Very low HDL levels: clinical assessment and management

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ABSTRACT

In individuals with very low high-density lipoprotein (HDL-C) cholesterol, such as Tangier disease, LCAT deficiency, and familial hypoalphalipoproteinemia, there is an increased risk of premature atherosclerosis. However, analyzes based on comparisons of populations with small variations in HDL-C mediated by polygenic alterations do not confirm these findings, suggesting that there is an indirect association or heterogeneity in the pathophysiological mechanisms related to the reduction of HDL-C. Trials that evaluated some of the HDL functions demonstrate a more robust degree of association between the HDL system and atherosclerotic risk, but as they were not designed to modify lipoprotein functionality, there is insufficient data to establish a causal relationship. We currently have randomized clinical trials of therapies that increase HDL-C concentration by various mechanisms, and this HDL-C elevation has not independently demonstrated a reduction in the risk of cardiovascular events. Therefore, this evidence shows that (a) measuring HDL-C as a way of estimating HDL-related atheroprotective system function is insufficient and (b) we still do not know how to increase cardiovascular protection with therapies aimed at modifying HDL metabolism. This leads us to a greater effort to understand the mechanisms of molecular action and cellular interaction of HDL, completely abandoning the traditional view focused on the plasma concentration of HDL-C. In this review, we will detail this new understanding and the new horizon for using the HDL system to mitigate residual atherosclerotic risk. Arch Endocrinol Metab. 2023;67(1):3-18

Keywords
High-density lipoprotein; Tangier disease; LCAT deficiency; familial hypoalphalipoproteinemia; polygenic dyslipidemias; atherosclerosis

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Received on May/2/2022
Accepted on Sep/18/2022

DOI: 10.20945/2359-3997000000585

INTRODUCTION

Important findings from the Framingham (1), Tromsø Heart (2) and Prospective Cardiovascular Munster (PROCAM) (3) studies revealed an inverse relationship between serum concentrations of high-density lipoprotein (HDL) and the risk of cardiovascular disease (CVD), independently of the levels of low-density lipoprotein cholesterol (LDL-C). However, in recent decades it has been increasingly questioned whether approaches to improve HDL-related atheroprotective system function will actually reduce the risk of atherosclerosis. The CANHEART (4) study showed that high levels of HDL cholesterol (HDL-C) did not reduce mortality from CVD, indicating that high HDL-C is not necessarily associated with cardioprotection. Also, a genetic study showed that three functional variants of hepatic lipase associated with a modest increase in HDL-C levels did not reduce cardiovascular risk (5). On the other hand, a 29.3% reduction in HDL-C levels due to functional mutations in the ATP Binding Cassette-A1 (ABCA1) transporter did not adversely affect cardiovascular risk (6). Mendelian randomization studies demonstrated a lack of causal link between low HDL-C and the development of atherosclerosis (7), that is, low HDL-C levels are strongly associated with an increased risk of myocardial infarction, but when these levels are genetically determined, an association does not exist (7). However, studies of HDL functionality showed an even more evident association with cardiovascular risk than HDL-C levels (8), indicating that HDL functionality plays a more relevant role in atheroprotection than its circulating levels.

Very low HDL-C is seen in clinical conditions that differ from each other in terms of their potential for

the development of atherosclerotic disease. Individuals afflicted with single-gene diseases are at high risk of premature atherosclerosis (9). On the other hand, less severe mutations in genes related to intravascular metabolism or HDL synthesis (10) do not result in an increased risk of atherosclerotic disease (11). In contrast, low plasma HDL-C can also be seen in insulin resistance and subsequent atherogenic dyslipidemia, characterized by low HDL-C levels, high triglyceride levels, and an increased proportion of small, dense lipoproteins both HDL and low-density lipoprotein (LDL) (12). In this review, we will detail the clinical conditions that occur with low levels of HDL-C.

HDL metabolism

HDL particles are present in the circulation in different sizes (7-12 nm) and densities (1,063-1,21 g/mL) and represent the HDL pool in the course of its maturation after hepatic and intestinal production of apolipoprotein (apo)A-I, which is functionally and structurally the most important protein of HDL. Pre-β, discoid, small and lipid-poor HDL captures free cholesterol after binding between apoA-I and the ABCA1 receptor of peripheral cells, allowing reverse cholesterol transport (13).

At the same time, HDL particles are also enriched with phospholipids derived from other lipoproteins, especially very low-density lipoprotein (VLDL), by phospholipid transfer protein (PLTP). For the formation of HDL particles with a lipid and hydrophilic core, one of the enzymes associated with HDL, the enzyme lecithin-cholesterol acyltransferase (LCAT), catalyzes the transfer of fatty acids from phospholipids to cholesterol, esterifying it and promoting the formation of HDL particles rich in cholesterol esters. Reverse cholesterol transport is completed when HDL is taken up by hepatic Scavenger Receptor-B1 (SR-B1) receptors, initiating the process of excretion through the bile. On the other hand, cholesteryl esters can also be transferred to lipoproteins that contain apoB by the action of Cholesteryl Ester Transfer Protein (CETP), through exchange for triglycerides (14).

As a carrier of several proteins, including acute phase enzymes, and a small amount of non-polar lipids, HDL is found in the circulation with different phenotypes and biological properties. While some of these actions (such as antioxidant activity) are intensely exerted by immature forms of HDL (HDL3), reverse cholesterol transport and anti-inflammatory action on the endothelium appear to require more mature forms of HDL (HDL2) (15). This broad set of actions is the result of several components of HDL, such as apoA-I, apoA-II, apoJ, as well as other proteins, enzymes, phospholipids and even probably microRNAs that are transported by HDL particles (16,17).

Monogenic dyslipidemias

Extremely low serum HDL-C levels (<30-35 mg/dL) in the absence of secondary causes occur in 1% of the general population (18) and correspond to rare and underdiagnosed genetic syndromes caused by mutations in genes that regulate HDL production or catabolism. According to population studies, 18.7% of individuals with very low HDL-C carry rare genetic variants of great effect and 19.3% carry common low-effect variants (19). Thus, the genetic basis of very low HDL-C disease is often polygenic.

Tangier disease

The ABCA1 gene resides on chromosome 9q22-q31, contains 50 exons and encodes a long membrane protein of 2,261 amino acids. It consists of two transmembrane domains, each formed by six alpha helices and two intracellular nucleotide-binding domains (20). Tangier disease is a rare monogenic autosomal recessive disorder that occurs due to mutations in both alleles of the ABCA1 gene, both exonic (21) and intronic in ABCA1 causing aberrant splicing of mRNA (22). Overall, as changes in the ABCA1 gene negatively influence cellular cholesterol uptake, the concentration of HDL-C decreases more sharply and the incidence of coronary artery disease (CAD) increases. Fibroblasts are very deficient in the export of cholesterol and, as a result, complete particles of HDL are not formed (23). Therefore, ABCA1 deficiency leads to intracellular accumulation of cholesteryl esters, precluding the conversion of the lipid-poor apoA-I particles into pre-β HDL (24) (Figure 1).

Clinical assessment

Characterized by the almost complete absence of HDL-C (always less than 5 mg/dL), homozygous individuals show a marked increase in apoA-I catabolism, with plasma residence time of about 0.5 days. On the other hand, heterozygous individuals show increased clearance with plasma residence time of about 2 days (25). Also, heterozygotes may show a reduction

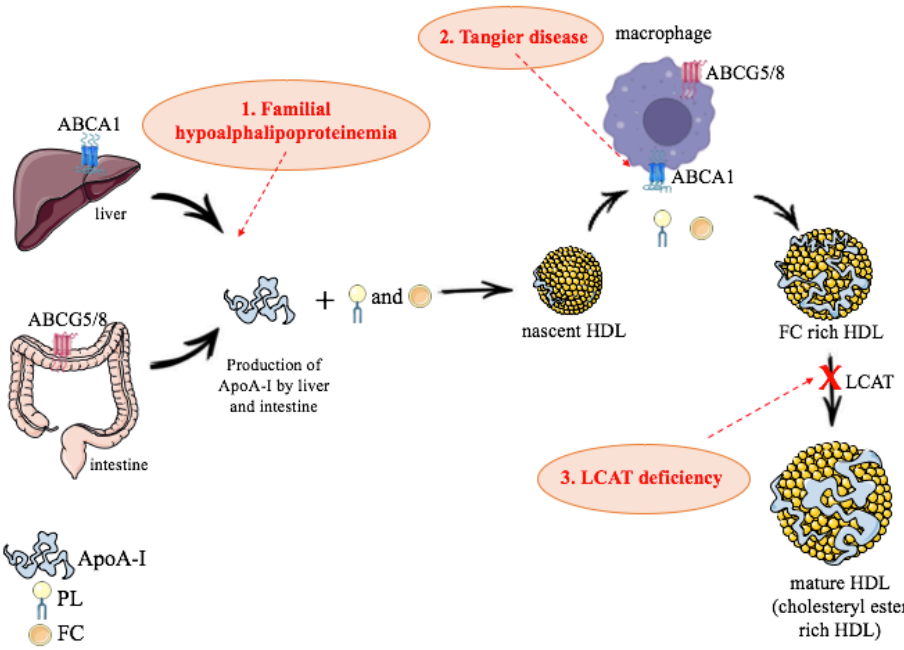

Figure 1. HDL regulation and monogenic disorders with low levels of HDL-C. Black arrows show HDL metabolism and red arrows where monogenic disorders occur in the three conditions reported in this review. **1.** The subjects with familial hypoalphalipoproteinemia have been reported to have either decreased HDL production or increased HDL ApoA-I catabolism. **2.** The disorder results from homozygous mutations in the ABCA1 transport protein, which mediates the efflux of cellular cholesterol to the HDL particle in plasma for transport to the liver. **3.** Both FLD and FED are caused by the mutations in the LCAT gene. Both disorder lead to a marked reduction in plasma HDL-C. ApoA-I: apolipoprotein A-I; PL: phospholipids; FC: free cholesterol; PLTP: Phospholipid Transfer Protein; LPL: lipoprotein lipase; ABCA1: ATP-binding cassette transporter A1; LCAT: Lecithin-cholesterol acyltransferase; ABCG5/8: ATP-binding cassette, subfamily G, member 5 and member 8.

of approximately 50% in ABCA1-mediated cellular cholesterol efflux (24). There is an accumulation of cholesterol esters in the reticuloendothelial system and adipose tissue, in addition to yellow-orange hyperplastic tonsils, which, together with very low levels of HDL-C, are considered indicative of the disease. Individuals have elevated TG and a reduction of up to 50% in LDL-C concentration.

There are controversies in the literature as to whether individuals who are homozygous for Tangiers have an increased risk of developing premature CVD. An analysis involving 185 cases showed that 25% had CVD but among individuals over 40 years of age this prevalence reached 52% compared to 11% in age- and gender-matched controls (25). This suggests that these individuals do not develop early CVD because LDL-C levels are about 50% of normal. Furthermore, this report suggested the presence of two distinct phenotypic groups: (i) patients with marked hepatosplenomegaly, anemia, low levels of non-HDL-C (<70 mg/dL) and absence of premature CAD; and (ii) patients without hepatosplenomegaly or severe anemia, normal or near-normal non-HDL-C levels (>70 mg/dL) and premature CAD (25). The variability in CVD risk in homozygotes may be, in part, explained by non-HDL-C levels.

In many cases, peripheral neuropathy is absent or only detectable by electrophysiological investigation of nerve conductance velocity. On the other hand, symptomatic individuals present: (i) a multifocal demyelinating form that is mononeuropathic or asymmetric polyneuropathic and affects the motor and sensory nerves of the limbs or head or (ii) a syndrome similar to syringomyelia, being progressive and often debilitating (20).

Clinical management

ABCA1 molecular gene sequencing is the gold standard for diagnosing Tangier disease. However, two tests can help make the diagnosis more likely: two-dimensional non-denaturing electrophoresis and anti-apoA-I immunoblotting help distinguish part of HDL that has alpha electrophoretic mobility (α-HDL) from a quantitatively smaller proportion that has pre-electrophoretic mobility (pre β1-HDL) (26).

Other complementary tests may be performed: nerve conduction studies and electroneuromyography

to determine the presence of peripheral neuropathy; ophthalmologic evaluation to identify any corneal opacities; abdominal ultrasound to assess hepatosplenomegaly; carotid Doppler ultrasound to identify the thickness of the intima and media layers of the carotid arteries (cIMT) and plaques (27); and echocardiogram to assess coronary atherosclerosis.

LCAT deficiency

LCAT deficiency is a very rare autosomal recessive disorder. The majority of described genetic variations are loss-of-function mutations leading to proteins with total or partial lack of LCAT activity (28). Genetic LCAT deficiency is associated with the development of two syndromes: (i) familial LCAT deficiency (FLD) and (ii) fish-eye disease (FED). Among the described mutations, 53 are associated with an FLD phenotype and 19 mutations lead to a FED phenotype (28). FLD is characterized by mutations that result in the absence or complete inactivity of the LCAT enzyme and present the disease in its severe form, while FED is the result of mutations that inhibit the ability of LCAT to esterify cholesterol to HDL, but do not affect the ability of esterifying cholesterol to lipoproteins that have apoB, so patients are relatively less symptomatic (29) (Figure 1).

In a case series of a Canadian family with LCAT deficiency, no cardiovascular events or deaths were reported for 25 years after the initial diagnosis. In the two homozygous individuals, cIMT was above the 75th percentile expected for age and sex. However, the abnormalities were much more pronounced in the heterozygous individuals, four of whom had detectable plaques, indicating that heterozygosity may be associated with an atherogenic lipid profile and vascular abnormalities (30). Notably, homozygous carriers have low plasma concentration of LDL-C, which would explain protection against atherogenesis.

A more extensive study evaluated cIMT in 40 carriers of LCAT gene mutations and in 80 healthy controls and found no significant difference between mutation carriers (31). Divergent results between studies remain unclear about whether low LCAT activity, genetically determined, is associated with increased preclinical atherosclerosis. LCAT, by itself, is not the only regulator of reverse cholesterol transport pathways (32). Both overexpression and LCAT deficiency showed reverse cholesterol transport from macrophages preserved in an animal model (33). Furthermore, plasma from LCAT-deficient individuals has the same ability to reduce the cholesterol content of macrophages compared to plasma from control individuals (34). Thus, it remains questionable whether the elevation of LCAT activity is a promising therapeutic strategy to reduce cardiovascular risk.

Clinical assessment

Individuals affected by FLD develop corneal opacification, anemia and notable proteinuria (35). Also, the patients develop early and progressive chronic kidney disease leading to early end-stage renal disease, which is the main cause of morbidity and mortality in this population (36). The reason for the deterioration of renal function remains unknown. Heterogeneous glomerular pathology implies several possible mechanisms, including abnormal LDL trapping and C3 complement deposition (37). The presence of anemia may occur in association with the disease and is attributed to an increase in the fragility of erythrocytes due to the abnormal lipid composition of their cell membrane. On the other hand, individuals with FED clinically have corneal opacification but are spared anemia and kidney disease and are therefore considered to have a milder form of LCAT deficiency (38).

Corneal opacification, the characteristic physical finding in LCAT deficiency state, is more severe than the accumulation of cholesterol in the cornea that can be sporadically seen in apoA-I deficiency and Tangier disease. Patients with FLD and FED slowly develop progressive corneal opacification accompanied by a white or gray ring at the corneal margin similar to arcus senilis (20). Surprisingly, vision remains intact in most cases.

Prevalence of CAD is higher in FED than in FLD, and this is supported by significantly lower LDL-C in carriers of FLD mutations compared with carriers of FED mutations (39); however, there are case reports of mutations in LCAT that present low or normal plasma levels of HDL-C without premature CAD (34). Assessment of cIMT, a surrogate imaging measure of cardiovascular risk, also suggests that there is no significant worsening of the vascular phenotype among individuals that are homozygous for LCAT mutations.

Clinical management

Initial clinical suspicion is raised based on corneal opacification. The diagnosis of these disorders can be performed through the quantification of LCAT.

Definitive diagnosis requires molecular genetic testing of the LCAT gene and functional analysis of the gene product.

Patients with FLD and FED have not only very low levels of HDL-C (<10 mg/dL), but also elevations in VLDL enriched with free cholesterol (25). In two-dimensional gel electrophoresis there is the presence of pre-β HDL and α4-HDL and the absence of mature α-HDL (28). ApoA-I levels are usually between 20-30 mg/dL and LDL-C concentration is often low. In addition, they have a large, heterogeneous LDL phenotype enriched in free cholesterol, phospholipids and TG, with a very low cholesterol ester content. These particles are also low in apoB and enriched in apoC. The lipid profile is also characterized by the presence of lipoprotein X (Lp-X). Lp-X is a particle that has low protein, esterified cholesterol and TG content, and high free cholesterol and phospholipid content (40). Experimental studies demonstrate that Lp-X is nephrotoxic, and there is an association with FLD-related kidney disease, showing distinctive lipid deposits in glomeruli in histology, but not with FED (41).

Familial hypoalphalipoproteinemia

Familial hypoalphalipoproteinemia is a very rare autosomal dominant disorder characterized by a heterogeneous group of mutations that cause apoA-I deficiency resulting from a biallelic mutation in the *APOA1* gene, located on chromosome 11q23.3, which contains four coding regions and is clustered with the apoC-III and apoC-IV genes (42). Functionally significant mutations have also been described, including gene disruptions, frame changes, nonsense mutations, chromosomal aberrations or deletions, as well as *APOA1/APOA3/APOA4* gene cluster inversion associated with decreased HDL-C levels (43-45). ApoA-I variants are generally heterozygous premature terminations, frameshifts, or amino acid substitutions in the 243 amino acid sequence of apoA-I (25) (Figure 1).

Clinical assessment

Although extremely low HDL-C can be detected in any patient from birth, the age of onset of symptoms and the clinical presentation vary widely. Homozygous or compound heterozygous carriers have two different clinical features: (i) xanthomas or (ii) corneal opacities. Cutaneous xanthomas (tuber-eruptive, tendinous, palmar or planar) have been described in adult patients who are homozygous or compound heterozygous carrying null alleles and therefore do not have apoA-I in their plasma. They often have premature CAD and carotid atherosclerosis (46).

Heterozygous variants of apoA-I that cause low HDL-C and decreased LCAT activation are not associated with premature CVD. However, apoA-I variants associated with low HDL-C and normal LCAT activity have been associated with premature CVD (25). Heterozygous carriers of apoA-I variants do not show specific clinical symptoms. An important exception is some structural variants of apoA-I with amino-terminus amino acid substitutions, detected in patients with familial amyloidosis (47-49). These amyloidogenic mutations lead to the accumulation of amyloid containing amino-terminus apoA-I fragments (9-11 kd N terminal fragments (25) in the liver, intestine, kidney, heart, peripheral nerves and skin (47-49). ApoA-I deficiency can also manifest with sensorineural signs such as cerebellar ataxia, sensorineural hearing loss, and proliferative retinopathy.

In addition, some apoA-I variants such as apoA-I (L178P) or apoA-I (L159P) were associated with increased risk of premature CAD or increased progression of cIMT (50,51), while others did not show this association, or even proved to reduce cardiovascular risk remarkably, such as apoA-I Milano (52).

Clinical management

Homozygous carriers have undetectable apoA-I (less than 5 mg/dL) and HDL-C lower than 10 mg/dL. On the other hand, heterozygous carriers generally have HDL-C levels that are often below the fifth percentile or, at least, below the cardiovascular risk threshold level of 40 mg/dL for men and 50 mg/dL for women. As would be expected, apoA-I levels are also frequently below the fifth percentile (<105 mg/dL in men and <110 mg/dL in women) (53).

In a patient with xanthomas, histological examination of the skin lesions reveals numerous foam cells. Molecular diagnosis can be performed by the technique of two-dimensional gel electrophoresis observing the absence or reduction of apoA-I. DNA analysis can also be useful for an accurate diagnosis, performed by sequencing the *APOA1* gene and demonstrating a functionally relevant mutation. Many structural variants of apoA-I can be detected by isoelectric focusing and anti-apoA-I immunoblotting (53).

Polygenic dyslipidemias

Recent studies indicate that the genetic basis of extreme concentrations of HDL-C identified clinically is often polygenic, having previously been considered an archetypal "monogenic" disorder. As mentioned above, about 18.7% of individuals with very low HDL-C are heterozygous for rare mutations of great effect and 19.3% of the cases of very low HDL-C show an accumulation of common mutations (19). In addition, some patients with polygenic dyslipidemia may also have mixed dyslipidemias (low HDL-C and elevations of TG) associated with a different clinical condition such as metabolic syndrome or obesity. Identification of single nucleotide polymorphisms (SNP) that have modest effects on HDL-C plasma have been used to confirm or refute the role of HDL in the development of atherosclerotic disease and as a tool to identify individuals with polygenic dyslipidemias. A classic Mendelian randomization study demonstrated that polymorphism in the lipase gene endothelial cell and a genetic score of 14 common SNP that specifically increased HDL-C were not associated with risk of acute myocardial infarction, suggesting that some genetic mechanisms that increase or decrease HDL-C do not reduce cardiovascular risk (8). Another study that used SNP of the target genes as an instrument demonstrated that not all metabolic alterations that modify serum HDL-C levels influence cardiovascular risk (54).

Consistently, studies that used randomization Mendelian research revealed that while the increase of polygenic origin in the concentration of lipoproteins associated with apoB is associated with increased risk of CVD, no association was found with SNP-mediated variation in lipoproteins associated with apoA-I (55,56). Although these findings may suggest the absence of a causal relationship, plasma levels of HDL-C or apoA-I do not represent reliable instrumental variables, considering that the increase in the circulating concentration of HDL-C or apoA-I does not always equate with a change of roles of the HDL particle or its interaction with cells, i.e., in the HDL system.

Secondary dyslipidemias with low HDL-C

Type 2 diabetes mellitus, insulin resistance, and obesity

Some dyslipidemias are not explained by mutations but are related to epigenetic mechanisms that may be influenced by drug interventions, lifestyle and environmental factors. Reduced levels of HDL-C are often present in resistance to insulin, obesity and type 2 diabetes mellitus (T2DM) and are associated with hypertension and dyslipidemia, factors that can lead to the early development of CAD. In fact, dyslipidemia in T2DM is observed in 60%-70% of patients and is characterized by high levels of TG and decrease in HDL-C, with this reduction being an independent factor not only for the development of CVD, but also for the manifestation of T2DM (57). Also, insulin resistance is known to be associated with lower circulating HDL-C (58). These changes together with the presence of small and dense LDL particles contribute to accelerating atherogenesis. In this clinical condition, one of the mechanisms that promote the reduction of HDL-C is elevation of TG-rich lipoprotein levels that, through CETP, transfer TG to HDL in exchange for cholesterol esters (59).

Subsequent removal of this excess HDL-TG by hepatic lipase results in smaller and denser HDL particles. HDL size of person with diabetes is altered, with loss of large and very large HDL2 and gain of small HDL3 (60). The same mechanism promotes the formation of small and dense LDL (61). In this group of individuals, sub analyses of studies with fibrates and studies with an eicosapentaenoic acid derivative, icosapent ethyl, were associated with a reduction in cardiovascular risk (62). It is not possible, however, to attribute the benefit of this therapy, even if partially, to the increase in HDL-C. So, although the isolated role of HDL is unclear in atherogenic dyslipidemia, its diagnosis remains a prognostic marker in therapies.

Use of anabolic androgenic steroids

Anabolic androgenic steroids (AAS) are synthetic derivatives of testosterone and are widely used by athletes to improve their physical performance. Observational studies have shown that the use of AAS is associated with adverse effects, including significant decrease in HDL-C levels and increase in LDL-C (63). The mechanisms by which AAS affect HDL-C concentrations are not completely elucidated. Until now, it is known that AAS stimulate hepatic lipase enzyme activity in order to favor the catabolism of HDL and inhibit the biosynthesis of apoA-I (64). In contrast to cross-sectional and prospective observational studies, one study showed hypogonadal patients, characterized by very low testosterone, with a lipoprotein profile within the normal range, suggesting a relationship with the absence of clearly defined obesity. However,

there was a marked reduction in HDL cholesterol efflux capacity and an increase in serum cholesterol carrying capacity (65). Also, there was a decrease in HDL-C concentrations during transgender hormone therapy. HDL cholesterol efflux capacity decreased during hormone therapy with specific reduction in ABCA1, contributing to an increased risk of CVD (66). Cholesterol efflux capacity is a metric of HDL functionality that quantifies the ability of an individual's HDL to extract cholesterol from macrophages. It has been shown to be a better predictor of atherosclerotic burden than HDL-C levels alone (67).

Infectious diseases

During infection, significant changes occur in lipid metabolism and lipoprotein composition. Lipoprotein concentrations rapidly change and can be reduced to 50% of recovery concentrations. Also, the levels of circulating HDL-C and LDL-C decrease, while the levels of TG and VLDL-C increase (68), so it is thought that HDL-C may be a negative marker for systemic or local inflammations. More importantly, endotoxemia modulates HDL composition and size: phospholipids and apoA-I are reduced, while serum amyloid A (SAA) and secretory phospholipase A2 (sPLA2) increase dramatically. Although the number of total HDL does not change, a significant reduction is observed in the number of small and medium-sized particles (69).

HDL can bind to and neutralize bacterial lipopolysaccharide gram-negative and gram-positive bacterial lipoteichoic acid, favoring the debugging of these products (70). Interestingly, HDLs also play a role in fighting infection parasites, and a specific component of HDL, the apolipoprotein L-1 (apoL-1), confers innate immunity against *Trypanosoma cruzi* by favoring the lysosomal swelling that kills the parasite (68). At the same time that HDL-C undergoes a reduction in infectious diseases, low concentrations of HDL-C are also associated with an increased risk of acquiring infections, and prospective cohort studies observed a U-shaped relationship between HDL levels and risk of infectious disease (71). In addition, a Mendelian randomization study demonstrated that, genetically, certain HDL-C levels have a significant influence on risk of hospitalization for infectious diseases (72).

Therapeutic approaches

Mortality from CVD remains the leading cause of death in industrialized countries, and although the use of lipid-lowering therapies focused on LDL-C reduction has made a remarkable contribution to its control, there is still a substantial residual risk of CVD mortality. The observation of this residual risk has driven the search for new therapeutic targets, including conventional and new pharmacological therapies that are still under development. The great challenge lies in improving the functionality of the HDL system to favor the antiatherothrombotic effect. In the following paragraphs, we will briefly comment on some tested or researched therapies for this purpose. A table summarizing the main clinical trials and their outcomes is found at the end of this review (Table 1).

Statins

Statin therapy has been shown to increase the level of plasma HDL-C and the mechanism most likely involves reduced transfer of cholesteryl ester from HDL to VLDL but other factors such as hepatic lipase and other statin-induced effects may also contribute (73). Due to the inhibition in HMG-CoA reductase and suppression of Rho activity, statins can stimulate the synthesis of apoA-I in a dose-dependent manner and increase ABCA1 expression (74,75). In parallel, statins inhibit CETP synthesis and bioavailability of lipoproteins rich in TG, which may contribute to the increase of HDL-C (76).

Data from randomized clinical trials observed a two-fold increase in HDL-C levels compared to apoA-I levels (77). Furthermore, the percentage increases in HDL-C levels were greater in those individuals who had lower baseline plasma HDL-C levels (78).

These data show that statins alter HDL to a more cholesterol-rich form, characteristic of healthy populations of low cardiovascular risk (78). According to the STELLAR clinical study, among a group of five statins, the ability to increase HDL-C was greatest with rosuvastatin (9.2%), followed by simvastatin (6.8%), atorvastatin (5.7%) and, finally, pravastatin (5.6%) (77). Data from large studies of morbidity and mortality suggested that the effects induced by statins in HDL-C and apoA-I were sustained over time, offering an interesting advantage in relation to HDL infusion therapies, for example, whose effect is short-term (79). The clinical impact of increased HDL-C by statin treatment is independent of its effects on LDL-C levels, TG-rich lipoproteins, or other side effects.

Table 1. Major clinical trials conducted involving therapies to increase plasma HD levels

Drug class	Study	Treatment	Comparator	Changes in HDL-C	Outcomes
iCETP	ILLUMINATE	Torcetrapibe plus Atorvastatin	Atorvastatin	Increase HDL-C by 72%	Increase in CV events and death
	REVEAL	Anacetrapib	Placebo Anacetrapib	Increase HDL-C by 104%	Lower incidence of majorcoronary events
	Dal-OUTCOMES	Dalcetrapibe	Placebo	Increase HDL-C by 30%	Treatment had no significant effect on major CV outcomes
	ACCELERATE	Evacetrapibe	Placebo	Increase HDL-C by 133%	Treatment did not result in a lower risk of death from CVcauses
Fibrates	FIELD	Fenofibrate	Placebo	Increase the levels of HDL-Cof 5%	The results showed a non- significant 11% relative reductionin the primary outcome of first MI or CHD death
	ACCORD	Fenofibrate	Placebo	Increase the levels of HDL-Cof 7.9%	The results showed that the combination of fenofibrate and simvastatin did not reduce the rate of fatal CV events
	PROMINENT	Pemafibrate	Placebo	-	Study data will be presented assoon as possible at a future conference
Niacin	AIM-HIGH	Extended-Release Niacin plus Statin	Placebo plus Statin	HDL-C level increased by25%	There was no incremental clinical benefit from the addition of niacinto statin therapy
	HPS2 - THRIVE	Niacin - Laropiprant	Placebo	HDL-C level increased by35%	Treatment increased the risk ofserious adverse events
Recombinant HDL	ERASE	CSL-111	Placebo	Not evaluated	Short-term infusions of reconstituted HDL resulted in nosignificant reductions in percentage change in atheroma volume
	AEGISII Phase 3 Study	CSL-112	Placebo	-	CSL-112 has been well toleratedand we will have more information soon
	MODE	CER-001	-	No significant changes wereobserved in HDL-C in patients with genetically confirmed homozygous or compound heterozygous FH	Reduction in the volume and areaof plaque on the vascular wall carotid
	CHI-SQUARE	CER-001	Placebo	-	CER-001 infusions did not reduce coronary atherosclerosison IVUS and QCA when compared with placebo
	MILANO-PILOT	MDCO-216	Placebo	MDCO-216–treated patients demonstrated reductions in HDL-C of 8%	Failed to show plate volume regression
Recombinant LCAT	Clinical Trials NCT01554800	ACP-501	-	Increase the levels of HDL-Cby 44%	ACP-501 had an acceptablesafety profile
	Clinical Trials NCT02601560	EDI6012	Placebo	Dose-dependent increases inHDL-C	MEDI6012 demonstrated an acceptable safety profile
ApoA-I transcriptional supraregulators	ASSURE	RVX-208	Placebo	HDL-C increased by 11.1%	There were no incremental reductions in other atherogeniclipid parameters or high-sensitivity CRP with RVX-208

CV: cardiovascular; MI: myocardial infarction; CHD: coronary heart disease; IVUS: intravascular ultrasonography; QCA: quantitative coronary angiography; CRP: C-reactive protein.

CETP inhibitors

CETP inhibitors were developed with the aim of blocking or interfering with CETP activity. They can be characterized into CETP inhibitors (torcetrapib, anacetrapib and evacetrapib) and CETP modulators (dalcetrapib) according to their chemical structure (80). The main function of CETP is the transfer of cholesteryl esters and TG between plasma lipoprotein particles. CETP inhibitors target a part of this mechanism by blocking the transfer of cholesteryl esters (81).

CETP inhibitors increase HDL-C levels significantly (40% to 160%) due to the decrease in the transfer of cholesterol from HDL particles to rich lipoproteins in TG (82). However, three clinical trials failed to demonstrate any cardiovascular benefits with treatment with these inhibitors (83-85). The REVEAL study (86) showed that cardiovascular events occurred less frequently in patients with atherosclerotic vascular disease treated with anacetrapib after 4.1 years of follow-up. In this last trial there was an 18% reduction in non-HDL cholesterol and a 104% increase in HDL-C with anacetrapib. A new CETP inhibitor, obicetrapib, reduced LDL-C and apoB levels by 45.3% and 33.7%, respectively. While HDL-C levels increased by 179.1% and ApoA-I by up to 63.4% (87).

A Mendelian 2×2 factorial randomization study including 425,354 UK Biobank participants showed an additive association of a genetically reduced combined concentration of CETP and PCSK9 for lipid levels and risk of CAD. Suggesting that the joint inhibition of CETP and PCSK9 has additive effects on lipid concentrations (88). However, the double-blind dal-GenE study in patients with acute coronary syndrome of 1-3 months and the AA genotype in the rs1967309 variant in the ADCY9 gene showed that dalcetrapib did not significantly reduce the risk of ischemic cardiovascular events at the end of the study (89). A prospective, multicenter, cohort study verified the association between very high HDL-C levels and mortality in patients with CAD and the association of HDL-C genotypes with high HDL-C outcomes. The authors found a U-shaped association with higher risk in those with low and high levels of HDL-C compared with those with medium values (90). Paradoxically, the study suggests that very high levels of HDL-C are associated with a higher risk of mortality in individuals with CAD.

Fibrates

Fibrates are agonist drugs at peroxisome proliferator-activated receptor-α (PPAR-α) nuclear receptors, responsible for regulating the transcription of the LPL, ApoC-III and ApoA-I genes, leading to the clearance of TG-rich lipoproteins (91). Fibrates promote stimulation of HDL production by inducing hepatic synthesis of ApoA-I and ApoA-II and reducing VLDL production due to the reduction of free fatty acids in the liver, in addition to inhibiting the exchange of cholesterol and TG between HDL and VLDL (92). By inducing elevation of HDL-C levels, reduction of TG-rich lipoproteins, and a shift in the phenotype from dense LDL to receptor-active, floating LDL, fibrates act to attenuate the atherosclerotic burden in atherogenic dyslipidemia (91).

A reduction in cardiovascular events was observed in patients with low HDL-C after treatment with gemfibrozil without the addition of statins (93,94). Although bezafibrate has been more effective than gemfibrozil in raising HDL-C levels, its use in secondary prevention has not proven to be beneficial in reducing cardiovascular events in patients with low HDL-C (95). In patients with T2DM, fenofibrate therapy also did not show cardiovascular benefits even in those with concomitant use of statins (96,97). A new category of PPAR-α selective modulators that has been studied, pemafibrate, significantly reduces TG, apoC-III, and cholesterol remnants, in addition to increasing HDL-C. The PROMINENT study aims to evaluate the effect of pemafibrate on cardiovascular events in approximately 10,000 persons with diabetes with moderately elevated TG and low HDL-C (98). However, the Kowa Research Institute announces the decision not to continue the Phase 3 PROMINENT study. Based on a review of a planned interim analysis, they concluded that the primary endpoint would likely not be met. Full study data will be presented as soon as possible at a future conference.

Niacin

Through its GPR109A receptor (G-protein-coupled receptor) present in adipocytes, niacin acts by inhibiting the mobilization of free fatty acids, thus decreasing the supply of substrate for hepatic synthesis. It is possible that niacin increases HDL-C by its ability to inhibit hepatic lipase, decrease the catabolic rate of HDL-C, and decrease catabolic HDL-C receptors. These various effects result in higher levels and larger HDL-C molecules and more efficient reverse cholesterol transport (99). In hepatocytes, niacin inhibits the activity of diacylglycerol O-acyltransferase 2 (DGAT-2), decreasing the hepatic synthesis of TG and VLDL (100), in addition to promoting selective inhibition of ApoA-I uptake. Among the therapies that increase the serum concentration of HDL-C, niacin has the greatest effect, with an increase of 15 to 40% (101), preferentially raising the HDL2 subfraction. A meta-

analysis showed that niacin was able to increase HDL-C levels by 23%, in addition to reducing TG levels by 40% and LDL-C levels by 20% (102). Despite being very effective in increasing HDL-C there is no evidence that the addition of niacin to therapy with statins results in cardiovascular benefit. Randomized clinical trials tested this hypothesis and failed to demonstrate any benefit from adding niacin to therapy with statins (103,104).

Therapies based on recombinant HDL

HDL infusion therapies induce a rapid, dose-proportional, time-dependent elevation in apoA-I and pre-βHDL particles. These effects were seen for recombinant HDL (CSL-111 and CSL-112), where plasma concentrations of apoA-I increased 2-fold and pre-βHDL increased >30-fold (79,105). Despite this, the ERASE trial (106) showed that CSL-111 infusions did not result in significant reductions in atheroma volume or nominal change in plaque volume but did significantly impact the plaque characterization index on intravascular ultrasound. The AEGISII Phase 3 Study (expected completion 2022) (NCT03473223) assesses the efficacy and safety of CSL-112 in reducing larger cardiovascular events and will provide more information about the effect of this treatment in the progression of CVD.

The CER-001, an engineered negatively charged lipoprotein particle that contains recombinant human apoA-I (107), induced dose-dependent increases in plasma HDL-C of up to 7-fold (108). In the MODE study (109), CER-001 was administered in serial infusions in 23 patients with homozygous familial hypercholesterolemia suggesting reduced mean carotid wall thickness. In the CHI-SQUARE study (110), however, its administration did not reduce the coronary atherosclerotic burden. Interestingly, CER-001 appears to have a therapeutic target in LCAT deficiency, as shown in LCAT-/- mice treated with CER-001, there was improvement in dyslipidemia and renal function (111). They also verified the ability of CER-001 to remove cholesterol, reducing the deposition burden on the kidney in a patient with FLD. The beneficial effect is mediated by a dual action of CER-001, which directly effuses cholesterol from podocytes, but also induces the normalization of plasma lipoproteins (112). This beneficial effect occurs earlier than predictable and may offer a new form of treatment for this serious condition (113).

In a phase 2 clinical study, administration of ETC-216, recombinant HDL with apoA-I Milano, produced significant regression in atherosclerotic plaque volume in subjects with acute coronary syndrome, measured by intravascular ultrasound (114) suggesting that infusion in the first weeks after an acute event would stimulate the reverse cholesterol transport. However, serious side effects prevented further evaluation of this formulation and development of this formulation stopped. MDCO-216, tested in a multicenter trial, showed that after five weekly infusions, the percentage volume of the atheroma in the diseased segment did not differ significantly between patients with coronary heart disease documented by angiogram and the control group, ending its development (115).

Recombinant LCAT (rhLCAT)

Most data from preclinical studies suggest that increasing the amount of LCAT stimulates reverse cholesterol transport and reduces atherosclerosis. These data are based on studies that observed a reduction in the progression of atherosclerosis in mice with increased expression of LCAT (116), in addition to the increase in atherosclerotic lesions in mice with enzyme deficiency (117). In this context, a phase I clinical trial demonstrated that a single infusion injection of rhLCAT (ACP-501) had an acceptable safety profile and favorably altered HDL metabolism, showing a dose-proportional increase in HDL-C, thus supporting the investigation of this therapy in individuals with atherosclerotic disease and LCAT deficiency (118). Next, in the FLD patient study, intravenous drip administration of ACP-501 improved the abnormal distribution of HDL subfractions (119). MEDI6012 is a more active rhLCAT that resulted in increased HDL function in a dose-related manner and also promoted endothelial protection (120). Furthermore, LCAT overexpression improved LDL receptor-mediated reverse cholesterol transport, leading to regression of atherosclerosis, suggesting synergistic effects of MEDI6012 with statins (121).

ApoA-I mimetic peptides

ApoA-I is the main apolipoprotein present in HDL particles. Although it is composed of 243 amino acids arranged in 10 amphipathic helices, there has been interest in using short apoA-I peptides containing at least one amphipathic helix to mimic the functions

of native apoA-I. The first apoA-I mimetic peptide was synthesized comprising 18 amino acids (18A). Subsequently, several modifications to 18A were made to create peptides that more closely mimic apoA-I in its antiatherogenic functions (122). Then the addition of an acetyl group and an amide group promoted stability and the lipid binding properties were improved, the peptide was named 2F. Although the 2F peptide mimicked many of the lipid-binding properties of apoA-I, it failed to alter the lesions in a mouse model of atherosclerosis (123). Subsequent, the administration of peptide 5F by injection significantly inhibited lesion formation in mice fed an atherogenic diet without significantly altering lipoprotein profiles (124). Another apoA-I mimetic peptide synthesized from D-amino acids (D-4F) to LDL receptor null mice on a Western diet made HDL anti-inflammatory and reduced lesions by 79% without altering HDL-C levels (125). Recently, P12 showed efficient binding with cytomembrane phospholipids, cholesterol and HDL, and showed the ability to reverse cholesterol transport and treat atherosclerosis (126). With its phospholipid affinity, P12 facilitated cholesterol transport through the ABCA1. Also, promoted the function of HDL by remodeling α-HDL into preβ-HDL which can more efficiently transport cholesterol in the atherosclerotic plaques to the liver and remove excess cholesterol from the arteries (126). The use of peptides that mimic HDL-associated apolipoproteins may prove to be a successful strategy in the treatment of vascular diseases.

ApoA-I transcriptional supraregulators

RVX-208 is a therapeutic agent that selectively induces hepatic de novo synthesis of apoA-I and thereby increases HDL levels accompanied by a change in the pattern of HDL distribution. In monkeys, it primarily increased the levels of pre-β1 and α-1 HDL particles, representing the lipid-poor cholesterol efflux receptors and the larger lipid-rich HDL particles, respectively (127). Treatment with RVX-208 may cause, through de novo synthesis of apoA-I and/or decrease in LCAT activity, favorable changes in HDL distribution. In humans, a 42% and 11% increase in pre-β1 HDL levels and ABCA1-mediated cholesterol efflux, respectively, occurred after only 7 days of RVX-208 therapy (127). However, the ASSURE study showed modest increases in apoA-I and HDL-C with RVX-208, these changes did not differ from the placebo group. These data demonstrate that treatment with RVX-208 did not result in any measurable incremental benefit in plaque regression for patients with CAD and low HDL-C levels (128).

microRNA antagonists

Studies have identified miR-33a/b as essential regulators of lipid metabolism, regulating HDL-C levels and the multi-step reverse cholesterol transport process, therefore, the therapeutic potential of miR-33 to treat CVD is promising. The antagonism of miR-33 significantly increased plasma levels of HDL-C directed macrophage polarization to an M2-like phenotype and improved atherosclerosis regression (129). However, two independent groups showed a beneficial effect of miR-33 inhibition in attenuating atherosclerosis progression (130,131), while another group did not observe any improvement in atherogenesis under similar conditions (132). Interestingly, all three studies demonstrated that miR-33 antagonism in hypercholesterolemic mice does not increase plasma levels of HDL-C. These findings suggest that miR-33 inhibition may promote atheroprotection through mechanisms independent of the increase in circulating HDL-C.

Antisense oligonucleotides for CETP and ApoC-III

One study compared an antisense oligonucleotides (ASO) inhibitor of CETP with the inhibitor of anacetrapib in hyperlipidemic mice and both therapies resulted in a decrease in total plasma cholesterol, decrease in CETP activity and increase in levels of HDL-C (133). ASO against ApoC-III decreases its production and, consequently, lipolysis enhancement of TG-rich lipoproteins results in an increase in HDL-C levels and a decrease in the levels of TG (134). These findings suggest that ASOs from CETP and ApoC-III may represent a promising therapeutic alternative.

Endothelial lipase inhibitors

Endothelial lipase (EL) knockout studies (135,136) and anti-EL antibodies (137) in mice demonstrated that inhibiting EL function resulted in increased plasma HDL-C levels. Furthermore, the overexpression of the human EL gene in mouse liver significantly reduced levels of circulating HDL-C and apoA-I (138). Loss-of-function mutations in EL expression have been observed to lead to increased levels of HDL-C and

support the idea that inhibition of endothelial lipase may be an effective mechanism to increase HDL-C (139). In contrast, some studies point to an atherogenic role of EL, with a positive association between plasma levels of this enzyme and coronary artery calcification and inflammation (140,141).

Liver X receptors (LXR) agonists

By coordinating the expression of target genes in various tissues, LXR agonists increase the flow of cholesterol from the periphery to the liver, where it is metabolized and excreted (142). Short-term administration of synthetic LXR agonist T0901317 in mice promoted reverse cholesterol transport in vivo from macrophages, at least in part, inducing an enrichment of HDL subclasses that enhance the plasma's ability to promote cholesterol efflux by passive diffusion. and mechanisms mediated by SR-BI (143). In healthy subjects and hypercholesterolemic patients, reverse cholesterol transport pathways were similarly induced as in animal models by BMS-852927. However, an increase in plasma and liver TG, plasma LDL-C, apoB, apoE and CETP were also evident (144). In addition, there are potent synthetic LXR agonists, including GW3965, LXR-623, GW6340, AZ876 and ATI-111. LXRs play a central role in the regulation of ABCA1 expression in macrophages (145), and also induce expression of ABCG1 (146), thus increasing the formation of HDL mediated by these transporters.

In conclusion, despite evidence from observational studies, there are no indications to use HDL-C as a risk marker or even to consider increased plasma HDL-C as a therapeutic means to prevent CAD. In patients with very low HDL-C, diagnosis and intervention is important to exclude secondary causes and identify single-gene causes in anticipation of potential risks. Therapeutic approaches targeting HDL such as niacin, fibrates, and CETP inhibitors increased plasma levels of HDL-C but failed to reduce cardiovascular events. Therefore, we can say that it is insufficient to measure plasma levels of HDL-C as a way of estimating its atheroprotective function. Still, ways to increase cardiovascular protection with therapies aimed at HDL metabolism are not well established. Thus, further studies are needed to understand the mechanisms of molecular action and cellular interaction of HDL, enhancing the function of the HDL system.

Disclosure: no potential conflict of interest relevant to this article was reported.

REFERENCES

1. Castelli WP, Doyle JT, Gordon T, Hames CG, Hjortland MC, Hulley SB, et al. HDL cholesterol and other lipids in coronary heart disease. The cooperative lipoprotein phenotyping study. Circulation. 1977;55(5):767-72.
2. Mora S, Glynn RJ, Ridker PM. High-density lipoprotein cholesterol, size, particle number, and residual vascular risk after potent statin therapy. Circulation. 2013;128(11):1189-97.
3. Assmann G, Schulte H, von Eckardstein A, Huang Y. High-density lipoprotein cholesterol as a predictor of coronary heart disease risk. The PROCAM experience and pathophysiological implications for reverse cholesterol transport. Atherosclerosis. 1996;124 Suppl:S11-20.
4. Ko DT, Alter DA, Guo H, Koh M, Lau G, Austin PC, et al. High-Density Lipoprotein Cholesterol and Cause-Specific Mortality in Individuals Without Previous Cardiovascular Conditions: The CANHEART Study. J Am Coll Cardiol. 2016;68(19):2073-83.
5. Vergeer M, Holleboom AG, Kastelein JJ, Kuivenhoven JA. The HDL hypothesis: does high-density lipoprotein protect from atherosclerosis? J Lipid Res. 2010;51(8):2058-73.
6. Frikke-Schmidt R, Nordestgaard BG, Stene MC, Sethi AA, Remaley AT, Schnohr P, et al. Association of loss-of-function mutations in the ABCA1 gene with high-density lipoprotein cholesterol levels and risk of ischemic heart disease. JAMA. 2008;299(21):2524-32.
7. Haase CL, Tybjærg-Hansen A, Qayyum AA, Schou J, Nordestgaard BG, Frikke-Schmidt R. LCAT, HDL cholesterol and ischemic cardiovascular disease: a Mendelian randomization study of HDL cholesterol in 54,500 individuals. J Clin Endocrinol Metab. 2012;97(2):E248-56.
8. Sposito AC. HDL metrics, let's call the number thing off? Atherosclerosis. 2016;251:525-7.
9. Posadas-Sánchez R, Posadas-Romero C, Ocampo-Arcos WA, Villarreal-Molina MT, Vargas-Alarcón G, Antúnez-Argüelles E, et al. Premature and severe cardiovascular disease in a Mexican male with markedly low high-density-lipoprotein-cholesterol levels and a mutation in the lecithin: cholesterol acyltransferase gene: a family study. Int J Mol Med. 2014;33(6):1570-6.
10. Brunham LR, Hayden MR. Human genetics of HDL: Insight into particle metabolism and function. Prog Lipid Res. 2015;58:14-25.
11. Voight BF, Peloso GM, Orho-Melander M, Frikke-Schmidt R, Barbalic M, Jensen MK, et al. Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study. Lancet. 2012;380(9841):572-80.
12. Nesto RW. Beyond low-density lipoprotein: addressing the atherogenic lipid triad in type 2 diabetes mellitus and the metabolic syndrome. Am J Cardiovasc Drugs. 2005;5(6):379-87.
13. Rothblat GH, Phillips MC. High-density lipoprotein heterogeneity and function in reverse cholesterol transport. Curr Opin Lipidol. 2010;21(3):229-38.
14. Eckardstein VA, Kardassis D. High Density Lipoproteins From biological understanding to clinical exploitation. Springer Open; 2015.
15. Kontush A, Chapman MJ. Antiatherogenic function of HDL particle subpopulations: focus on antioxidative activities. Curr Opin Lipidol. 2010;21(4):312-8.
16. Prosser HC, Ng MKC, Bursill CA. The role of cholesterol efflux in mechanisms of endothelial protection by HDL. Curr Opin Lipidol. 2012;23(3):182-9.
17. Vickers KC, Palmisano BT, Shoucri BM, Shamburek RD, Remaley AT. MicroRNAs are transported in plasma and delivered to recipient cells by high-density lipoproteins. Nat Cell Biol. 2011;13(4):423-33.
18. Beheshti SO, Madsen CM, Varbo A, Nordestgaard BG. Worldwide Prevalence of Familial Hypercholesterolemia: Meta-Analyses of 11 Million Subjects. J Am Coll Cardiol. 2020;75(20):2553-66.

19. Dron JS, Wang J, Low-Kam C, Khetarpal SA, Robinson JF, McIntyre AD, et al. Polygenic determinants in extremes of high-density lipoprotein cholesterol. J Lipid Res. 2017;58(11):2162-70.
20. von Eckardstein A. Differential diagnosis of familial high density lipoprotein deficiency syndromes. Atherosclerosis. 2006;186(2):231-9.
21. El Khoury P, Couvert P, Elbitar S, Ghaleb Y, Abou-Khalil Y, Azar Y, et al. Identification of the first Tangier disease patient in Lebanon carrying a new pathogenic variant in ABCA1. J Clin Lipidol. 2018;12(6):1374-82.
22. Maranghi M, Truglio G, Gallo A, Grieco E, Verrienti A, Montali A, et al. A novel splicing mutation in the ABCA1 gene, causing Tangier disease and familial HDL deficiency in a large family. Biochem Biophys Res Commun. 2019;508(2):487-93.
23. Quintão ECR, Nakandakare ER, Passarelli M. Lípides: do metabolismo à aterosclerose. 1ª ed. São Paulo: Sarvier; 2011.
24. Ceccanti M, Cambieri C, Frasca V, Onesti E, Biasiotta A, Giordano C, et al. A Novel Mutation in ABCA1 Gene Causing Tangier Disease in an Italian Family with Uncommon Neurological Presentation. Front Neurol. 2016;7:185.
25. Schaefer EJ, Anthanont P, Diffenderfer MR, Polisecki E, Asztalos BF. Diagnosis and treatment of high density lipoprotein deficiency. Prog Cardiovasc Dis. 2016;59(2):97-106.
26. von Eckardstein A, Huang Y, Kastelein JJ, Geisel J, Real JT, Kuivenhoven JA, et al. Lipid-free apolipoprotein (apo) A-I is converted into alpha-migrating high density lipoproteins by lipoprotein-depleted plasma of normolipidemic donors and apo A-I-deficient patients but not of Tangier disease patients. Atherosclerosis. 1998;138(1):25-34.
27. Alshaikhli A, Vaqar S. Tangier Disease. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022 January.
28. Ossoli A, Lucca F, Boscutti G, Remaley AT, Calabresei L. Familial LCAT deficiency: from pathology to enzyme replacement therapy. Clin Lipidol. 2015;10:405-13.
29. Saeedi R, Li M, Frohlich J. A review on lecithin: cholesterol acyltransferase deficiency. Clin Biochem. 2015;48(7-8):472-5.
30. Ayyobi AF, McGladdery SH, Chan S, John Mancini GB, Hill JS, Frohlich JJ. Lecithin: cholesterol acyltransferase (LCAT) deficiency and risk of vascular disease: 25 year follow-up. Atherosclerosis. 2004;177(2):361-6.
31. Calabresi L, Baldassarre D, Castelnuovo S, Conca P, Bocchi L, Candini C, et al. Functional lecithin: cholesterol acyltransferase is not required for efficient atheroprotection in humans. Circulation. 2009;120(7):628-35
32. Kunnen S, Van Eck M. Lecithin: cholesterol acyltransferase: old friend or foe in atherosclerosis? J Lipid Res. 2012;53(9):1783-99.
33. Tanigawa H, Billheimer JT, Tohyama J, Fuki IV, Ng DS, Rothblat GH, et al. Lecithin: cholesterol acyltransferase expression has minimal effects on macrophage reverse cholesterol transport in vivo. Circulation. 2009;120(2):160-9.
34. Calabresi L, Favari E, Moleri E, Adorni MP, Pedrelli M, Costa S, et al. Functional LCAT is not required for macrophage cholesterol efflux to human serum. Atherosclerosis. 2009;204(1):141-6.
35. Kuivenhoven JA, Pritchard H, Hill J, Frohlich J, Assmann G, Kastelein J. The molecular pathology of lecithin: cholesterol acyltransferase (LCAT) deficiency syndromes. J Lipid Res. 1997;38(2):191-205.
36. Vitali C, Bajaj A, Nguyen C, Schnall J, Chen J, Stylianou K, et al. A systematic review of the natural history and biomarkers of primary Lecithin: Cholesterol Acyltransferase (LCAT) deficiency. J Lipid Res. 2022;63(3):100169.
37. Strøm EH, Sund S, Reier-Nilsen M, Dørje C, Leren TP. Lecithin: Cholesterol Acyltransferase (LCAT) Deficiency: renal lesions with early graft recurrence. Ultrastruct Pathol. 2011;35(3):139-45.
38. Suda T, Akamatsu A, Nakaya Y, Masuda Y, Desaki J. Alterations in erythrocyte membrane lipid and its fragility in a patient with familial lecithin: cholesterol acyltrasferase (LCAT) deficiency. J Med Invest. 2002;49(3-4):147-55.
39. Oldoni F, Baldassarre D, Castelnuovo S, Ossoli A, Amato M, van Capelleveen J, et al. Complete and Partial Lecithin:Cholesterol Acyltransferase Deficiency Is Differentially Associated With Atherosclerosis. Circulation. 2018;138(10):1000-7.
40. Fellin R, Manzato E. Lipoprotein-X fifty years after its original discovery. Nutr Metab Cardiovasc Dis. 2019;29(1):4-8.
41. Narayanan S. Lipoprotein-X. CRC Crit Rev Clin Lab Sci. 1979;11(1):31-51.
42. Hegele RA, Borén J, Ginsberg HN, Arca M, Averna M, Binder CJ, et al. Rare dyslipidaemias, from phenotype to genotype to management: a European Atherosclerosis Society task force consensus statement. Lancet Diabetes Endocrinol. 2020;8(1):50-67.
43. Schaefer EJ, Genest JJ, Ordovas JM, Salem DN, Wilson PW. Familial lipoprotein disorders and premature coronary artery disease. Atherosclerosis. 1994;108 Suppl:S41-54.
44. Pisciotta L, Miccoli R, Cantafora A, Calabresi L, Tarugi P, Alessandrini P, et al. Recurrent mutations of the apolipoprotein A-I gene in three kindreds with severe HDL deficiency. Atherosclerosis. 2003;167(2):335-45.
45. Ikewaki K, Matsunaga A, Han H, Watanabe H, Endo A, Tohyama J, et al. A novel two nucleotide deletion in the apolipoprotein A-I gene, apoA-I Shinbashi, associated with high density lipoprotein deficiency, corneal opacities, planar xanthomas, and premature coronary artery disease. Atherosclerosis. 2004;172(1):39-45.
46. Schaefer EJ, Santos RD, Asztalos BF. Marked HDL deficiency and premature coronary heart disease. Curr Opin Lipidol. 2010;21(4):289-97.
47. Andreola A, Bellotti V, Giorgetti S, Mangione P, Obici L, Stoppini M, et al. Conformational switching and fibrillogenesis in the amyloidogenic fragment of apolipoprotein a-I. J Biol Chem. 2003;278(4):2444-51.
48. Joy T, Wang J, Hahn A, Hegele RA. APOA1 related amyloidosis: a case report and literature review. Clin Biochem. 2003;36(8):641-5.
49. Obici L, Palladini G, Giorgetti S, Bellotti V, Gregorini G, Arbustini E, et al. Liver biopsy discloses a new apolipoprotein A-I hereditary amyloidosis in several unrelated Italian families. Gastroenterology. 2004;126(5):1416-22.
50. Miller M, Aiello D, Pritchard H, Friel G, Zeller K. Apolipoprotein A-I(Zavalla) (Leu159-->Pro): HDL cholesterol deficiency in a kindred associated with premature coronary artery disease. Arterioscler Thromb Vasc Biol. 1998;18(8):1242-7.
51. Hovingh GK, Brownlie A, Bisoendial RJ, Dube MP, Levels JH, Petersen W, et al. A novel apoA-I mutation (L178P) leads to endothelial dysfunction, increased arterial wall thickness, and premature coronary artery disease. J Am Coll Cardiol. 2004;44(7):1429-35.
52. Chiesa G, Sirtori CR. Apolipoprotein A-I(Milano): current perspectives. Curr Opin Lipidol. 2003;14(2):159-63.
53. von Eckardstein A, Funke H, Walter M, Altland K, Benninghoven A, Assmann G. Structural analysis of human apolipoprotein A-I variants. Amino acid substitutions are nonrandomly distributed throughout the apolipoprotein A-I primary structure. J Biol Chem. 1990;265(15):8610-7.
54. Rohatgi A, Khera A, Berry JD, Givens EG, Ayers CR, Wedin KE, et al. HDL cholesterol efflux capacity and incident cardiovascular events. N Engl J Med. 2014;371(25):2383-93.
55. Richardson TG, Sanderson E, Palmer TM, Ala-Korpela M, Ference BA, Davey Smith G, et al. Evaluating the relationship between circulating lipoprotein lipids and apolipoproteins with risk of

coronary heart disease: A multivariable Mendelian randomisation analysis. PLoS Med. 2020;17(3):e1003062.

56. Karjalainen MK, Holmes MV, Wang Q, Anufrieva O, Kähönen M, Lehtimäki T, et al. Apolipoprotein A-I concentrations and risk of coronary artery disease: A Mendelian randomization study. Atherosclerosis. 2020;299:56-63.
57. Abbasi A, Corpeleijn E, Gansevoort RT, Gans RO, Hillege HL, Stolk RP, et al. Role of HDL cholesterol and estimates of HDL particle composition in future development of type 2 diabetes in the general population: the PREVEND study. J Clin Endocrinol Metab. 2013;98(8):E1352-9.
58. DeFronzo RA, Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care. 1991;14(3):173-94.
59. 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(6):421-9.
60. Bonilha I, Zimetti F, Zanotti I, Papotti B, Sposito AC. Dysfunctional High-Density Lipoproteins in Type 2 Diabetes Mellitus: Molecular Mechanisms and Therapeutic Implications. J Clin Med. 2021;10(11).
61. Bonilha I, Hajduch E, Luchiari B, Nadruz W, Le Goff W, Sposito AC. The Reciprocal Relationship between LDL Metabolism and Type 2 Diabetes Mellitus. Metabolites. 2021;11(12).
62. Jakob T, Nordmann AJ, Schandelmaier S, Ferreira-González I, Briel M. Fibrates for primary prevention of cardiovascular disease events. Cochrane Database Syst Rev. 2016;11:CD009753.
63. Fontana K, Oliveira HC, Leonardo MB, Mandarim-de-Lacerda CA, da Cruz-Höfling MA. Adverse effect of the anabolic-androgenic steroid mesterolone on cardiac remodelling and lipoprotein profile is attenuated by aerobicz exercise training. Int J Exp Pathol. 2008;89(5):358-66.
64. Langfort J, Jagsz S, Dobrzyn P, Brzezinska Z, Klapcinska B, Galbo H, et al. Testosterone affects hormone-sensitive lipase (HSL) activity and lipid metabolism in the left ventricle. Biochem Biophys Res Commun. 2010;399(4):670-6.
65. Adorni MP, Zimetti F, Cangiano B, Vezzoli V, Bernini F, Caruso D, et al. High-Density Lipoprotein Function Is Reduced in Patients Affected by Genetic or Idiopathic Hypogonadism. J Clin Endocrinol Metab. 2019;104(8):3097-107.
66. van Velzen DM, Adorni MP, Zimetti F, Strazzella A, Simsek S, Sirtori CR, et al. The effect of transgender hormonal treatment on high density lipoprotein cholesterol efflux capacity. Atherosclerosis. 2021;323:44-53
67. Khera AV, Demler OV, Adelman SJ, Collins HL, Glynn RJ, Ridker PM, et al. Cholesterol Efflux Capacity, High-Density Lipoprotein Particle Number, and Incident Cardiovascular Events: An Analysis From the JUPITER Trial (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin). Circulation. 2017;135(25):2494-504.
68. Miao Q, Ndao M. Trypanosoma cruzi infection and host lipid metabolism. Mediators Inflamm. 2014;2014:902038.
69. de la Llera Moya M, McGillicuddy FC, Hinkle CC, Byrne M, Joshi MR, Nguyen V, et al. Inflammation modulates human HDL composition and function in vivo. Atherosclerosis. 2012;222(2):390-4.
70. Parker TS, Levine DM, Chang JC, Laxer J, Coffin CC, Rubin AL. Reconstituted high-density lipoprotein neutralizes gram-negative bacterial lipopolysaccharides in human whole blood. Infect Immun. 1995;63(1):253-8.
71. Madsen CM, Varbo A, Tybjærg-Hansen A, Frikke-Schmidt R, Nordestgaard BG. U-shaped relationship of HDL and risk of infectious disease: two prospective population-based cohort studies. Eur Heart J. 2018;39(14):1181-90.
72. Trinder M, Walley KR, Boyd JH, Brunham LR. Causal Inference for Genetically Determined Levels of High-Density Lipoprotein Cholesterol and Risk of Infectious Disease. Arterioscler Thromb Vasc Biol. 2020;40(1):267-78.
73. McTaggart F, Jones P. Effects of statins on high-density lipoproteins: a potential contribution to cardiovascular benefit. Cardiovasc Drugs Ther. 2008;22(4):321-38.
74. Maejima T, Yamazaki H, Aoki T, Tamaki T, Sato F, Kitahara M, et al. Effect of pitavastatin on apolipoprotein A-I production in HepG2 cell. Biochem Biophys Res Commun. 2004;324(2):835-9.
75. Zanotti I, Favari E, Sposito AC, Rothblat GH, Bernini F. Pitavastatin increases ABCA1-mediated lipid efflux from Fu5AH rat hepatoma cells. Biochem Biophys Res Commun. 2004;321(3):670-4.
76. Sposito AC, Carmo HR, Barreto J, Sun L, Carvalho LSF, Feinstein SB, et al. HDL-Targeted Therapies During Myocardial Infarction. Cardiovasc Drugs Ther. 2019;33(3):371-81.
77. 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(2):152-60.
78. Barter PJ, Brandrup-Wognsen G, Palmer MK, Nicholls SJ. Effect of statins on HDL-C: a complex process unrelated to changes in LDL-C: analysis of the VOYAGER Database. J Lipid Res. 2010;51(6):1546-53.
79. Kingwell BA, Chapman MJ. Future of high-density lipoprotein infusion therapies: potential for clinical management of vascular disease. Circulation. 2013;128(10):1112-21.
80. Ferri N, Corsini A, Sirtori CR, Ruscica M. Present therapeutic role of cholesteryl ester transfer protein inhibitors. Pharmacol Res. 2018;128:29-41.
81. Nurmohamed NS, Ditmarsch M, Kastelein JJP. CETP-inhibitors: from HDL-C to LDL-C lowering agents? Cardiovasc Res. 2021:cvab350.
82. Tall AR, Rader DJ. Trials and Tribulations of CETP Inhibitors. Circ Res. 2018;122(1):106-12.
83. Moreno C, Greil R, Demirkan F, Tedeschi A, Anz B, Larratt L, et al. Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (iLLUMINATE): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2019;20(1):43-56.
84. Schwartz GG, Olsson AG, Abt M, Ballantyne CM, Barter PJ, Brumm J, et al. Effects of dalcetrapib in patients with a recent acute coronary syndrome. N Engl J Med. 2012;367(22):2089-99.
85. Lincoff AM, Nicholls SJ, Riesmeyer JS, Barter PJ, Brewer HB, Fox KAA, et al. Evacetrapib and Cardiovascular Outcomes in High-Risk Vascular Disease. N Engl J Med. 2017;376(20):1933-42.
86. HPS3/TIMI55–REVEAL Collaborative Group, Bowman L, Hopewell JC, Chen F, Wallendszus K, Stevens W, Collins R, et al. Effects of Anacetrapib in Patients with Atherosclerotic Vascular Disease. N Engl J Med. 2017;377(13):1217-27.
87. Hovingh GK, Kastelein JJ, van Deventer SJ, Round P, Ford J, Saleheen D, et al. Cholesterol ester transfer protein inhibition by TA-8995 in patients with mild dyslipidaemia (TULIP): a randomised, double-blind, placebo-controlled phase 2 trial. Lancet. 2015;386(9992):452-60.
88. Cupido AJ, Reeskamp LF, Hingorani AD, Finan C, Asselbergs FW, Hovingh GK, et al. Joint Genetic Inhibition of PCSK9 and CETP and the Association With Coronary Artery Disease: A Factorial Mendelian Randomization Study. JAMA Cardiol. 2022;7(9):955-64.
89. Tardif JC, Pfeffer MA, Kouz S, Koenig W, Maggioni AP, McMurray JJV, et al. Pharmacogenetics-guided dalcetrapib therapy after

an acute coronary syndrome: the dal-GenE trial. Eur Heart J. 2022;43(39):3947-56.

90. Liu C, Dhindsa D, Almuwaqqat Z, Ko YA, Mehta A, Alkhoder AA, et al. Association Between High-Density Lipoprotein Cholesterol Levels and Adverse Cardiovascular Outcomes in High-risk Populations. JAMA Cardiol. 2022;7(7):672-80.
91. Chapman MJ. Fibrates in 2003: therapeutic action in atherogenic dyslipidaemia and future perspectives. Atherosclerosis. 2003;171(1):1-13.
92. Woudberg NJ, Pedretti S, Lecour S, Schulz R, Vuilleumier N, James RW, et al. Pharmacological Intervention to Modulate HDL: What Do We Target? Front Pharmacol. 2017;8:989.
93. Manninen V, Tenkanen L, Koskinen P, Huttunen JK, Mänttäri M, Heinonen OP, et al. Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study. Implications for treatment. Circulation. 1992;85(1):37-45.
94. Robins SJ, Collins D, Wittes JT, Papademetriou V, Deedwania PC, Schaefer EJ, et al. Relation of gemfibrozil treatment and lipid levels with major coronary events: VA-HIT: a randomized controlled trial. JAMA. 2001;285(12):1585-91.
95. Bezafibrate Infarction Prevention (BIP) study. Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease. Circulation. 2000;102(1):21-7.
96. Elam M, Lovato L, Ginsberg H. The ACCORD-Lipid study: implications for treatment of dyslipidemia in Type 2 diabetes mellitus. Clin Lipidol. 2011;6(1):9-20.
97. Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet. 2005;366(9500):1849-61.
98. Pradhan AD, Paynter NP, Everett BM, Glynn RJ, Amarenco P, Elam M, et al. Rationale and design of the Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes (PROMINENT) study. Am Heart J. 2018;206:80-93.
99. Kamanna VS, Kashyap ML. Mechanism of action of niacin. Am J Cardiol. 2008;101(8A):20B-26B.
100. Song WL, FitzGerald GA. Niacin, an old drug with a new twist. J Lipid Res. 2013;54(10):2586-94.
101. McKenney JM, Proctor JD, Harris S, Chinchili VM. A comparison of the efficacy and toxic effects of sustained- vs immediate-release niacin in hypercholesterolemic patients. JAMA. 1994;271(9):672-7.
102. Birjmohun RS, Hutten BA, Kastelein JJ, Stroes ES. Efficacy and safety of high-density lipoprotein cholesterol-increasing compounds: a meta-analysis of randomized controlled trials. J Am Coll Cardiol. 2005;45(2):185-97.
103. AIM-HIGH Investigators, Boden WE, Probstfield JL, Anderson T, Chaitman BR, Desvignes-Nickens P, Koprowicz K, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med. 2011;365(24):2255-67.
104. HPS2-THRIVE Collaborative Group. HPS2-THRIVE randomized placebo-controlled trial in 25 673 high-risk patients of ER niacin/laropiprant: trial design, pre-specified muscle and liver outcomes, and reasons for stopping study treatment. Eur Heart J. 2013;34(17):1279-91.
105. Patel S, Drew BG, Nakhla S, Duffy SJ, Murphy AJ, Barter PJ, et al. Reconstituted high-density lipoprotein increases plasma high-density lipoprotein anti-inflammatory properties and cholesterol efflux capacity in patients with type 2 diabetes. J Am Coll Cardiol. 2009;53(11):962-71.
106. Tardif JC, Grégoire J, L'Allier PL, Ibrahim R, Lespérance J, Heinonen TM, et al. Effects of reconstituted high-density lipoprotein infusions on coronary atherosclerosis: a randomized controlled trial. JAMA. 2007;297(15):1675-82.
107. Kalayci A, Gibson CM, Ridker PM, Wright SD, Kingwell BA, Korjian S, et al. ApoA-I Infusion Therapies Following Acute Coronary Syndrome: Past, Present, and Future. Curr Atheroscler Rep. 2022;24(7):585-97.
108. Kee P, Rye KA, Taylor JL, Barrett PH, Barter PJ. Metabolism of apoA-I as lipid-free protein or as component of discoidal and spherical reconstituted HDLs: studies in wild-type and hepatic lipase transgenic rabbits. Arterioscler Thromb Vasc Biol. 2002;22(11):1912-7.
109. Hovingh GK, Smits LP, Stefanutti C, Soran H, Kwok S, de Graaf J, et al. The effect of an apolipoprotein A-I-containing high-density lipoprotein-mimetic particle (CER-001) on carotid artery wall thickness in patients with homozygous familial hypercholesterolemia: The Modifying Orphan Disease Evaluation (MODE) study. Am Heart J. 2015;169(5):736-42.e1.
110. Tardif JC, Ballantyne CM, Barter P, Dasseux JL, Fayad ZA, Guertin MC, et al. Effects of the high-density lipoprotein mimetic agent CER-001 on coronary atherosclerosis in patients with acute coronary syndromes: a randomized trial. Eur Heart J. 2014;35(46):3277-86.
111. Ossoli A, Strazzella A, Rottoli D, Zanchi C, Locatelli M, Zoja C, et al. CER-001 ameliorates lipid profile and kidney disease in a mouse model of familial LCAT deficiency. Metabolism. 2021;116:154464.
112. Pavanello C, Turri M, Strazzella A, Tulissi P, Pizzolitto S, De Maglio G, et al. The HDL mimetic CER-001 remodels plasma lipoproteins and reduces kidney lipid deposits in inherited lecithin:cholesterol acyltransferase deficiency. J Intern Med. 2022;291(3):364-70.
113. Faguer S, Colombat M, Chauveau D, Bernadet-Monrozies P, Beq A, Delas A, et al. Administration of the High-Density Lipoprotein Mimetic CER-001 for Inherited Lecithin-Cholesterol Acyltransferase Deficiency. Ann Intern Med. 2021;174(7):1022-5.
114. Nissen SE, Tsunoda T, Tuzcu EM, Schoenhagen P, Cooper CJ, Yasin M, et al. Effect of recombinant ApoA-I Milano on coronary atherosclerosis in patients with acute coronary syndromes: a randomized controlled trial. JAMA. 2003;290(17):2292-300.
115. Reijers JAA, Kallend DG, Malone KE, Jukema JW, Wijngaard PLJ, Burggraaf J, et al. MDCO-216 Does Not Induce Adverse Immunostimulation, in Contrast to Its Predecessor ETC-216. Cardiovasc Drugs Ther. 2017;31(4):381-9.
116. Mertens A, Verhamme P, Bielicki JK, Phillips MC, Quarck R, Verreth W, et al. Increased low-density lipoprotein oxidation and impaired high-density lipoprotein antioxidant defense are associated with increased macrophage homing and atherosclerosis in dyslipidemic obese mice: LCAT gene transfer decreases atherosclerosis. Circulation. 2003;107(12):1640-6.
117. Furbee JW, Sawyer JK, Parks JS. Lecithin:cholesterol acyltransferase deficiency increases atherosclerosis in the low density lipoprotein receptor and apolipoprotein E knockout mice. J Biol Chem. 2002;277(5):3511-9.
118. Shamburek RD, Bakker-Arkema R, Shamburek AM, Freeman LA, Amar MJ, Auerbach B, et al. Safety and Tolerability of ACP-501, a Recombinant Human Lecithin:Cholesterol Acyltransferase, in a Phase 1 Single-Dose Escalation Study. Circ Res. 2016;118(1):73-82.
119. Shamburek RD, Bakker-Arkema R, Auerbach BJ, Krause BR, Homan R, Amar MJ, et al. Familial lecithin:cholesterol acyltransferase deficiency: First-in-human treatment with enzyme replacement. J Clin Lipidol. 2016;10(2):356-67.
120. Ossoli A, Simonelli S, Varrenti M, Morici N, Oliva F, Stucchi M, et al. Recombinant LCAT (Lecithin:Cholesterol Acyltransferase) Rescues Defective HDL (High-Density Lipoprotein)-Mediated Endothelial Protection in Acute Coronary Syndrome. Arterioscler Thromb Vasc Biol. 2019;39(5):915-24.

121. George RT, Abuhatzira L, Stoughton SM, Karathanasis SK, She D, Jin C, et al. MEDI6012: Recombinant Human Lecithin Cholesterol Acyltransferase, High-Density Lipoprotein, and Low-Density Lipoprotein Receptor-Mediated Reverse Cholesterol Transport. J Am Heart Assoc. 2021;10(13):e014572.
122. Anantharamaiah GM, Jones JL, Brouillette CG, Schmidt CF, Chung BH, Hughes TA, et al. Studies of synthetic peptide analogs of the amphipathic helix. Structure of complexes with dimyristoyl phosphatidylcholine. J Biol Chem. 1985;260(18):10248-55.
123. Datta G, Chaddha M, Hama S, Navab M, Fogelman AM, Garber DW, et al. Effects of increasing hydrophobicity on the physical-chemical and biological properties of a class A amphipathic helical peptide. J Lipid Res. 2001;42(7):1096-104.
124. Garber DW, Datta G, Chaddha M, algunachari MN, Hama SY, Navab M, et al. A new synthetic class A amphipathic peptide analogue protects mice from diet-induced atherosclerosis. J Lipid Res. 2001;42(4):545-52.
125. Navab M, Anantharamaiah GM, Hama S, Garber DW, Chaddha M, Hough G, et al. Oral administration of an Apo A-I mimetic Peptide synthesized from D-amino acids dramatically reduces atherosclerosis in mice independent of plasma cholesterol. Circulation. 2002;105(3):290-2.
126. Gou S, Wang L, Zhong C, Chen X, Ouyang X, Li B, et al. A novel apoA-I mimetic peptide suppresses atherosclerosis by promoting physiological HDL function in apoE. Br J Pharmacol. 2020;177(20):4627-444.
127. Bailey D, Jahagirdar R, Gordon A, Hafiane A, Campbell S, Chatur S, et al. RVX-208: a small molecule that increases apolipoprotein A-I and high-density lipoprotein cholesterol in vitro and in vivo. J Am Coll Cardiol. 2010;55(23):2580-9.
128. Nicholls SJ, Puri R, Wolski K, Ballantyne CM, Barter PJ, Brewer HB, et al. Effect of the BET Protein Inhibitor, RVX-208, on Progression of Coronary Atherosclerosis: Results of the Phase 2b, Randomized, Double-Blind, Multicenter, ASSURE Trial. Am J Cardiovasc Drugs. 2016;16(1):55-65.
129. Rayner KJ, Sheedy FJ, Esau CC, Hussain FN, Temel RE, Parathath S, et al. Antagonism of miR-33 in mice promotes reverse cholesterol transport and regression of atherosclerosis. J Clin Invest. 2011;121(7):2921-31.
130. Rotllan N, Ramírez CM, Aryal B, Esau CC, Fernández-Hernando C. Therapeutic silencing of microRNA-33 inhibits the progression of atherosclerosis in Ldlr-/- mice--brief report. Arterioscler Thromb Vasc Biol. 2013;33(8):1973-7.
131. Ouimet M, Ediriweera HN, Gundra UM, Sheedy FJ, Ramkhelawon B, Hutchison SB, et al. MicroRNA-33-dependent regulation of macrophage metabolism directs immune cell polarization in atherosclerosis. J Clin Invest. 2015;125(12):4334-48.
132. Marquart TJ, Wu J, Lusis AJ, Baldán Á. Anti-miR-33 therapy does not alter the progression of atherosclerosis in low-density lipoprotein receptor-deficient mice. Arterioscler Thromb Vasc Biol. 2013;33(3):455-8.
133. Bell TA, Graham MJ, Lee RG, Mullick AE, Fu W, Norris D, et al. Antisense oligonucleotide inhibition of cholesteryl ester transfer protein enhances RCT in hyperlipidemic, CETP transgenic, LDLr-/- mice. J Lipid Res. 2013;54(10):2647-57.
134. Schmitz J, Gouni-Berthold I. APOC-III Antisense Oligonucleotides: A New Option for the Treatment of Hypertriglyceridemia. Curr Med Chem. 2018;25(13):1567-76.
135. Ishida T, Choi S, Kundu RK, Hirata K, Rubin EM, Cooper AD, et al. Endothelial lipase is a major determinant of HDL level. J Clin Invest. 2003;111(3):347-55.
136. Ishida T, Choi SY, Kundu RK, Spin J, Yamashita T, Hirata K, et al. Endothelial lipase modulates susceptibility to atherosclerosis in apolipoprotein-E-deficient mice. J Biol Chem. 2004;279(43):45085-92.
137. Jin W, Millar JS, Broedl U, Glick JM, Rader DJ. Inhibition of endothelial lipase causes increased HDL cholesterol levels in vivo. J Clin Invest. 2003;111(3):357-62.
138. Goodman KB, Bury MJ, Cheung M, Cichy-Knight MA, Dowdell SE, Dunn AK, et al. Discovery of potent, selective sulfonylfuran urea endothelial lipase inhibitors. Bioorg Med Chem Lett. 2009;19(1):27-30.
139. Edmondson AC, Brown RJ, Kathiresan S, Cupples LA, Demissie S, Manning AK, et al. Loss-of-function variants in endothelial lipase are a cause of elevated HDL cholesterol in humans. J Clin Invest. 2009;119(4):1042-50.
140. Badellino KO, Wolfe ML, Reilly MP, Rader DJ. Endothelial lipase concentrations are increased in metabolic syndrome and associated with coronary atherosclerosis. PLoS Med. 2006;3(2):e22.
141. Badellino KO, Wolfe ML, Reilly MP, Rader DJ. Endothelial lipase is increased in vivo by inflammation in humans. Circulation. 2008;117(5):678-85.
142. Zelcer N, Tontonoz P. Liver X receptors as integrators of metabolic and inflammatory signaling. J Clin Invest. 2006;116(3):607-14.
143. Zanotti I, Potì F, Pedrelli M, Favari E, Moleri E, Franceschini G, et al. The LXR agonist T0901317 promotes the reverse cholesterol transport from macrophages by increasing plasma efflux potential. J Lipid Res. 2008;49(5):954-60.
144. Kirchgessner TG, Sleph P, Ostrowski J, Lupisella J, Ryan CS, Liu X, et al. Beneficial and Adverse Effects of an LXR Agonist on Human Lipid and Lipoprotein Metabolism and Circulating Neutrophils. Cell Metab. 2016;24(2):223-33.
145. Laffitte BA, Repa JJ, Joseph SB, Wilpitz DC, Kast HR, Mangelsdorf DJ, et al. LXRs control lipid-inducible expression of the apolipoprotein E gene in macrophages and adipocytes. Proc Natl Acad Sci U S A. 2001;98(2):507-12.
146. Baldán A, Bojanic DD, Edwards PA. The ABCs of sterol transport. J Lipid Res. 2009;50 Suppl:S80-5.