, a treatment goal of <500 mg/dL is recommended. Below this level, the main effort should be directed toward prevention of premature atherosclerosis. In patients with high TG levels, LDL cholesterol (LDL-C) levels may increase during therapy, likely due to an increased conversion of VLDL to LDL, while LDL-C levels may decrease in mild HTG. Fibrates are contraindicated in patients with renal insufficiency and liver or gall bladder disease and their concomitant use with statins should be monitored due to increased risk of myositis.

In in vitro studies, niacin was found to inhibit diacylglycerol acyltransferase (DGAT) 2, a microsomal enzyme that plays a central role in the esterification of fatty acids to form TGs. This inhibition of DGAT2 activity in liver may result in a decreased rate of TG synthesis.¹⁰⁰ Nevertheless, recent placebo-controlled studies have not shown any incremental benefit in CVD outcomes by adding niacin to statin therapy¹⁰¹; niacin lowers TG levels and increases HDL-C levels. The most described side effect of niacin is flushing, which can be reduced by concomitant administration of aspirin. Complications of niacin therapy include

hepatotoxicity, impaired glucose tolerance and hyperuricemia. Niacin is contraindicated in patients with active peptic ulcer disease, but can be used safely in patients with glucose intolerance and can be considered in patients with T2DM who have moderate to good glycemic control.

Omega-3 fatty acids are FDA indicated for treatment of severe and very severe HTG (>1000 mg/dL). To achieve a reduction of HTG by 20%–50%, administration of 3 to 4 g/day of EPA plus DHA is required.¹⁰² In patients with TG levels above 500 mg/dL, 4 g/day of EPA and DHA reduces TG levels 45% and VLDL cholesterol levels by more than 50%.¹⁰³ Use of EPA alone in the Marine Trial of 229 patients with TG >500 mg/dL showed a significant lowering of TG levels by 33% without an increase in LDL levels.¹⁰⁴ Although this trial might suggest that EPA does not raise LDL, as was found with other treatments, the selection of a very high baseline TG is not comparable to that of many other trials. Amarin is an omega-3 fatty acid agent containing 96% pure icosapentethyl (IPE), the ethyl ester of EPA. The 12-week ANCHOR study evaluated the efficacy and safety of IPE in patients with diabetes with TG levels between 200 and 500 mg/dL while on optimized statin therapy. An omega-3 carboxylic acid product, Epanova, is the first prescription omega-3 product in free fatty acid form. It is indicated as an adjunct to diet to reduce TG levels in adults with severe HTG (TG ≥ 500 mg/dL).

The pancreatic lipase inhibitor, orlistat, reduces the absorption of dietary fats by ~30%.¹⁰⁵ It reduces post-prandial lipemia and in overweight patients with T2DM, orlistat reduced plasma TG and free fatty acids in the early post-prandial period.¹⁰⁶ Orlistat has been safely used for obesity management. The weight loss due to this drug improves insulin sensitivity and metabolic profile.¹⁰⁷

Statins can reduce CVD risk in patients with mild-to-moderate HTG and elevated non-HDL-C, though their TG-lowering effect is modest, typically about 10%–15%, and dose-dependent.

Developing therapies

A number of new TG reducing therapies are in clinical trials. In Europe, an adeno-associated viral expression of an active genetic form of LpL (LpL247) has been approved and leads to transient LpL expression in skeletal muscle at the site of injection.^{108,109} Other methods in development include the use of antibodies against LpL inhibitory proteins Angptl4 and Angptl3; however, Angptl4 inhibition has led to intra-abdominal inflammation, which will likely prevent its continued development.¹¹⁰

The most promising new therapy appears to be the use of an anti-sense oligonucleotide to apoC-III, which leads to a 50% reduction in TG levels with injections every 2 weeks.¹¹¹ This therapy is also effective in LpL deficient subjects,¹¹² likely because loss of apoC-III improves lipoprotein clearance in the liver.

Conclusions

In 1973, Goldstein reported on the common prevalence of HTG in patients who developed CVD.⁹ Thereafter, his work and that of others focused on LDL and cholesterol reduction, which led to the current metabolic therapies for primary and secondary prevention of CVD events. However, the residual CVD risk attributed to elevated levels of TG remains. Experimental models showing the toxic influence of TG on atherosclerosis or plaque instability are still being sought. Clinical trials that appear to confirm a benefit from TG reduction rely on sub-group analyses and thus are non-conclusive. But with new and more potent TG-reducing therapies on the horizon, both the clinical and pathobiological relationship between TG and CVD is likely to be clarified.

Abbreviations and Acronyms

Angptl	Angiopoietin-like protein
CM	chylomicron
CVD	cardiovascular disease
CETP	cholesteryl ester transfer protein
CHD	coronary heart disease
DGAT	diacylglycerol acyltransferase
DHA	docosahexaenoic acid
EPA	eicosapentaenoic acid
FCHL	familial combined hyperlipidemia
FDA	Federal Drug Administration
FHTG	familial hypertriglyceridemia
GPIHBP1	glycosylphosphatidylinositol anchored HDL binding protein 1
HTGL	hepatic triglyceride lipase
HDL	high density lipoprotein
HDL-C	high density lipoprotein cholesterol
hs-CRP	high-sensitivity C-reactive protein
HTG	hypertriglyceridemia or hypertriglyceridemic
LDL	low density lipoprotein
LDL-C	low density lipoprotein cholesterol
LDLR	low density lipoprotein receptor

LRP1	low density lipoprotein receptor related protein 1
LMF1	lipase maturation factor 1
LpL	lipoprotein lipase
MetS	metabolic syndrome
MI	myocardial infarction
MTTP	microsomal triglyceride transport protein
NAFLD	non-alcoholic fatty liver disease
TG	triglyceride
TGRL	triglyceride rich lipoprotein
T2DM	type 2 diabetes mellitus
VLDL	very low density lipoproteins

References

1. Goldberg IJ. Hypertriglyceridemia: impact and treatment. *Endocrinol Metab Clin North Am.* 2009; 38:137–149. [PubMed: 19217516]
2. Merkel M, Eckel RH, Goldberg IJ. Lipoprotein lipase: genetics, lipid uptake, and regulation. *J Lipid Res.* 2002; 43:1997–2006. [PubMed: 12454259]
3. Dijk W, Kersten S. Regulation of lipid metabolism by angiopoietin-like proteins. *Curr Opin Lipidol.* 2016; 27:249–256. [PubMed: 27023631]
4. Goldberg IJ, Eckel RH, Abumrad NA. Regulation of fatty acid uptake into tissues: lipoprotein lipase- and CD36-mediated pathways. *J Lipid Res.* 2009; 50:S86–S90. [Suppl.]. [PubMed: 19033209]
5. Surendran RP, Visser ME, Heemelaar S, Wang J, Peter J, Defesche JC, et al. Mutations in LPL, APOC2, APOA5, GPIHBP1 and LMF1 in patients with severe hypertriglyceridaemia. *J Intern Med.* 2012; 272:185–196. [PubMed: 22239554]
6. Myocardial Infarction G, Investigators CAEC. Coding variation in ANGPTL4, LPL, and SVEP1 and the risk of coronary disease. *N Engl J Med.* 2016
7. Havel RJ. Conversion of plasma free fatty acids into triglycerides of plasma lipoprotein fractions in man. *Metabolism.* 1961; 10:1031–1034. [PubMed: 13905468]
8. Brunzell JD, Hazzard WR, Porte D Jr, Bierman EL. Evidence for a common, saturable, triglyceride removal mechanism for chylomicrons and very low density lipoproteins in man. *J Clin Invest.* 1973; 52:1578–1585. [PubMed: 4352459]
9. Goldstein JL, Hazzard WR, Schrott HG, Bierman EL, Motulsky AG. Hyperlipidemia in coronary heart disease. I. Lipid levels in 500 survivors of myocardial infarction. *J Clin Invest.* 1973; 52:1533–1543. [PubMed: 4718952]
10. Benlian P, De Gennes JL, Foubert L, Zhang H, Gagne SE, Hayden M. Premature atherosclerosis in patients with familial chylomicronemia caused by mutations in the lipoprotein lipase gene. *N Engl J Med.* 1996; 335:848–854. [PubMed: 8778602]
11. Wittekoek ME, Pimstone SN, Reymer PW, Feuth L, Botma GJ, Defesche JC, et al. A common mutation in the lipoprotein lipase gene (N291S) alters the lipoprotein phenotype and risk for cardiovascular disease in patients with familial hypercholesterolemia. *Circulation.* 1998; 97:729–735. [PubMed: 9498535]

12. Wittrup HH, Tybjaerg-Hansen A, Abildgaard S, Steffensen R, Schnohr P, Nordestgaard BG. A common substitution (Asn291Ser) in lipoprotein lipase is associated with increased risk of ischemic heart disease. *J Clin Invest.* 1997; 99:1606–1613. [PubMed: 9120004]
13. Brunzell JD, Davidson M, Furberg CD, Goldberg RB, Howard BV, Stein JH, et al. Lipoprotein management in patients with cardiometabolic risk: consensus conference report from the American Diabetes Association and the American College of Cardiology Foundation. *J Am Coll Cardiol.* 2008; 51:1512–1524. [PubMed: 18402913]
14. Burkhardt R, Toh SA, Lagor WR, Birkeland A, Levin M, Li X, et al. Trib 1 is a lipid- and myocardial infarction-associated gene that regulates hepatic lipogenesis and VLDL production in mice. *J Clin Invest.* 2010; 120:4410–4414. [PubMed: 21084752]
15. Fisher RM, Humphries SE, Talmud PJ. Common variation in the lipoprotein lipase gene: effects on plasma lipids and risk of atherosclerosis. *Atherosclerosis.* 1997; 135:145–159. [PubMed: 9430364]
16. Shachter NS. Apolipoproteins C-I and C-III as important modulators of lipoprotein metabolism. *Curr Opin Lipidol.* 2001; 12:297–304. [PubMed: 11353333]
17. Gordts P, Nock R, Son N, Ramms B, Lew I, Gonzales J, et al. ApoC-III modulates clearance of triglyceride-rich lipoproteins in mice through low density lipoprotein family receptors. *J Clin Invest.* 2016 [accepted for publication].
18. TG, HDL Working Group of the Exome Sequencing Project NHL, Blood I, et al. Loss-of-function mutations in APOC3, triglycerides, and coronary disease. *N Engl J Med.* 2014; 371:22–31. [PubMed: 24941081]
19. Sacks FM, Alaupovic P, Moye LA, Cole TG, Sussex B, Stampfer MJ, et al. VLDL, apolipoproteins B, CIII, and E, and risk of recurrent coronary events in the Cholesterol and Recurrent Events (CARE) trial. *Circulation.* 2000; 102:1886–1892. [PubMed: 11034934]
20. Zilversmit DB. A proposal linking atherogenesis to the interaction of endothelial lipoprotein lipase with triglyceride-rich lipoproteins. *Circ Res.* 1973; 33:633–638. [PubMed: 4361710]
21. Yla-Herttuala S, Lipton BA, Rosenfeld ME, Goldberg IJ, Steinberg D, Witztum JL. Macrophages and smooth muscle cells express lipoprotein lipase in human and rabbit atherosclerotic lesions. *Proc Natl Acad Sci U S A.* 1991; 88:10143–10147. [PubMed: 1719546]
22. Rutledge JC, Mullick AE, Gardner G, Goldberg IJ. Direct visualization of lipid deposition and reverse lipid transport in a perfused artery: roles of VLDL and HDL. *Circ Res.* 2000; 86:768–773. [PubMed: 10764410]
23. Rutledge JC, Woo MM, Rezai AA, Curtiss LK, Goldberg IJ. Lipoprotein lipase increases lipoprotein binding to the artery wall and increases endothelial layer permeability by formation of lipolysis products. *Circ Res.* 1997; 80:819–828. [PubMed: 9168784]
24. Fellin R, Baggio G, Poli A, Augustin J, Baiocchi MR, Baldo G, et al. Familial lipoprotein lipase and apolipoprotein C-II deficiency. Lipoprotein and apoprotein analysis, adipose tissue and hepatic lipoprotein lipase levels in seven patients and their first degree relatives. *Atherosclerosis.* 1983; 49:55–68. [PubMed: 6651913]
25. Babirak SP, Iverius PH, Fujimoto WY, Brunzell JD. Detection and characterization of the heterozygote state for lipoprotein lipase deficiency. *Arteriosclerosis.* 1989; 9:326–334. [PubMed: 2719595]
26. Goldberg IJ, Blaner WS, Vanni TM, Moukides M, Ramakrishnan R. Role of lipoprotein lipase in the regulation of high density lipoprotein apolipoprotein metabolism. Studies in normal and lipoprotein lipase-inhibited monkeys. *J Clin Invest.* 1990; 86:463–473. [PubMed: 2117022]
27. Rashid S, Watanabe T, Sakaue T, Lewis GF. Mechanisms of HDL lowering in insulin resistant, hypertriglyceridemic states: the combined effect of HDL triglyceride enrichment and elevated hepatic lipase activity. *Clin Biochem.* 2003; 36:421–429. [PubMed: 12951168]
28. Goldberg IJ, Le NA, Paterniti JR Jr, Ginsberg HN, Lindgren FT, Brown WV. Lipoprotein metabolism during acute inhibition of hepatic triglyceride lipase in the cynomolgus monkey. *J Clin Invest.* 1982; 70:1184–1192. [PubMed: 7174789]
29. Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. *J Cardiovasc Risk.* 1996; 3:213–219. [PubMed: 8836866]

30. Abdel-Maksoud M, Sazonov V, Gutkin SW, Hokanson JE. Effects of modifying triglycerides and triglyceride-rich lipoproteins on cardiovascular outcomes. *J Cardiovasc Pharmacol*. 2008; 51:331–351. [PubMed: 18427276]
31. Sarwar N, Danesh J, Eiriksdottir G, Sigurdsson G, Wareham N, Bingham S, et al. Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262, 525 participants in 29 western prospective studies. *Circulation*. 2007; 115:450–458. [PubMed: 17190864]
32. Stalenhoef AF, de Graaf J. Association of fasting and nonfasting serum triglycerides with cardiovascular disease and the role of remnant-like lipoproteins and small dense LDL. *Curr Opin Lipidol*. 2008; 19:355–361. [PubMed: 18607182]
33. Kirchmair R, Ebenbichler CF, Patsch JR. Post-prandial lipaemia. *Baillieres Clin Endocrinol Metab*. 1995; 9:705–719. [PubMed: 8593121]
34. Chan DC, Pang J, Romic G, Watts GF. Postprandial hypertriglyceridemia and cardiovascular disease: current and future therapies. *Curr Atheroscler Rep*. 2013; 15:309. [PubMed: 23345190]
35. Patsch W, Esterbauer H, Foger B, Patsch JR. Postprandial lipemia and coronary risk. *Curr Atheroscler Rep*. 2000; 2:232–242. [PubMed: 11122749]
36. Patsch JR, Prasad S, Gotto AM Jr, Bengtsson-Olivecrona G. Postprandial lipemia. A key for the conversion of high density lipoprotein2 into high density lipoprotein3 by hepatic lipase. *J Clin Invest*. 1984; 74:2017–2023. [PubMed: 6439739]
37. Ginsburg GS, Safran C, Pasternak RC. Frequency of low serum high-density lipoprotein cholesterol levels in hospitalized patients with “desirable” total cholesterol levels. *Am J Cardiol*. 1991; 68:187–192. [PubMed: 2063780]
38. Lamarche B, Lemieux I, Despres JP. The small, dense LDL phenotype and the risk of coronary heart disease: epidemiology, pathophysiology and therapeutic aspects. *Diabetes Metab*. 1999; 25:199–211. [PubMed: 10499189]
39. Goldberg IJ, Mazlen RG, Rubenstein A, Gibson JC, Paterniti JR Jr, Lindgren FT, et al. Plasma lipoprotein abnormalities associated with acquired hepatic triglyceride lipase deficiency. *Metabolism*. 1985; 34:832–835. [PubMed: 4033424]
40. Campos H, Khoo C, Sacks FM. Diurnal and acute patterns of postprandial apolipoprotein B-48 in VLDL, IDL, and LDL from normolipidemic humans. *Atherosclerosis*. 2005; 181:345–351. [PubMed: 16039289]
41. Otvos JD, Mora S, Shalaurova I, Greenland P, Mackey RH, Goff DC Jr. Clinical implications of discordance between low-density lipoprotein cholesterol and particle number. *J Clin Lipidol*. 2011; 5:105–113. [PubMed: 21392724]
42. St-Pierre AC, Cantin B, Dagenais GR, Maurieg P, Bernard PM, Despres JP, et al. Low-density lipoprotein subfractions and the long-term risk of ischemic heart disease in men: 13-year follow-up data from the Quebec cardiovascular study. *Arterioscler Thromb Vasc Biol*. 2005; 25:553–559. [PubMed: 15618542]
43. Shimano H, Arai H, Harada-Shiba M, Ueshima H, Ohta T, Yamashita S, et al. Proposed guidelines for hypertriglyceridemia in Japan with non-HDL cholesterol as the second target. *J Atheroscler Thromb*. 2008; 15:116–121. [PubMed: 18603817]
44. Kimura T, Tse K, Sette A, Ley K. Vaccination to modulate atherosclerosis. *Autoimmunity*. 2015; 48:152–160. [PubMed: 25683179]
45. Goldstein JL, Schrott HG, Hazzard WR, Bierman EL, Motulsky AG. Hyperlipidemia in coronary heart disease. II. Genetic analysis of lipid levels in 176 families and delineation of a new inherited disorder, combined hyperlipidemia. *J Clin Invest*. 1973; 52:1544–1568. [PubMed: 4718953]
46. Pajukanta P, Nuotio I, Terwilliger JD, Porkka KV, Ylitalo K, Pihlajamäki J, et al. Linkage of familial combined hyperlipidaemia to chromosome 1q21–q23. *Nat Genet*. 1998; 18:369–373. [PubMed: 9537421]
47. Mar R, Pajukanta P, Allayee H, Groenendijk M, Dallinga-Thie G, Krauss RM, et al. Association of the APOLIPOPROTEIN A1/C3/A4/A5 gene cluster with triglyceride levels and LDL particle size in familial combined hyperlipidemia. *Circ Res*. 2004; 94:993–999. [PubMed: 15001527]
48. Johansen CT, Wang J, Lanktree MB, McIntyre AD, Ban MR, Martins RA, et al. An increased burden of common and rare lipid-associated risk alleles contributes to the phenotypic spectrum of hypertriglyceridemia. *Arterioscler Thromb Vasc Biol*. 2011; 31:1916–1926. [PubMed: 21597005]

49. Johansen CT, Kathiresan S, Hegele RA. Genetic determinants of plasma triglycerides. *J Lipid Res.* 2011; 52:189–206. [PubMed: 21041806]
50. Johansen CT, Wang J, Lanktree MB, Cao H, McIntyre AD, Ban MR, et al. Excess of rare variants in genes identified by genome-wide association study of hypertriglyceridemia. *Nat Genet.* 2010; 42:684–687. [PubMed: 20657596]
51. Rashid S, Uffelman KD, Lewis GF. The mechanism of HDL lowering in hypertriglyceridemic, insulin-resistant states. *J Diabetes Complications.* 2002; 16:24–28. [PubMed: 11872362]
52. Wu L, Parhofer KG. Diabetic dyslipidemia. *Metabolism.* 2014; 63:1469–1479. [PubMed: 25242435]
53. Garcia-Arcos I, Hiyama Y, Drosatos K, Bharadwaj KG, Hu Y, Son NH, et al. Adipose-specific lipoprotein lipase deficiency more profoundly affects brown than white fat biology. *J Biol Chem.* 2013; 288:14046–14058. [PubMed: 23542081]
54. Joseph J, Shamburek RD, Cochran EK, Gorden P, Brown RJ. Lipid regulation in lipodystrophy versus the obesity-associated metabolic syndrome: the dissociation of HDL-C and triglycerides. *J Clin Endocrinol Metab.* 2014; 99:E1676–E1680. [PubMed: 24926953]
55. Weissglas-Volkov D, Pajukanta P. Genetic causes of high and low serum HDL-cholesterol. *J Lipid Res.* 2010; 51:2032–2057. [PubMed: 20421590]
56. Hegele RA. Premature atherosclerosis associated with monogenic insulin resistance. *Circulation.* 2001; 103:2225–2229. [PubMed: 11342468]
57. Murase T, Uchimura H. A selective decline of postheparin plasma hepatic triglyceride lipase in hypothyroid rats. *Metabolism.* 1980; 29:797–801. [PubMed: 7402081]
58. Applebaum DM, Goldberg AP, Pykalisto OJ, Brunzell JD, Hazzard WR. Effect of estrogen on post-heparin lipolytic activity. Selective decline in hepatic triglyceride lipase. *J Clin Invest.* 1977; 59:601–608. [PubMed: 845252]
59. Dashti N, Kelley JL, Thayer RH, Ontko JA. Concurrent inductions of avian hepatic lipogenesis, plasma lipids, and plasma apolipoprotein B by estrogen. *J Lipid Res.* 1983; 24:368–380. [PubMed: 6854148]
60. Klop B, Do Rego AT, Cabezas MC. Alcohol and plasma triglycerides. *Curr Opin Lipidol.* 2013; 24:321–326. [PubMed: 23511381]
61. Van de Wiel A. The effect of alcohol on postprandial and fasting triglycerides. *Int J Vasc Med.* 2012; 2012:862504. [PubMed: 21961068]
62. Grimm RH Jr. Antihypertensive therapy: taking lipids into consideration. *Am Heart J.* 1991; 122:910–918. [PubMed: 1678922]
63. Weidmann P, de Courten M, Ferrari P, Bohlen L. Serum lipoproteins during treatment with antihypertensive drugs. *J Cardiovasc Pharmacol.* 1993; 22(Suppl 6):S98–105.
64. Weidmann P, de Courten M, Ferrari P. Effect of diuretics on the plasma lipid profile. *Eur Heart J.* 1992; 13(Suppl G):61–67.
65. Lehtonen A. Effect of beta blockers on blood lipid profile. *Am Heart J.* 1985; 109:1192–1196. [PubMed: 2859784]
66. Krone W, Nagele H. Effects of antihypertensives on plasma lipids and lipoprotein metabolism. *Am Heart J.* 1988; 116:1729–1734. [PubMed: 3059788]
67. Weidmann P, Gerber A, Mordasini R. Effects of antihypertensive therapy on serum lipoproteins. *Hypertension.* 1983; 5:III120–III131. [PubMed: 6138309]
68. Keane WF, Tomassini JE, Neff DR. Lipid abnormalities in patients with chronic kidney disease: implications for the pathophysiology of atherosclerosis. *J Atheroscler Thromb.* 2013; 20:123–133. [PubMed: 23095239]
69. Clement LC, Mace C, Avila-Casado C, Joles JA, Kersten S, Chugh SS. Circulating angiopoietin-like 4 links proteinuria with hypertriglyceridemia in nephrotic syndrome. *Nat Med.* 2014; 20:37–46. [PubMed: 24317117]
70. Kaysen GA. Lipid and lipoprotein metabolism in chronic kidney disease. *J Ren Nutr.* 2009; 19:73–77. [PubMed: 19121776]
71. Vaziri ND, Norris K. Lipid disorders and their relevance to outcomes in chronic kidney disease. *Blood Purif.* 2011; 31:189–196. [PubMed: 21228589]

72. Stegmayr B, Olivecrona T, Olivecrona G. Lipoprotein lipase disturbances induced by uremia and hemodialysis. *Semin Dial.* 2009; 22:442–444. [PubMed: 19708998]
73. Moradi H, Vaziri ND, Kashyap ML, Said HM, Kalantar-Zadeh K. Role of HDL dysfunction in end-stage renal disease: a double-edged sword. *J Ren Nutr.* 2013; 23:203–206. [PubMed: 23611547]
74. Carr A, Samaras K, Thorisdottir A, Kaufmann GR, Chisholm DJ, Cooper DA. Diagnosis, prediction, and natural course of HIV-1 protease-inhibitor-associated lipodystrophy, hyperlipidaemia, and diabetes mellitus: a cohort study. *Lancet.* 1999; 353:2093–2099. [PubMed: 10382692]
75. Hadigan C, Meigs JB, Corcoran C, Rietschel P, Piecuch S, Basgoz N, et al. Metabolic abnormalities and cardiovascular disease risk factors in adults with human immunodeficiency virus infection and lipodystrophy. *Clin Infect Dis.* 2001; 32:130–139. [PubMed: 11118392]
76. Periard D, Telenti A, Sudre P, Cheseaux JJ, Halfon P, Reymond MJ, et al. Atherogenic dyslipidemia in HIV-infected individuals treated with protease inhibitors. The Swiss HIV cohort study. *Circulation.* 1999; 100:700–705. [PubMed: 10449690]
77. Lichtenstein KA, Ward DJ, Moorman AC, Delaney KM, Young B, Palella FJ, et al. Clinical assessment of HIV-associated lipodystrophy in an ambulatory population. *AIDS.* 2001; 15:1389–1398. [PubMed: 11504960]
78. Grunfeld C, Pang M, Doerrler W, Shigenaga JK, Jensen P, Feingold KR. Lipids, lipoproteins, triglyceride clearance, and cytokines in human immunodeficiency virus infection and the acquired immunodeficiency syndrome. *J Clin Endocrinol Metab.* 1992; 74:1045–1052. [PubMed: 1373735]
79. Pillarisetti S, Saxena U. Lipoprotein lipase as a therapeutic target for dyslipidemia. *Front Biosci.* 2003; 8:d238–d241. [PubMed: 12456348]
80. Semb H, Peterson J, Tavernier J, Olivecrona T. Multiple effects of tumor necrosis factor on lipoprotein lipase in vivo. *J Biol Chem.* 1987; 262:8390–8394. [PubMed: 3597377]
81. Lewis GF, Rader DJ. New insights into the regulation of HDL metabolism and reverse cholesterol transport. *Circ Res.* 2005; 96:1221–1232. [PubMed: 15976321]
82. Haim M, Benderly M, Boyko V, Goldenberg I, Tanne D, Battler A, et al. Decrease in triglyceride level by bezafibrate is related to reduction of recurrent coronary events: a bezafibrate infarction prevention substudy. *Coron Artery Dis.* 2006; 17:455–461. [PubMed: 16845254]
83. Jamshidi Y, Flavell DM, Hawe E, MacCallum PK, Meade TW, Humphries SE. Genetic determinants of the response to bezafibrate treatment in the lower extremity arterial disease event reduction (LEADER) trial. *Atherosclerosis.* 2002; 163:183–192. [PubMed: 12048138]
84. Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med.* 1999; 341:410–418. [PubMed: 10438259]
85. Wierzbicki AS. FIELDs of dreams, fields of tears: a perspective on the fibrate trials. *Int J Clin Pract.* 2006; 60:442–449. [PubMed: 16620358]
86. Group AS, Ginsberg HN, Elam MB, Lovato LC, Crouse JR 3rd, Leiter LA, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med.* 2010; 362:1563–1574. [PubMed: 20228404]
87. Ting RD, Keech AC, Drury PL, Donoghoe MW, Hedley J, Jenkins AJ, et al. Benefits and safety of long-term fenofibrate therapy in people with type 2 diabetes and renal impairment: the FIELD study. *Diabetes Care.* 2012; 35:218–225. [PubMed: 22210576]
88. Bosch J, Gerstein HC, Dagenais GR, Diaz R, Dyal L, et al. Investigators OT. N-3 fatty acids and cardiovascular outcomes in patients with dysglycemia. *N Engl J Med.* 2012; 367:309–318. [PubMed: 22686415]
89. Kastelein JJ, Maki KC, Susekov A, Ezhov M, Nordestgaard BG, Machielse BN, et al. Omega-3 free fatty acids for the treatment of severe hypertriglyceridemia: the EpanoVa fOr lowering very high triglycerideS (EVOLVE) trial. *J Clin Lipidol.* 2014; 8:94–106. [PubMed: 24528690]
90. Berglund L, Brunzell JD, Goldberg AC, Goldberg IJ, Sacks F, Murad MH, et al. Evaluation and treatment of hypertriglyceridemia: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2012; 97:2969–2989. [PubMed: 22962670]

91. Brunzell JD, Schrott HG. The interaction of familial and secondary causes of hypertriglyceridemia: role in pancreatitis. *J Clin Lipidol.* 2012; 6:409–412. [PubMed: 23009776]
92. Chait A, Brunzell JD. Severe hypertriglyceridemia: role of familial and acquired disorders. *Metabolism.* 1983; 32:209–214. [PubMed: 6827992]
93. Jellinger PS, Dickey RA, Ganda OP, Mehta AE, Nguyen TT, Rodbard HW, et al. AACE medical guidelines for clinical practice for the diagnosis and treatment of dyslipidemia and prevention of atherogenesis. *Endocr Pract.* 2000; 6:162–213. [PubMed: 11428356]
94. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2014; 63:2889–2934. [PubMed: 24239923]
95. Berglund L, Brunzell JD, Goldberg AC, Goldberg IJ, Stalenhoef A. Treatment options for hypertriglyceridemia: from risk reduction to pancreatitis. *Best Pract Res Clin Endocrinol Metab.* 2014; 28:423–437. [PubMed: 24840268]
96. Havel PJ. Dietary fructose: implications for dysregulation of energy homeostasis and lipid/carbohydrate metabolism. *Nutr Rev.* 2005; 63:133–157. [PubMed: 15971409]
97. Graham TE. Exercise, postprandial triacylglyceridemia, and cardiovascular disease risk. *Can J Appl Physiol.* 2004; 29:781–799. [PubMed: 15630150]
98. Chait A, Brunzell JD. Chylomicronemia syndrome. *Adv Intern Med.* 1992; 37:249–273. [PubMed: 1557997]
99. Tonelli M, Collins D, Robins S, Bloomfield H, Curhan GC. Veterans' Affairs high-density lipoprotein intervention trial I. Gemfibrozil for secondary prevention of cardiovascular events in mild to moderate chronic renal insufficiency. *Kidney Int.* 2004; 66:1123–1130. [PubMed: 15327407]
100. Ganji SH, Tavintharan S, Zhu D, Xing Y, Kamanna VS, Kashyap ML. Niacin noncompetitively inhibits DGAT2 but not DGAT1 activity in HepG2 cells. *J Lipid Res.* 2004; 45:1835–1845. [PubMed: 15258194]
101. Brown BG, Zhao XQ, Chait A, Fisher LD, Cheung MC, Morse JS, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med.* 2001; 345:1583–1592. [PubMed: 11757504]
102. Musa-Veloso K, Binns MA, Kocenas AC, Poon T, Elliot JA, Rice H, et al. Long-chain omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid dose-dependently reduce fasting serum triglycerides. *Nutr Rev.* 2010; 68:155–167. [PubMed: 20384846]
103. McKenney JM, Sica D. Role of prescription omega-3 fatty acids in the treatment of hypertriglyceridemia. *Pharmacotherapy.* 2007; 27:715–728. [PubMed: 17461707]
104. Brinton EA, Ballantyne CM, Bays HE, Kastelein JJ, Braeckman RA, Soni PN. Effects of icosapent ethyl on lipid and inflammatory parameters in patients with diabetes mellitus-2, residual elevated triglycerides (200–500 mg/dL), and on statin therapy at LDL-C goal: the ANCHOR study. *Cardiovasc Diabetol.* 2013; 12:100. [PubMed: 23835245]
105. Heck AM, Yanovski JA, Calis KA. Orlistat, a new lipase inhibitor for the management of obesity. *Pharmacotherapy.* 2000; 20:270–279. [PubMed: 10730683]
106. Tan KC, Tso AW, Tam SC, Pang RW, Lam KS. Acute effect of orlistat on post-prandial lipaemia and free fatty acids in overweight patients with type 2 diabetes mellitus. *Diabet Med.* 2002; 19:944–948. [PubMed: 12421432]
107. Hollander PA, Elbein SC, Hirsch IB, Kelley D, McGill J, Taylor T, et al. Role of orlistat in the treatment of obese patients with type 2 diabetes. A 1-year randomized double-blind study. *Diabetes Care.* 1998; 21:1288–1294. [PubMed: 9702435]
108. Yla-Herttuala S. Endgame: glybera finally recommended for approval as the first gene therapy drug in the European Union. *Mol Ther.* 2012; 20:1831–1832. [PubMed: 23023051]
109. Miller N. Glybera and the future of gene therapy in the European Union. *Nat Rev Drug Discov.* 2012; 11:419.
110. Kersten S. The genetics of dyslipidemia—when less is more. *N Engl J Med.* 2016; 374:1192–1193. [PubMed: 26934667]

111. Gaudet D, Alexander VJ, Baker BF, Brisson D, Tremblay K, Singleton W, et al. Antisense inhibition of apolipoprotein C-III in patients with hypertriglyceridemia. *N Engl J Med*. 2015; 373:438–447. [PubMed: 26222559]
112. Gaudet D, Brisson D, Tremblay K, Alexander VJ, Singleton W, Hughes SG, et al. Targeting APOC3 in the familial chylomicronemia syndrome. *N Engl J Med*. 2014; 371:2200–2206. [PubMed: 25470695]
113. Jones PH, Davidson MH, Stein EA, Bays HE, McKenney JM, Miller E, et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR* trial). *Am J Cardiol*. 2003; 92:152–160. [PubMed: 12860216]
114. Kastelein JJ, Sager PT, de Groot E, Veltri E. Comparison of ezetimibe plus simvastatin versus simvastatin monotherapy on atherosclerosis progression in familial hypercholesterolemia. Design and rationale of the ezetimibe and simvastatin in hypercholesterolemia enhances atherosclerosis regression (ENHANCE) trial. *Am Heart J*. 2005; 149:234–239. [PubMed: 15846260]
115. Ballantyne CM, Bays HE, Kastelein JJ, Stein E, Isaacsohn JL, Braeckman RA, et al. Efficacy and safety of eicosapentaenoic acid ethyl ester (AMR101) therapy in statin-treated patients with persistent high triglycerides (from the ANCHOR study). *Am J Cardiol*. 2012; 110:984–992. [PubMed: 22819432]
116. Bays HE, Ballantyne CM, Kastelein JJ, Isaacsohn JL, Braeckman RA, Soni PN. Eicosapentaenoic acid ethyl ester (AMR101) therapy in patients with very high triglyceride levels (from the Multi-center, placebo-controlled, Randomized, double-blIND, 12-week study with an open-label Extension [MARINE] trial). *Am J Cardiol*. 2011; 108:682–690. [PubMed: 21683321]
117. Teo KK, Goldstein LB, Chaitman BR, Grant S, Weintraub WS, Anderson DC, et al. Extended-release niacin therapy and risk of ischemic stroke in patients with cardiovascular disease: the Atherothrombosis intervention in metabolic syndrome with low HDL/high triglycerides: impact on Global Health Outcome (AIM-HIGH) trial. *Stroke*. 2013; 44:2688–2693. [PubMed: 23881958]

Fig 1.

Chylomicron metabolism. Dietary TG and apoB48 are assembled into chylomicrons and are secreted into the lymph. They enter the bloodstream via the thoracic duct and the TG is broken into free fatty acids via the actions of LpL bound to endothelial surfaces via GPIHBP1 and HSPGs. The smaller atherogenic remnants are cleared by the liver.

Fig 2.

Margination of TG-rich lipoproteins. Chylomicrons are much more likely to interact with the wall of the capillary and hence their catabolism is much faster than the smaller VLDL. This figure was originally published in the *Journal of Lipid Research*. I J Goldberg. Lipoprotein lipase and lipolysis: central roles in lipoprotein metabolism and atherogenesis. *Journal of Lipid Research*. 1996; 37: 693–707. © The American Society for Biochemistry and Molecular Biology.

Fig 3.

TGRLs regulate HDL formation and composition. During lipolysis of TGRLs surface lipids and apoproteins are transferred to smaller HDL. In humans, hypertriglyceridemia also reduces HDL cholesterol by accelerating the CETP-mediated exchange of TGRL TG for HDL cholesterol.

Table 1

Anti-hyperlipidemic medications and their effect on triglyceride lowering.

Drug Class	Lipid Effects	Mechanism of Action of TG Reduction	Outcomes Data/Pertinent Trials
Statins	LDL decrease: 18%–55% HDL increase: 5%–15% TG decrease 10%–20%	- Inhibition of HMG CoA reductase - Decreased production of apoB-containing VLDL particles and upregulation of LDL receptors - Upregulation of LDL receptors enhances clearance of TG-rich VLDL and chylomicrons and additionally lower apoB levels	STELLAR trial: No difference in TG lowering between high dose rosuvastatin and atorvastatin; however, rosuvastatin is the superior statin monotherapy for lowering non-HDL cholesterol, apoB and LDL-P. ¹¹³ ENHANCE trial and other statin/ezetimibe trials show significantly more TG-lowering when ezetimibe (Zetia) was added to a statin, as opposed to statin monotherapy. ¹¹⁴
Fibric acid derivatives	LDL decrease: 20% HDL increase: 11% TG decrease: 24%–51%	- Fibrates activate peroxisome proliferator activated receptor (PPAR) alpha which increases the activity of lipoprotein lipase - Increased HDL production - Decreased release of free fatty acids from adipose tissue.	Per trials in text above
Ezetimibe	LDL decrease: 18% HDL increase: 1% TG decrease: 8%	Ezetimibe is a cholesterol absorption inhibitor which inhibits the passage of cholesterol of dietary and biliary origin across the intestinal wall	ENHANCE trial and other statin/ezetimibe trials show significantly more TG-lowering when ezetimibe (Zetia) was added to a statin than statin monotherapy. ¹¹⁴
Fish Oils (EPA and DHA)	LDL decrease: 5% HDL decrease: 4% TG decreases by up to 30%–50%	- Fish oils act by decreasing VLDL production and increasing its clearance - They specifically target Non-Esterified Fatty Acids (NEFAs) which are the largest contributor - Fish oil is also known to counteract intracellular lipolysis and decreasing adipose tissue inflammation	The MARINE and ANCHOR trials have both shown that EPA improves HTG and also helps to decrease the levels of the vascular inflammatory biomarkers of cardiovascular risk. ^{115,116}
Niacin	LDL decrease: 14%–17% HDL increase: 22%–26% TG decrease: 20%–50%	- Niacin favorably acts on apoB-containing particles including - Niacin directly inhibits hepatocyte DGAT2 which catalyzes the formation of TG.	AIM-HIGH showed no clinical benefit/ cardiovascular benefit in patients with high TG who were treated with high dose extended release niacin in combination with high dose statins. The increase in adverse events associated with niacin led to early discontinuation of the study as well. ¹¹⁷ As statin add-on, reduces carotid intima-media thickness (surrogate marker) compared with ezetimibe as statin add-on in patients with lower HDL