



High density lipoprotein as a therapeutic target: Focus on its functionality

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Abstract: Cardiovascular diseases (CVDs) are the leading cause of death globally. CVDs are a group of disorders of the heart and blood vessels and include coronary heart disease, cerebrovascular disease and rheumatic heart disease among other conditions. There are multiple independent risk factors for CVD, including hypertension, age, smoking, insulin resistance, elevated low-density lipoprotein cholesterol (LDL-C) levels, and triglyceride levels. LDL-C levels have traditionally been the target for therapies aimed at reducing CVD risk. High density lipoprotein (HDL) constitutes the only lipoprotein fraction with atheroprotective functions. Early HDL-targeted therapies have focused on increasing HDL-C levels. However, clinical trials have shown that raising HDL-C with niacin failed to achieve CVD reduction. A possible explanation for these findings is that these drugs could interfere with lipid metabolism and cause alterations in HDL structure and composition, leading to loss of functionality. As a result, targeting HDL-C levels would be insufficient to achieve CVD risk reduction, making HDL functionality a more desirable focus for HDL-directed therapies. There are several drugs which show the potential to improve HDL functionality. These drugs include molecules already approved for human use, such as statins and niacin, and particularly, compounds currently undergoing development such as apolipoprotein A-I mimetics and reconstituted HDL preparations. These therapies show promising potential to improve HDL functionality specifically. Future therapeutic strategies should incorporate HDL functionality as a main target of interest.

Introduction

HDL as a therapeutic target

Cardiovascular diseases (CVDs) stand as the primary global cause of mortality, accounting for 17.9 million fatalities annually. CVDs encompass a range of heart and blood vessel disorders, including coronary heart disease, cerebrovascular disease, and rheumatic heart disease, among other conditions ([Cardiovascular Diseases](#)). Numerous distinct risk factors contribute to the development of CVD, such as hypertension, age, smoking, insulin resistance, elevated concentration of low-density lipoprotein cholesterol (LDL-C), and triglyceride levels ([Linton et al., 2019](#); [Huang et al., 2020](#)). In the majority of individuals, atherosclerotic

plaques start to form during young adulthood, emphasizing the importance of focusing on plaque regression as the preferred therapeutic strategy ([Huang et al., 2020](#)). LDL-C levels have traditionally been the target for therapies aimed at reducing CVD risk ([Karalis, 2009](#)). However, despite 78 weeks of treatment, the most potent LDL-lowering agent, the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor evolocumab, only resulted in a modest regression of coronary atheroma volume, as measured through serial coronary intravascular ultrasound, with a decrease of just 0.95%, despite lowering LDL-C levels by 60% ([Nicholls et al., 2016](#); [Puri et al., 2016](#)).

For quite some time, it has been established that decreased levels of high density lipoprotein cholesterol (HDL-C) in the bloodstream is associated with increased risk of atherosclerotic CVD ([Miller and Miller, 1975](#); [Gordon et al., 1977](#)). Remarkably, HDL constitutes the only lipoprotein fraction with atheroprotective functions ([Navab et al., 2011](#)). These functions include its ability to promote reverse cholesterol transport (RCT) and its antioxidant,

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antiinflammatory and antiapoptotic activities, among others (Navab *et al.*, 2011). Traditionally, HDL particles have been evaluated in the clinical setting by measuring their cholesterol content and the concentration of their main apolipoprotein (apo), apo A-I (Walldius and Jungner, 2007). In this context, it is worth discussing the role of cholesteryl ester transfer protein (CETP) and lecithin:cholesterol acyltransferase (LCAT). CETP plays a crucial role in HDL metabolism by facilitating the transfer of cholesteryl esters from HDL to apolipoprotein (apo) B-containing lipoproteins in exchange for TG. Thus, CETP deficiency has been associated with an increase in HDL particle size and HDL-C content, while CETP overexpression has been linked to smaller HDL particles and a decrease in HDL-C levels (Chapman *et al.*, 2010). On the other hand, LCAT is an enzyme whose function is to convert free cholesterol to esterified cholesterol, increasing its hydrophobicity. As a result, cholesterol is sequestered towards the core of the lipoprotein particle, causing it to acquire a spherical shape (Dobiášová and Frohlich, 1999). Deficiency in the activity of this enzyme is associated with low levels of HDL-cholesterol (HDL-C) (Calabresi *et al.*, 2012). However, there is controversy regarding the association between this deficiency and an increased risk of atherosclerosis (Savel *et al.*, 2012).

Early HDL-targeted therapies have focused on increasing HDL-C levels. Indeed, significant strides have been taken to increase plasma HDL-C levels with medications like niacin and CETP inhibitors (Huang *et al.*, 2020; Mani and Rohatgi, 2015; Tall and Rader, 2017). Nevertheless, clinical trials have demonstrated that raising HDL-C levels with niacin did not result in a reduction in CVD (Mani and Rohatgi, 2015; Hung *et al.*, 2019). Similar findings have been observed with CETP inhibitors (Tall and Rader, 2017; Bowman *et al.*, 2017). One plausible explanation for these outcomes is that these drugs might affect lipid metabolism, inducing changes in the structure and composition of HDL, ultimately leading to a loss of its functional properties (Marsche, 2015). It is worth noting that plasma HDL particles exhibit significant heterogeneity in terms of their structure, size, composition, and biological roles, that may explain why measures of HDL-C and cardiovascular risk do not always correlate well. HDL can be separated by sequential ultracentrifugation on the basis of density, resulting in the large buoyant HDL2 and the small dense HDL3, which can be further subfractionated into 5 distinct subpopulations (HDL2b, HDL2a, HDL3a, HDL3b and HDL3c) (Camont *et al.*, 2011). HDL subpopulations interact with different cellular receptors to remove excess cholesterol from cells, a key pathway by which HDL may contribute to atheroprotection (Camont *et al.*, 2011). In fact, elevating HDL-C levels through pharmaceutical means using niacin and CETP inhibitors can potentially impact HDL subpopulations, resulting in elevated cholesterol levels within HDLs and an enlargement of HDL particles (Zanoni *et al.*, 2016; Timón-Zapata *et al.*, 2011; Madsen *et al.*, 2018). When compared to the smaller, denser HDL3 particles, these larger HDL subtypes may not interact as effectively with ATP-binding cassette transporter A1 (ABCA1) and ABCG (Marsche, 2015). The interaction between HDL with ABCA1 and

ABCG1 is crucial in facilitating the process of cholesterol efflux from macrophages to HDLs, which represents the initial step of RCT. Moreover, CETP inhibition could increase insulin resistance and cause fatty liver in CETP expressing transgenic mice fed with a high-fat diet (Zhu *et al.*, 2018). Importantly, there is compelling evidence indicating that the capacity of HDL to promote cholesterol efflux is inversely correlated with CV events, even after adjusting for other risk factors, such as HDL-C and apo A-I levels (Rohatgi *et al.*, 2014; Ebtehaj *et al.*, 2019). Nevertheless, it remains challenging to determine, considering both clinical and biological perspectives, whether certain subfractions exhibit superior *in vivo* antiatherogenic properties than others. This may be attributed to the fact that the antiatherogenic functions exerted by HDL are based on dynamic processes, and static assessment of isolated particles would not reflect the coordinated work that different subfractions exert *in vivo*. As a result, targeting HDL-C levels would be insufficient to achieve CVD risk reduction, making the incorporation of total HDL functionality a desirable outcome for HDL-directed therapies.

HDL components

HDL is a circulating heterogenic complex of about 50% lipids and 50% proteins, which in circulation carries different enzymes and lipid transport proteins. In fact, proteomic and lipidomic studies have identified hundreds of individual proteins and more than 200 lipid species in these particles (Kontush *et al.*, 2013; Davidson *et al.*, 2022).

Regarding HDL lipidome, it is well known that HDL particles carry free cholesterol, cholesteryl esters and triglycerides (Kontush *et al.*, 2013). In addition, they also contain numerous lipid species such as sphingomyelin, ceramide, phosphatidylcholine, lysophosphatidylcholine, phosphatidic acid, phosphatidyl serine, and sphingosine-1 phosphate, among others (Kontush *et al.*, 2013; Brites *et al.*, 2017).

In terms of HDL proteome, apo A-I and apo A-II constitute the two most abundant apolipoproteins present in HDL particles (Davidson *et al.*, 2022). Beyond them, HDLs also contain apo A-IV, apo C-II, apo C-III, apo C-IV, apo D, apo E, apo F, apo H, apo J, apo L-1 and apo M (Brites *et al.*, 2017; Heinecke, 2009). Moreover, in plasma, HDL is associated to enzymes and lipid transport proteins responsible for its metabolism such as LCAT, phospholipid transfer protein (PLTP) and CETP (Brites *et al.*, 2017). In addition, HDL particles can become enriched in proinflammatory and prooxidant markers, such as serum amyloid A (SAA) 1, SAA 2, SAA 4 and myeloperoxidase (Heinecke, 2009). In contrast HDL carries several antioxidant enzymes like paraoxonase (PON) 1, PON 3, glutathione peroxidase 3 and lipoprotein-associated phospholipase A2 (Brites *et al.*, 2017). Finally, there are additional proteins associated with HDL (more than 200), that are relatively scarce and often only weakly bound to HDL particles. Despite their low abundance, these auxiliary proteins may play crucial roles in different biological processes (Davidson *et al.*, 2022; Goetze *et al.*, 2021).

The presence and interaction of these lipids, proteins and enzymes determine HDL atheroprotective capacity, highlighting the importance of HDL individual components.

HDL functionality

HDL particles present multiple atheroprotective activities. Among these, the two most studied are their capability to facilitate RCT and to inhibit the oxidation of LDL particles. (Brites *et al.*, 2017; Toth, 2003). As previously mentioned, RCT involves multiple steps, with the first being the promotion of cholesterol efflux from cells to HDL particles (Martin *et al.*, 2022). The second and third steps are carried out by LCAT and CETP, respectively (Martin *et al.*, 2022). However, it should be noted that HDL has other properties such as its antiinflammatory, antithrombotic and antiapoptotic activities. In particular, HDL suppresses the expression of adhesion molecules on endothelial cells, consequently reducing the recruitment of blood monocytes to the arterial wall, in addition to inhibiting cytokine expression on these inflammatory cells (Barter *et al.*, 2004). HDL also increases nitric oxide (NO) production through upregulation of endothelial NO synthase (eNOS) expression. In fact, HDL stimulates eNOS through activation of the kinase cascade by HDL scavenger class B receptor type 1 (SRB1) (Mineo *et al.*, 2006; Kosmas *et al.*, 2018). HDL's antithrombotic role can be manifested by stimulating prostacyclin synthesis, as well as by reducing tissue factor and selectin expression, resulting in the subsequent suppression of thrombin generation via the protein C pathway, inhibiting platelet activation (Mineo *et al.*, 2006; Kosmas *et al.*, 2018). Furthermore, the potential

cytoprotective impact of HDL on endothelial cells may involve the inhibition of the apoptotic pathway responsible for endothelial cell self-destruction, achieved through a reduction in the activity of P32-like proteases (Kosmas *et al.*, 2018; Sugano *et al.*, 2000). Fig. 1 shows the main cardioprotective functions of HDL.

Alterations in HDL functionality in different pathologies

Different pathologies can affect HDL quality and functionality. In particular, dysfunctional HDL particles are frequently found in pathologies characterized by the presence of inflammation and oxidative stress (Bonizzi *et al.*, 2021). Our group has described alterations of HDL functionality in multiple pathologies. In a prior study we reported impaired capacity to promote cholesterol efflux in HDL from patients with metabolic diseases such as hypertriglyceridemia, obesity and type 2 diabetes (Martin *et al.*, 2022; Brites *et al.*, 1999, 2000). Furthermore, we also reported impaired cholesterol efflux in pathologies that affect iron metabolism like iron deficiency and iron overload (Meroño *et al.*, 2015, 2017). Moreover, we described diminished cholesterol efflux in an autoimmune pathology such as rheumatoid arthritis (Pierini *et al.*, 2021). In addition to alterations in reverse cholesterol transport, our group also reported impaired HDL antioxidant activity in a wide array of pathologies such as metabolic syndrome, type 2 diabetes, obesity, iron deficiency, iron overload and rheumatoid arthritis (Martin *et al.*, 2022; Gomez Rosso *et al.*, 2017, 2014; Gómez Rosso *et al.*, 2008; Meroño *et al.*, 2011; Meroño *et al.*, 2010). Furthermore, other authors have described alterations in HDL functionality in pathologies

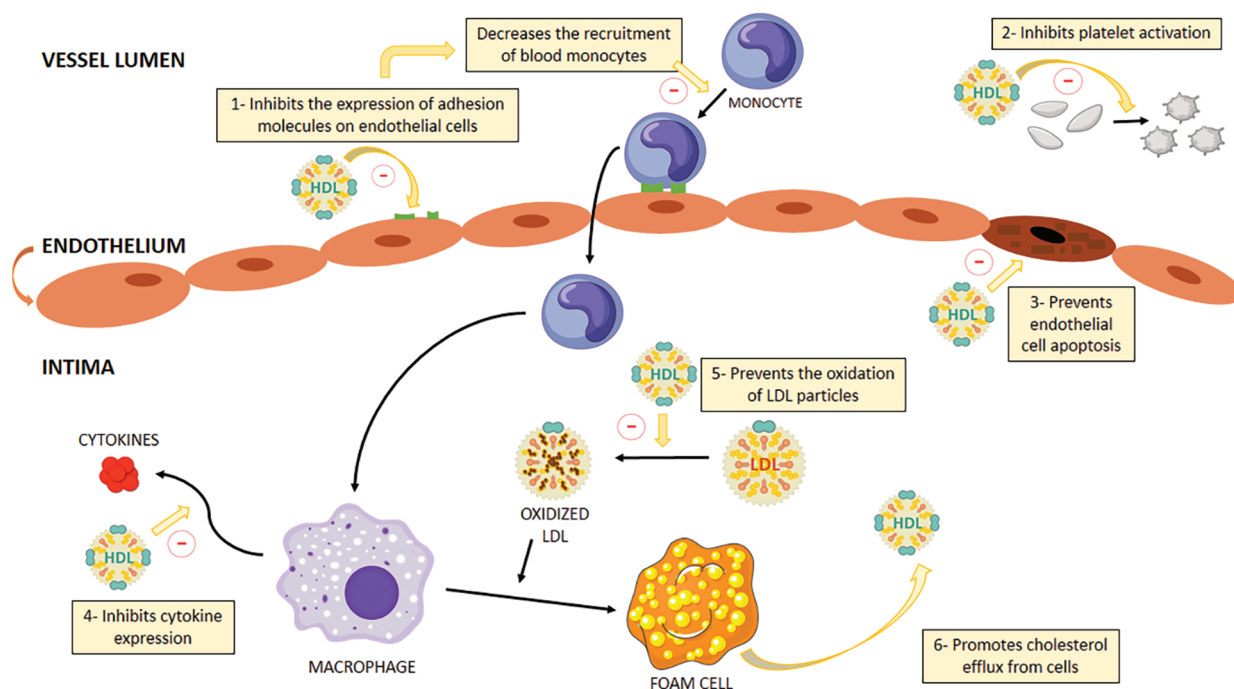


FIGURE 1. HDL multiple atheroprotective activities. 1) Inhibits the expression of adhesion molecules on endothelial cells and thus decreases the recruitment of blood monocytes to the arterial wall. 2) Antithrombotic function: Inhibits platelet activation by activating prostacyclin synthesis and attenuating tissue factor and selectin expression, regulating negatively thrombin generation through the protein C pathway. 3) Antiapoptotic function: prevention of the suicide pathway on endothelial cells. 4) Anti-inflammatory function: Inhibits cytokine expression. 5) Anti-oxidant function: prevents the oxidation of LDL particles. 6) Promotes RCT by promoting cholesterol efflux from cells to HDL particles. HDL, high density lipoprotein; LDL, low density lipoprotein.

such as cancer (Ganjali *et al.*, 2019), endocrine disorders (van der Boom *et al.*, 2020) and autoimmune diseases (Sánchez-Pérez *et al.*, 2020).

Evaluation of HDL functionality

The complexities of HDL metabolism offer a huge challenge that researchers must face and that are relevant to the understanding of human biology to transform them into clinical tools. To assess the issue of HDL function as a potential therapeutic target, robust and simple analytical methods are required for its evaluation. In this regard, the complex pleiotropic effects of HDL make the development of a single measurement challenging. Laboratory assays that accurately measure HDL functionality must be developed, validated and brought to high-throughput for clinical purposes (Hafiane and Genest, 2015; Sacks and Jensen, 2018). Furthermore, HDL particles present multiple atheroprotective functions, so developing a single measure that can account for all of HDL properties makes the challenge even greater (Hafiane and Genest, 2015). A major confounding factor that makes the development of standardized assays difficult is the method by which HDL particles are isolated (Hafiane and Genest, 2015). Indeed, HDL can be isolated by selective precipitation, ultracentrifugation and electrophoresis, among other methods (Hafiane and Genest, 2015). These techniques can influence the results observed. Cholesterol efflux has received much attention as a biomarker that could reflect HDL functionality *in vivo* (Sacks and Jensen, 2018). Nevertheless, it remains unclear whether therapies directed at increasing cholesterol efflux can be atheroprotective (Ronsein and Heinecke, 2017). Furthermore, even though increasing HDL-C levels has shown little benefit to CVD, there is no doubt about the inverse association between HDL-C and CVD. However, the benefit of HDL-C appears to plateau at 61 mg/dL (Pownall and Gotto, 2019; di Angelantonio *et al.*, 2009). In our opinion, the preferable approach to HDL-directed therapies should seek to achieve a balance between classic measures of HDL status such as HDL-C and new measures that better reflect HDL quality.

HDL Functionality and Pharmacological Therapy

There are several drugs in use or in development which show the potential to improve HDL functionality in conditions that show impairment of these atheroprotective functions. These therapies include, niacin, CETP and PCSK9 inhibitors, recombinant LCAT, statins, pioglitazone, metformin, ezetimibe, fibrates, lomitapide, RNA based drugs, apo A-I mimetics and rHDL (Niacin-Health Professional, 2022; Wu and Zhao, 2009; Zhang *et al.*, 2017; Ward *et al.*, 2019; Muñoz-Hernandez *et al.*, 2018; Durairaj *et al.*, 2017; Weinreich and Frishman, 2014; Smith, 2001; Rena *et al.*, 2017; Islam *et al.*, 2018; Darabi *et al.*, 2016). Therefore, these drugs which have been shown to be capable of affecting HDL functionality will be the main subject of the present review.

Niacin

Niacin is available in two forms, oral extended-release tablets (ERT) and immediate-release tablets (IRT). Administration of 1 to 3 grams per day of ERT has been shown to lower serum LDL-C levels while elevating HDL-C levels. Fig. 2 shows niacin proposed mechanism of action. IRT are available in formulations ranging from 50 to 500 mg. It is advisable to initiate therapy with the lowest feasible dosage to minimize the occurrence of adverse reactions (Djado and Bajaj, 2023). Niacin adverse effects include severe skin flushing, tachycardia, palpitations, diarrhea and nausea (Habibe and Kellar, 2023). Niacin can also present adverse interactions with alcohol, antidiabetic drugs, and statins among others (Habibe and Kellar, 2023). Evidence suggests that several genetic markers associated with levels of traditional lipid parameters such as TG, LDL-C and HDL-C can influence the response to niacin treatment (Tuteja *et al.*, 2018). Niacin originally received approval from the US Food and Drug Administration (FDA) for the purpose of secondary prevention of CVD (Kamanna *et al.*, 2009). Over time, its approved indications were expanded to include managing primary hyperlipidemia and mixed dyslipidemia, reducing triglyceride levels, and preventing CV events when

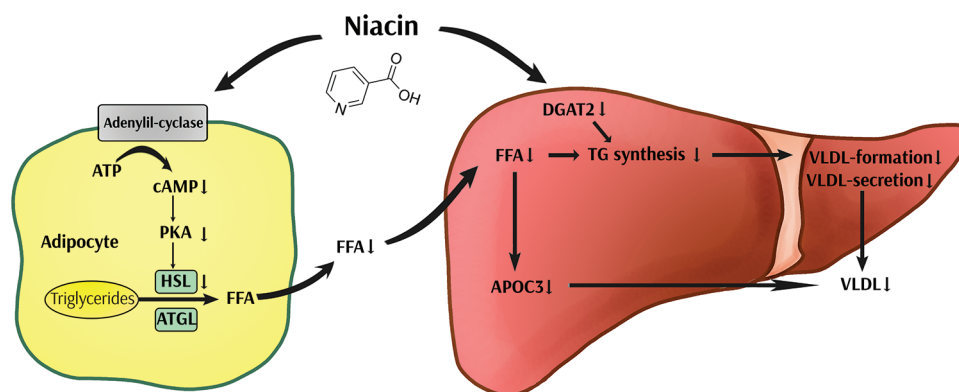


FIGURE 2. Hypothetical hypolipidemic mechanisms of niacin. Niacin inhibits adenylyl cyclase, resulting in decreased activation of protein kinase A (PKA) and cAMP levels, which together lead to reduced lipolysis. As a result, free fatty acid (FFA) plasma levels drop, and triglyceride (TG) synthesis and apolipoprotein C3 (apo C3) expression in the liver are reduced, leading to decreased very low-density lipoprotein (VLDL) formation. In addition, *in vitro* studies suggest that niacin also reduces TG synthesis and VLDL secretion by a direct inhibitory effect on diacylglycerol acyltransferase 2 (DGAT2). HSL, hormone sensitive lipase; ATGL, adipose TG lipase.

combined with statins (D'Andrea *et al.*, 2019). However, the FDA has recently announced withdrawal of previously approved indications for the use of extended-release niacin co-administered with a statin, based on evidence showing that reducing triglycerides or raising HDL-C with any drug does not improve CV risk in patients on statins (Ronsein *et al.*, 2021). In accordance, a recent study quantifying the HDL proteome of subjects in 2 niacin clinical trials, the CPC study (Carotid Plaque Composition) and the HDL Proteomics analysis of the AIM-HIGH trial (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides), showed that adding niacin to statin therapy increases the abundance of auxiliary proteins linked to atherogenesis, suggesting a possible explanation why niacin therapy fails to provide cardioprotection (Masana *et al.*, 2015).

Regarding HDL function, pharmacological treatment with niacin reduced CETP and LCAT mass and activity in type 2 diabetic patients. In addition, HDL antioxidant associated enzymes, PON1 and Lp-PLA2, were significantly decreased. However, niacin treatment was not associated with modifications of the oxidative process according to the lipoperoxide concentration in apo B-depleted plasma, which is an indirect index of HDL oxidation, and the capability of HDL to protect LDL against oxidation (Yvan-Charvet *et al.*, 2010). In addition, another study showed that niacin treatment increased HDL cholesterol efflux from macrophage foam cells and inhibited inflammatory responses induced by toll-like receptor 4 (Yvan-Charvet *et al.*, 2010; Lukasova *et al.*, 2011). Finally, a mouse model study has demonstrated that, in response to niacin, the G-protein coupled receptor, hydroxycarboxylic acid receptor-2 (HCAR2) on monocytoïd cells and macrophages leads to suppression of inflammatory responses and increased cholesterol efflux (Lukasova *et al.*, 2011). This evidence suggests a new potential application for niacin in pharmacology.

CETP inhibitors

In the bloodstream, CETP predominantly associates with HDL and plays a key role in facilitating the transfer of cholesteryl ester and triglycerides between HDL particles and apolipoprotein B-containing lipoproteins, as well as among different subtypes of the latter (Barter *et al.*, 2003). Studies using pharmacological CETP inhibitors have shown promising results in animal models, with reductions in atherosclerotic plaque burden when CETP activity was inhibited (Nelson *et al.*, 2022). Nevertheless, different clinical trials using orally taken pharmacological CETP inhibitors torcetrapib, dalcetrapib, evacetrapib, and anacetrapib have shown that the risk of CVD did not decrease even when substantial increases in HDL-C levels were achieved (Barter *et al.*, 2007; Nicholls *et al.*, 2017; Lincoff *et al.*, 2017; Schwartz *et al.*, 2012). Furthermore, some CETP inhibitors showed adverse effects such as increased blood pressure, inflammation and mortality (Taheri *et al.*, 2020; Tardif *et al.*, 2017). Genetic polymorphisms are one of the factors that could influence individual response to CETP inhibition and contribute to explain the results discussed above. In this regard, a

pharmacogenomics study reported that dalcetrapib could lead to a significant reduction of cardiovascular events only in the carriers of the AA genotype for the rs1967309 single-nucleotide polymorphism of adenylate cyclase 9 (Tardif *et al.*, 2015). However, these results could not be confirmed in a later study carried out in patients who presented acute coronary syndrome (Tardif *et al.*, 2022).

Pharmacological CETP inhibition may result in the dysfunction of HDL by extending the half-life of HDL particles. This can, in turn, make them more vulnerable to adverse changes in their lipid and protein composition, as well as oxidative and enzymatic modifications of their protein and/or lipid components (von Eckardstein, 2022). However, different studies in human patients showed that cholesterol efflux was rather increased upon treatment with CETP inhibitors (Brodeur *et al.*, 2017; Metzinger *et al.*, 2020; Nicholls *et al.*, 2015).

A recent work showed that the CETP inhibitors evacetrapib and torcetrapib increase apo A-I in HDL subspecies that also contain apo C-III (Furtado *et al.*, 2022). The presence of apo C-III on HDL that also contain apo E eliminates its protective association against coronary heart disease by impairing metabolic pathways active in RCT that carries cholesterol from macrophages to the liver (Morton *et al.*, 2018). By contrast, in another study including 377 dyslipidemic patients, evacetrapib monotherapy increased dose-dependent total and non-ABCA1-specific cell cholesterol efflux and also increased ABCA1-specific cell cholesterol efflux. Comparing with statin monotherapy, evacetrapib associated with statins also increased total, non-ABCA1- and ABCA1-specific cell cholesterol efflux (Nicholls *et al.*, 2015), suggesting that cholesterol efflux capacity is substantially increased when potent CETP inhibitors are used alone *vs.* when they are added to statins.

These results reveal the complex effects of potent CETP inhibition on HDL remodeling and function that require further investigation.

PCSK9 inhibitors

A promising area of research is the inhibition of PCSK9, a protein that plays a key role in regulating cholesterol levels in the body. PCSK9 works by binding to LDL receptors (LDLR) on the surface of liver cells, causing the receptors to be internalized and degraded (Suchowerska *et al.*, 2022). Fig. 3 shows PCSK9 mechanism of action. At present, there are two FDA-approved monoclonal antibodies that effectively inhibit the activity of PCSK9: alirocumab and evolocumab. Both can be administrated subcutaneously every two weeks or once monthly, depending on the dose (Tsouka *et al.*, 2018). Recently, both the European Union and the FDA have granted approval for inclisiran, which is a small interfering mRNA designed to hinder the intracellular synthesis of PCSK9. The recommended dosing regimen involves an initial 284 mg subcutaneous injection, followed by another injection at 3-month, and subsequent injections every 6 months thereafter (Ray *et al.*, 2023). The elevated cost of this particular treatment and the route of administration have a significant impact on the adherence of patients to this pharmacological alternative. The most common side effects of PCSK9 inhibitors are injection-site

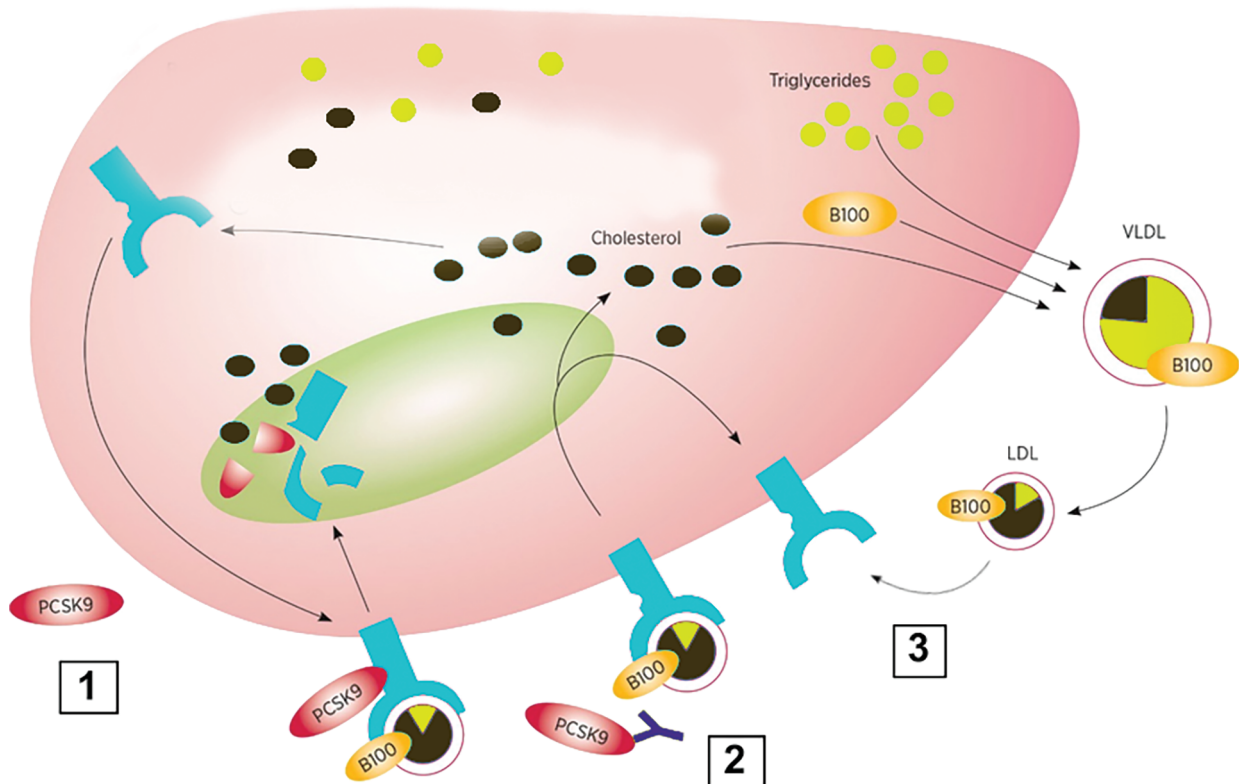


FIGURE 3. Mechanism of action of anti-proprotein convertase subtilisin kexin 9 (PCSK9) monoclonal antibodies. 1) PCSK9 binds to the low density lipoprotein receptor (LDLR) and directs it for degradation in lysosomes; 2) Anti-PCSK9 antibodies bind to PCSK9 and prevent it from attaching to LDLR; 3) Without PSK9 attached, LDLR can be recycled to the cell surface increasing the uptake of LDL particles from circulation.

reactions and Influenza-like symptoms (Gürgöze *et al.*, 2019). Pharmacogenomic studies carried out in individuals with familial hypercholesterolemia have reported that the efficacy of PCSK9 inhibitors such as evolocumab and alirocumab are affected by polymorphisms in apo B, low density lipoprotein receptor (LDL-R) and LDL-R adapter protein 1 genes (Hindi *et al.*, 2021). Remarkably, a recent meta-analysis provided evidence that the efficacy of PCSK9 inhibitors could be similar for different ethnicities (Sawant and Wang, 2023).

The interaction between human PCSK9 and HDL particles remains a subject of ongoing debate, and research findings in this regard vary. Some recent studies have indeed indicated that PCSK9 binds to HDL in the bloodstream (Dafnis *et al.*, 2022; Burnap *et al.*, 2020), whereas another study did not find any association (Kosenko *et al.*, 2013). An important question that has arisen in the context of PCSK9 inhibition is its potential effect on HDL function. Recent research has suggested that PCSK9 inhibitors may have a negative effect on HDL function, while other studies have found no such effect or even a beneficial effect on HDL function. In this context, an earlier study has proposed that PCSK9 hinders ABCA1-dependent cholesterol efflux from macrophages when apo A-I is present as the acceptor (Adorni *et al.*, 2017a). Additionally, another study has demonstrated that PCSK9 impedes ABCA1-mediated cholesterol efflux from macrophages. This inhibition, attributed to the downregulation of the Abca1 gene and ABCA1 protein expression, implies that PCSK9 may have extrahepatic

effects that can potentially impact key aspects of atherosclerosis development, such as the formation of foam cells (Adorni *et al.*, 2017b). In addition, a recent investigation has indicated that PCSK9 may have an impact on the functional properties of HDL. Specifically, it was found that PCSK9 reduces HDL's ability to facilitate endothelial cell migration and hinder the formation of reactive oxygen species. Conversely, deactivating PCSK9 within HDL appears to enhance the atheroprotective functions of HDL (Dafnis *et al.*, 2022). In contrast, Palumbo *et al.* (2022) evaluated a cohort of heterozygous familial hypercholesterolemic patients and observed that inhibition of PCSK9 has been shown to markedly enhance HDL cholesterol efflux, primarily through pathways involving ABCG1 and aqueous diffusion. Additionally, it reduces the serum's ability to load macrophages with cholesterol, which is considered a proatherogenic marker and is associated with an elevated CV risk (Adorni *et al.*, 2019).

Recombinant LCAT

About 90% of esterified cholesterol in plasma is synthesized by LCAT. Thus, LCAT plays a crucial role in HDL metabolism and RCT (Vitali and Cuchel, 2021). However, studies in humans and animals reported different results (Duan *et al.*, 2022).

Recently, 2 different recombinant human LCAT enzymes (MEDI6012 and ACP-501) were shown to be safe in clinical studies including subjects with stable CVD (George *et al.*, 2021; Shamburek *et al.*, 2016). Hence, in a phase 2a double-blind study, 48 subjects with stable coronary heart disease

were randomized on a statin to a single dose of MEDI6012 or placebo. Administration of recombinant LCAT resulted in dose-dependent increases in global and non-ABCA1 cell cholesterol efflux (George *et al.*, 2021), suggesting that treatment with MEDI6012 may enhance RCT. In addition, in a phase I trial, infusion of ACP-501 was shown to increase HDL-C levels, cholesterol efflux and to favorably alter HDL metabolism, decreasing small and intermediate-sized HDL, and increasing large HDL particles (Shamburek *et al.*, 2016).

More recent, findings suggest that, in addition to improving RCT, LCAT treatment may also improve other antiatherogenic properties of HDL, such as its ability to stimulate NO production from endothelial cells. HDL isolated from patients with myocardial infarction (MI) progressively lose the capacity to promote NO production by endothelial cells, and the reduction is related to decreased LCAT concentration. *In vitro* incubation of MI patients' plasma with recombinant human LCAT restores HDL ability to promote endothelial NO production, possibly related to significant modification in HDL phospholipid classes (Ossoli *et al.*, 2019).

It should be noted that both MEDI6012 and ACP-501 are administered subcutaneously, representing a noteworthy challenge in terms of patient adherence (Yang *et al.*, 2022a). In addition, adverse effects of recombinant LCAT therapy seem to involve skin and subcutaneous issue disorders (Shamburek *et al.*, 2016).

Statins

Statins are the most common drugs used for the treatment of dyslipidemia (Ward *et al.*, 2019). Statins are selective inhibitors of β -hydroxy- β -methylglutaryl coenzyme A reductase (HMGCR), an enzyme involved in cholesterol synthesis (Ward *et al.*, 2019). Fig. 4 shows statins mechanism of action. Side effects of statins include fibromyalgia, headache, dizziness and tiredness (Side Effects, 2022). Moreover, statins present harmful interactions with some immunosuppressors, protease inhibitors and antibiotics (Side Effects of Metformin, 2022). Most statins are orally administered once daily and peak plasma concentrations achieved in 1–3 h. It takes about 6 weeks before LDL-C levels are stabilized (Ward *et al.*, 2019). Pharmacogenomics studies on statins have reported several genes that could influence both the response to these drugs and the apparition of adverse effects (Zineh, 2007; Canestaro *et al.*, 2014). The effect of these genes would depend on the specific statin considered (Zineh, 2007). Similarly, polymorphisms in genes involved in lipid metabolism such as ABCA 1, LDL-R and HMGCR can influence the efficacy of statins (Hindi *et al.*, 2021). Moreover, there is evidence of interracial differences in the response to statins (Lee *et al.*, 2005). However, a later meta-analysis reported that response to statins would be similar regardless of ethnicity (Sawant and Wang, 2023). On the other hand, statin effect on HDL functionality remains controversial (Muñoz-Hernandez *et al.*, 2018; Lamon-Fava, 2013). In this regard, in a recent study, HDL proteome correlated with statin use, reporting a less antiatherogenic proteome in HDL3 particles from patients with type 1

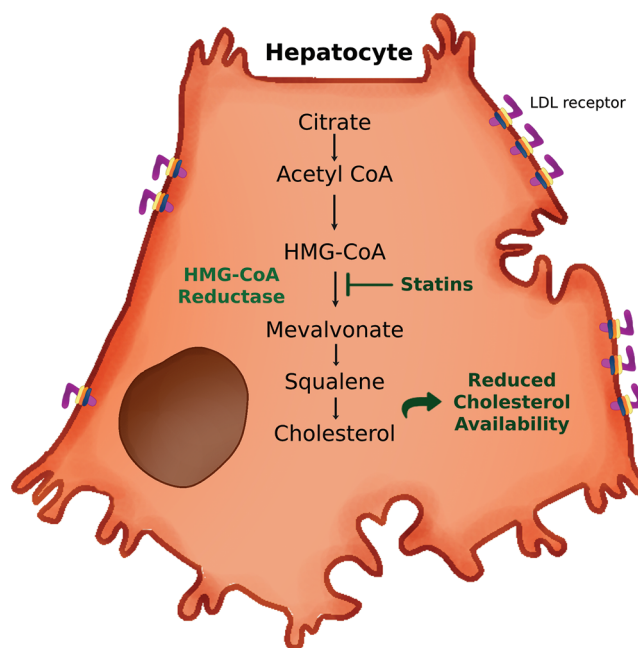


FIGURE 4. Mechanism of action of statins. Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase in hepatocytes. HMG-CoA reductase catalyzes the conversion of HMG-CoA into mevalonate, a key step for cholesterol synthesis, leading to reduced cholesterol availability. LDL, low density lipoprotein.

diabetes mellitus (Toyoshima *et al.*, 2023). On the other hand, in a study carried out in hypercholesterolemic patients both pravastatin and atorvastatin showed no effect on cholesterol efflux (Khera *et al.*, 2011). In another study, atorvastatin failed to increase cholesterol efflux to total HDL, HDL2b and HDL3c in diabetic patients (Muñoz-Hernandez *et al.*, 2018). Similarly, atorvastatin showed no effect in cholesterol efflux to apo B-depleted plasma in normolipidemic men (Ying *et al.*, 2022). Furthermore, atorvastatin and simvastatin have been shown to decrease ABCA1 expression in macrophages and peripheral mononuclear cells (Qiu and Hill, 2008; Genvigir *et al.*, 2010). Nevertheless, this effect could be abolished by loading the macrophages with cholesterol (Song *et al.*, 2011). Moreover, statins would reduce the activity of CETP and PLTP, both involved in HDL metabolism and maturation (de Haan *et al.*, 2008; Karalis *et al.*, 2010). On the contrary, pitavastatin and, to a lesser extent, atorvastatin and simvastatin would increase ABCA1 expression in hepatocytes (Maejima *et al.*, 2011). In fact, pitavastatin (but not atorvastatin) could increase ABCA1 half-life in hepatocytes (Kobayashi *et al.*, 2011). Consistently, pitavastatin would increase HDL ability to promote cholesterol efflux and its antioxidant activity (Pirillo and Catapano, 2017; Miyamoto-Sasaki *et al.*, 2013). In another study, atorvastatin alone or in combination with ezetimibe increased cholesterol efflux in a randomized clinical trial (Lee *et al.*, 2017). Similarly, simvastatin with or without bezafibrate increased cholesterol efflux, but not HDL antioxidant and antiinflammatory activities in diabetic patients (Triolo *et al.*, 2014). Moreover, rosuvastatin increased cholesterol efflux and PON 1 concentration in

diabetic patients (Nareesh *et al.*, 2021). Consistently, *in vitro* studies show that statins could promote PON 1 activity (Marathe *et al.*, 2019). Moreover, in a study carried out *in vitro*, rosuvastatin inhibited foam cell formation and stimulated ABCA1 and ABCG1 expression by promoting autophagy in macrophages (Zhang *et al.*, 2021). Similarly, atorvastatin increased cholesterol efflux by promoting foam cell lipophagy (Zheng *et al.*, 2021). Furthermore, pravastatin enhanced cholesterol efflux in chondrocytes (Wu *et al.*, 2022). In summary, the effect of statin therapy on HDL functionality would depend on the statin employed and the target organ.

Another factor that could affect the response to statin therapy is the route of administration. Different strategies have been developed to improve the efficiency of drug-delivery to the target organ and prevent leakage in circulation. Indeed, in a recent study, copolymer modified atorvastatin-loaded discoidal rHDL strongly promoted macrophage differentiation into antiinflammatory M2 phenotype (Zhang *et al.*, 2021). Similarly, LIPOSTAT, a simvastatin-loaded nanoliposome, was shown to enhance cholesterol efflux from foam cells (Rakshit *et al.*, 2021). Furthermore, the combination of β -cyclodextrin and simvastatin-loaded rHDL in a sink/shuttle structure showed remarkable capacity to promote cholesterol efflux and decrease inflammation in macrophages (He *et al.*, 2020). Importantly, the effect of statins on HDL functionality could extend beyond CVD therapy and be useful for the treatment of certain cancers and conditions such as osteoarthritis and glaucoma (Wu *et al.*, 2022; Yang *et al.*, 2022b; Yang *et al.*, 2023).

Pioglitazone

Pioglitazone is an antidiabetic medication (Smith, 2001). It is administered orally once a day and peak plasma concentration is achieved 2 h after administration (Pioglitazone, 2017). Similar to statins, it takes several weeks before the desired effect can be achieved (Smith, 2001). Adverse effects of pioglitazone include headache, vision loss, pain or difficulty urinating, muscle pain, and weight gain among others (Pioglitazone, 2017). Pioglitazone selectively stimulates PPAR- α and PPAR- γ (Smith, 2001). Pharmacogenomic studies show that polymorphisms in PPAR- γ , Adiponectin, resistin, lipoprotein lipase (LPL), tumor necrosis factor- α and interleukin 6 (IL-6) genes could potentially influence the response to pioglitazone (Kawaguchi-Suzuki and Frye, 2013). The fact that pioglitazone regulates PPAR- α raises the possibility that this drug could affect HDL functionality, considering that the major role of PPAR- α deals with regulating HDL metabolism (Yoon, 2009). Indeed, there is evidence that pioglitazone could increase HDL functionality. In a study carried out *in vitro*, pioglitazone stimulated apo A-I secretion in HepG2 cells (Qin *et al.*, 2007). These pioglitazone-induced apo A-I particles were capable of promoting cholesterol efflux from THP 1 macrophages (Qin *et al.*, 2007). In another study pioglitazone increased ABCA1 expression in THP 1 macrophages (Liu *et al.*, 2014). Furthermore, pioglitazone was capable of enhancing cholesterol efflux to HDL via both ABCA1 and ABCG1 transporters *in vitro* and *ex vivo*, employing sera from diabetic patients (Ozasa *et al.*, 2011).

This effect of pioglitazone would depend on PPAR- α activation (Ozasa *et al.*, 2011). Furthermore, pioglitazone enhanced cholesterol efflux from macrophages by simulating PPAR- γ in mice (Ye *et al.*, 2019). On the contrary, in another study, PPAR- γ stimulation by pioglitazone reduced ABCA1 expression in macrophages (Jiang and Li, 2017). In another study, pioglitazone stimulated cholesterol efflux and ABCA1 expression in gallbladder epithelial cells (Wang *et al.*, 2015). In summary, the effect of pioglitazone on cholesterol efflux would depend on the type of cell and pathway involved. In addition to cholesterol efflux, pioglitazone could restore LCAT activity (Mirmiranpour *et al.*, 2013).

Some studies have provided evidence that pioglitazone could also affect HDL antioxidant capacity. Both in humans and mouse models pioglitazone improved PON 1 activity (Mirmiranpour *et al.*, 2013; Mahmoudi *et al.*, 2019). In fact, pioglitazone was also proved to affect HDL resistance to oxidation (McEneny *et al.*, 2013).

Metformin

Metformin is usually employed as the first-line medication against type 2 diabetes. In addition, large clinical trials have shown that metformin can counteract diabetes-associated CV complications (He *et al.*, 2019). Metformin is administered orally once or twice a day (He *et al.*, 2019). Peak plasma concentrations are observed 3 h. and glucose lowering approximately 8 weeks after administration (He *et al.*, 2019). Side effects of metformin include nausea, diarrhea, stomach ache and vitamin B 12 deficiency among others (NIH, 2022). In addition, metformin can interact with other antidiabetic medication such as insulin, plus with some diuretics and corticosteroids (NIH, 2022). Evidence suggests that the heritability of metformin response ranges between 20% and 34% (Florez, 2017). Nevertheless, the genetic markers identified thus far account for a small fraction of the variability observed in response to stains (Florez, 2017; Damanhoury *et al.*, 2023). These findings suggest that many other genetic determinants of metformin action remain to be discovered and further pharmacogenomics studies are needed. The mechanism responsible for metformin-induced reduction of CV complications is still unknown. In this regard, different studies have suggested a positive effect of metformin on HDL functionality. In a study carried out in THP 1 human macrophages, metformin blunted foam cell formation induced by palmitic acid (Song *et al.*, 2010). Moreover, in another study, metformin reduced foam cell formation, increased cholesterol efflux and upregulated both ABCA1 and ABCG1 in macrophages (Damanhoury *et al.*, 2023). Metformin-mediated upregulation of ABCA1 and ABCG1 would depend on stimulation of fibroblast growth factor 21 (Luo *et al.*, 2016). Similarly, metformin in combination with atorvastatin stimulated cholesterol efflux and both ABCA1 and ABCG1 expression in rabbits (Luo *et al.*, 2017). In fact, metformin would be capable of restoring HDL ability to promote cholesterol efflux impaired by glycation (Matsuki *et al.*, 2009). Furthermore, metformin could increase HDL-induced cholesterol efflux in vascular smooth muscle cells (Robichaud *et al.*, 2022). This process would be mediated by autophagy induced by metformin (Robichaud *et al.*, 2022).

In another study, metformin inhibited foam cell formation by stimulating autophagy in macrophages from mice (Wu *et al.*, 2021). Moreover, metformin could promote cholesterol efflux in chondrocytes (Xing *et al.*, 2022). However, it should be noted that metformin did not induce changes in ABCA1 expression in a study carried out in diabetic patients (Fakhoury *et al.*, 2022). Furthermore, metformin failed to promote cholesterol efflux in young individuals with type 1 diabetes (Gourgari *et al.*, 2021).

Beyond RCT, evidence suggests that metformin could also affect HDL antioxidant activity. Metformin, alone or in combination with lycopene simulated PON 1 activity in obese mice (Motta *et al.*, 2022). These results were replicated in diabetic rats for both metformin with or without lycopene (Figueiredo *et al.*, 2020) and metformin with or without curcumin (Roxo *et al.*, 2019). In fact, metformin-induced PON 1 activity resulted in a significant decrease in lipid peroxidation in diabetic rats (Wójcicka *et al.*, 2016). Moreover, metformin could not only stimulate PON 1 activity, but also upregulate its expression (Camps *et al.*, 2016). Furthermore, there is evidence that metformin could, via AMPK activation, improve HDL antioxidant and antiinflammatory activities in mice (Ma *et al.*, 2017).

Ezetimibe

Ezetimibe is another LDL-C-lowering drug highly used in the clinical setting (Savarese *et al.*, 2015). It interacts with Niemann–Pick C1-Like 1 (NPC1L1) protein to decrease intestinal absorption of LDL (Savarese *et al.*, 2015; Phan *et al.*, 2012). It is usually employed in combination with statins and capable of achieving a further 25% reduction of LDL-C compared to treatment with statins alone (Savarese *et al.*, 2015). Ezetimibe is administered orally and peak concentration is achieved 4–12 h after administration (Drugbank, 2023a). LDL-C lowering is usually observed 2 weeks after the initiation of therapy (Side Effects of Ezetimibe, 2023). Its side effects include diarrhea, abdominal pain and tiredness (Side Effects of Ezetimibe, 2023). Genetic studies on the efficacy of ezetimibe suggest that it could be influenced by polymorphisms on genes associated with lipid metabolism such as NPC1L1, HMGCR and the transcription factor sterol regulatory binding protein 1 (Hindi *et al.*, 2021). Interestingly, a recent meta-analysis found that there are no major differences in the response to ezetimibe treatment among the different ethnicities (Sawant and Wang, 2023). Regarding its effect on HDL, Ezetimibe can produce modest increases in HDL-C (About Ezetimibe, 2023). In terms of HDL functionality, results are controversial. Ezetimibe was reported to increase PON 1 expression and activity in an animal model of non-alcoholic fatty liver disease (Hussein *et al.*, 2012). On the contrary, ezetimibe reduced PON 1 activity in subjects who were receiving statin therapy (Tang *et al.*, 2012). The fact that ezetimibe is usually administered with statins constitutes a confounding factor and further studies on ezetimibe effect over HDL are needed.

Fibrates

Fibrates are amphipathic derivatives of fibric acid (Grundy *et al.*, 2005). Fibrates are employed to treat atherogenic

dyslipemia characterized by high TG and low HDL-C levels (Grundy *et al.*, 2005). Fibrates are administered orally and peak concentrations depend on the type of fibrate (Balendiran *et al.*, 2007). Several weeks are needed before desired effects can be observed (Balendiran *et al.*, 2007). Side effects include diarrhea, abdominal pain, dizziness, jaundice and headaches (Fibrates, 2022). Furthermore, fibrates can interact with blood thinners and immunosuppressors with harmful results (Fibrates, 2022). Fibrates stimulate peroxisome proliferator activated receptor alpha resulting in reduced fatty acids, TG and VLDL synthesis (Steiner, 2007). In parallel, production of Apo A-I and ABCA 1 is up-regulated (Steiner, 2007). Pharmacogenomic studies show that response to fibrates could be influenced by polymorphisms in PPAR- α , Apo E, Apo A-I, Apo B, Apo C-III, Apo AV, IL-6 and LPL genes (House and Motsinger-Reif, 2020). Furthermore, the efficacy of fibrates could also be affected by epigenetic modifications, specifically methylation levels, on the gene CEMIP2, which codifies a cell-surface transmembrane protein (House and Motsinger-Reif, 2020). Fibrates have been shown to be capable of increasing cholesterol efflux to HDL in animal models (Balendiran *et al.*, 2007; Fournier *et al.*, 2013). Nevertheless, studies carried out in humans have been contradictory (Gomaschi *et al.*, 2015). In a previous study fenofibrate increased ABCA 1 dependent cholesterol efflux to HDL in dyslipidemic patients (Franceschini *et al.*, 2007). However, those results could not be replicated in a later study by the same group (Franceschini *et al.*, 2013). In another study, fenofibrate also failed to increase cholesterol efflux to HDL (Maranghi *et al.*, 2011). In contrast, bezafibrate increased cholesterol efflux in patients with type 2 diabetes (Triolo *et al.*, 2014). Interestingly fenofibrate shows greater capacity to stimulate PON 1 activity than bezafibrate (Sahebkar *et al.*, 2016). In summary, the effect of fibrates on HDL functionality would depend not only on the type of fibrate, but also on the specific function studied.

Lomitapide

Lomitapide specifically inhibits microsomal triglyceride transport protein (MTP) (Ahn and Choi, 2015). MTP plays a crucial role in the assembly of VLDL particles (Ahn and Choi, 2015). As a result, lomitapide shows great efficiency at reducing both apo B and LDL-C levels (Ahn and Choi, 2015). Lomitapide is administered orally and peak concentrations are achieved in 6 h (Drugbank, 2023b). Lipid lowering is usually achieved after 6 weeks (Perry, 2013). Importantly, in addition to the usual diarrhea, dizziness and headaches, side effects of lomitapide include liver damage (Cuchel *et al.*, 2007). Regarding HDL, lomitapide reduces HDL-C levels and evidence suggests it could also decrease ABCA 1 dependent cholesterol efflux, without changes in ABCG 1- and SRBI- mediated efflux (Yahya *et al.*, 2016).

RNA-based therapy

An innovative approach to the treatment of CVD involves targeting upstream processes, inhibiting the mRNA translation of proteins specifically implicated in lipid metabolism. Two categories of compounds have been primarily employed for this purpose: antisense

oligonucleotides (ASO) and double-stranded short interfering RNA (siRNA) (Gareri et al., 2022). An important advantage of this approach is that it allows the targeting of several grams of a specific protein with a single RNA molecule, extending the intervals between doses (Gareri et al., 2022). Side effects depend on the specific therapy, but a main disadvantage of RNA-based drugs is that they need to be injected, potentially lowering patient adherence (Gareri et al., 2022). FDA-approved Mipomersen, an ASO that targets apo B, has shown remarkable capability to reduce apo-B, LDL-C, TG and non-HDL-C; however, it exerts no significant effect on HDL (Fogacci et al., 2019). Another FDA approved RNA-based drug, the previously mentioned Inclisiran, a siRNA targeted against PCSK9, has displayed the ability to increase HDL-C levels in addition to decreasing parameters associated with apo B-containing lipoproteins (Cupido and Kastelein, 2020). Similar results have been observed with Volanesorsen, an ASO directed against apo C-III (Kolovou et al., 2022). Nevertheless, the effect of these drugs on HDL functionality has not been tested. In this regard, evidence from animal models suggests that ASOs against angiotensin-like protein 3, which inhibits endothelial lipase and is involved in HDL metabolism, increase RCT (Bell et al., 2021). Moreover, the same group reported previously that ASOs against CETP could also increase RCT (Bell et al., 2013). In conclusion, the focus of RNA-based therapy for CVD has been directed to molecules associated with apo B containing lipoproteins, developing RNA drugs for HDL-associated enzymes and proteins could be a fertile ground for new therapeutic developments.

Apo A-I mimetics

Short synthetic peptides with sequences that mimic those found in natural apo A-I have been studied since the 1980's for their potential to generate HDL-like nanoparticles and improve the function of endogenous HDL. These peptides are designed to replicate the behavior of apo A-I in promoting the formation and functions of endogenous HDL. Among the reported properties of apolipoprotein mimetic peptides are: 1) lipid-associating ability, 2) stimulation of HDL maturation and remodeling, 3) promotion of cholesterol efflux, and 4) antiinflammatory and antioxidant activities (Leman, 2015). However, it is important to note that most mimetics need to be administered intravenously, which constitutes a disadvantage when compared to drugs, such as statins, that can be administered orally. In addition, it should be noted that many of the studies with apo A-I mimetics have been carried out in mice, which do not naturally express CETP (Hogarth et al., 2003). The effect of CETP on apo A-I mimetics is unknown and makes extrapolation of results from animal models to humans difficult. Fig. 5 shows the effect of apo A-I mimetics on RCT.

The first apo A-I mimetics were based on the class A amphipathic helix structure that apo A-I residues 41 to 243 form (Smith, 2010). Two of the first mimetics developed were 18A and 37pA. 18A is the prototype 18-residue peptide, and 37pA is a dimer of two 18A peptides with a proline spacer (Anantharamaiah et al., 1985). Similar to apo A-I, these peptides can transform a phospholipid emulsion

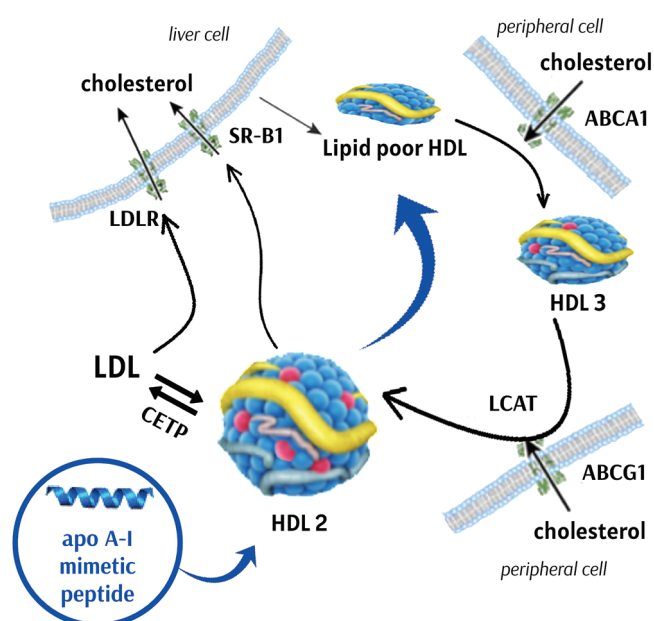


FIGURE 5. Effect of apolipoprotein A-I mimetics on reverse cholesterol transport. Apolipoprotein (apo) A-I mimetics have the potential to increase cholesterol efflux from cells to high density lipoproteins (HDL) via ATP binding cassette subfamily (ABC) A1, ABCG1 and scavenger receptor class B type 1 (SRB1). Additionally, apo A-I mimetics can increase lecithin:cholesterol acyltransferase (LCAT) activity and HDL maturation. Mature HDL particles present increased lipid exchange with apo B containing lipoproteins via cholesteryl ester transfer protein (CETP), increasing cholesterol delivery to the liver. LDL, low density lipoprotein. LDLR, low density lipoprotein receptor.

of dimyristoylphosphatidylcholine (DMPC), into disc-like rHDL particles (Anantharamaiah et al., 1985). The same group developed a series of more hydrophobic analogs with an increasing number of phenylalanine substitutions (referred to as 2F, 3F, 4F and 5F) (Datta et al., 2001). Several of these analogs exhibited increased lipid association activity and the 4F peptide demonstrated the strongest ability to absorb oxidized fatty acids and antiinflammatory activity (van Lenten et al., 2008). Similar to apo A-I, a considerable subset of these peptides has the potential to function as acceptors for cellular cholesterol through ABCA1. Nevertheless, it is noteworthy that when present in elevated concentrations, these peptides manifest detergent-like characteristics and possess the capability to extricate cholesterol from cells in an ABCA1-independent manner (Remaley et al., 2003). Remarkably, 5F peptide reduced aortic root atherosclerosis when injected to C57BL/6 mice fed a high cholesterol atherogenic diet (Garber et al., 2001).

Peptide 4F has been the most studied of apo A-I mimetics and has shown the most promising results to date. APP-018, an analog of 4F which can be administered orally, reduced aortic root lesion in apo E-deficient mice (Navab et al., 2002). Moreover, APP-018 treatment increased small pre β -HDL levels and HDL antiinflammatory activity (Navab et al., 2004). In one study, APP-018 and statins were capable of triggering the regression of lesions in the aortic root and the entire aorta in apo E deficient mice (Navab et al., 2005). Nevertheless, in another study, these results could not be replicated when APP-018 was administered

without statins in apo E-deficient mice (Li *et al.*, 2004). Furthermore, in two other animal studies, 4F presented potent antiinflammatory activity (van Lenten *et al.*, 2008; Navab *et al.*, 2012). In a phase I clinical trial, which included 50 patients with coronary artery disease, APP-018 increased HDL antiinflammatory activity when administered orally in high doses (Bloedon *et al.*, 2008). However, in another study, in which 4F was administered by intravenous infusion or by subcutaneous injection, 4F failed to raise HDL antiinflammatory or antioxidant activities (Watson *et al.*, 2011). Interestingly, in a recent study, 4F restored HDL antioxidant activity when added to a mixture that contained dysfunctional HDL isolated from diabetic patients (Feng *et al.*, 2022). Furthermore, 4F decreased oxidation and increased NO production in mice fed a western diet (Ning *et al.*, 2021). In fact, 4F could protect against oxidation and inflammation even after hypoxia exposure (Paul *et al.*, 2021). Moreover, evidence suggests that 4F protects against endothelial dysfunction (Jiang *et al.*, 2021). Similarly, 4F could improve left-ventricular hypertrophy, which results from coronary artery disease, in rabbits (Kraler *et al.*, 2021). Furthermore, 4F could inhibit cardiac remodeling after MI (Hamid *et al.*, 2020).

Another peptide, ATI-5261, a single amphipathic helix, was shown to be highly efficient promoting cholesterol efflux and reducing plaque lipid content in apo E deficient mice (Bielicki *et al.*, 2010). 6F is another apo A-I mimetic with potent antioxidant and antiinflammatory effects. Its main advantage over other mimetics is that it does not require end blocking for its production, raising the possibility that it could be synthesized by living organisms and facilitating large scale production (Chattopadhyay *et al.*, 2013; Navab *et al.*, 2013). In fact, tomatoes have been genetically engineered to express 6F. When fed to mice, these tomatoes have produced impressive reductions in atherogenic lesions (Chattopadhyay *et al.*, 2013). The reason for these findings would be that oral administration of apo A-I mimetics is more effective due to the intestine being the main site of action (Hogarth *et al.*, 2003). The apo A-I mimetic peptide 37pA is highly capable of inducing cholesterol efflux; however, its high lipid affinity makes it cytotoxic (Ning *et al.*, 2021). As a result, another peptide named 5A was designed by replacing 5 amino acids of 37pA with alanine residues making it less cytotoxic, but retaining its capacity to promote cholesterol efflux (Sethi *et al.*, 2008). In fact, 5A can promote efflux via both ABCA1 and ABCG1 transporters (Amar *et al.*, 2010). Moreover, 5A presents antiinflammatory and antioxidant activities (Tabet *et al.*, 2010). Another apo A-I mimetic is etc-642, a complex of a 22-amino acid peptide that forms an amphipathic helix and phospholipids. etc-642 causes a shift in HDL subfractions towards the highly antiatherogenic pre β -HDL and increases cholesterol efflux and antiinflammatory activity by blunting the expression of necrosis factor (NF)- κ B and endothelial adhesion molecules in endothelial cells (di Bartolo *et al.*, 2011a, 2011b; Iwata *et al.*, 2011).

D'Souza *et al.* (2010) conducted a noteworthy investigation into the impact of 22 distinct bihelical apolipoprotein A-I mimetic peptides on cholesterol efflux, as well as their anti-inflammatory and antioxidant properties.

Intriguingly, none of the examined compounds exhibited superiority across all antiatherogenic functions. These results indicate that apo A-I mimetic peptides more closely resembling apo A-I do not necessarily improve all various antiatherosclerotic functions. Moreover, combining several apo A-I mimetic peptides, each mimicking different structural aspects of apo A-I, may prove to be a valuable strategy to mimic the various antiatherosclerotic properties of apo A-I (Stoekenbroek *et al.*, 2015).

It is important to note, that apo A-I mimetics are currently being studied for the treatment of other diseases apart from CVD. The disease models in which apolipoprotein mimetic peptides have shown benefit include cancer (Hogarth *et al.*, 2003), colitis (Hogarth *et al.*, 2003), asthma (Ghosh *et al.*, 2022), sickle cell disease (Reddy *et al.*, 2014), insulin resistance (Reddy *et al.*, 2014), endotoxemia (Reddy *et al.*, 2014), lung fibrosis (Wygrecka *et al.*, 2023), HIV infection (Daskou *et al.*, 2022), Parkinson's disease (Jiang and Bai, 2022), and cognitive function and Alzheimer's disease (Hogarth *et al.*, 2003; Vanherle *et al.*, 2022). Moreover, 4F was shown to inhibit *in vitro* replication of SARS-COV-2 (Kelesidis *et al.*, 2021).

In summary, apo A-I mimetics are a promising tool for the treatment not only of CVD and related complications, but also of a number of other diseases. In fact, in recent years, researchers have produced mimetics for other apolipoproteins, such as apo E, apo C-III and apo J. Overall, there are currently 60 different peptides that have been approved for human use and over 150 peptides that are in various stages of clinical development (Wolska *et al.*, 2021).

Reconstituted HDL

HDL is highly heterogeneous and composed of hundreds of lipids and proteins. rHDL provides tools that allow a better understanding of HDL composition and its roles in CVD. Infusion of exogenous HDL is known as HDL replacement therapy. rHDL is synthesized by the combination of apo A-I (or its mimetics) and phospholipids (Huang *et al.*, 2020). One of the first and most studied rHDL particles was etc-216, composed of apo A-I Milano and phosphatidylcholine (POPC). Apo A-I Milano is a naturally occurring mutant of apo A-I that was shown to possess cardioprotective properties superior to wild type apo A-I (Franceschini *et al.*, 1980). These particles increased cholesterol efflux and reduced atherosclerotic plaques in mice (Nicholls *et al.*, 2011). Moreover, etc-216 showed higher antiinflammatory activity and plaque regression than wild type HDL in rabbits (Nissen *et al.*, 2003; Ibanez *et al.*, 2012). Unfortunately, clinical trials had to be stopped due to increases in neutrophil and decreases in lymphocyte count (Huang *et al.*, 2020). As a result, another rHDL containing apo A-I Milano and POPC was designed and named MDCO-216. It was tested in patients with coronary artery disease and it showed none of the adverse effects of its predecessor whilst increasing cholesterol efflux (Reijers *et al.*, 2017; Kempen *et al.*, 2014). Moreover, MDCO-216 increased pre β -HDL concentration and cholesterol efflux in healthy volunteers and patients with stable coronary artery disease (Kempen *et al.*, 2016; Kallend *et al.*, 2016). Nevertheless, MDCO-216

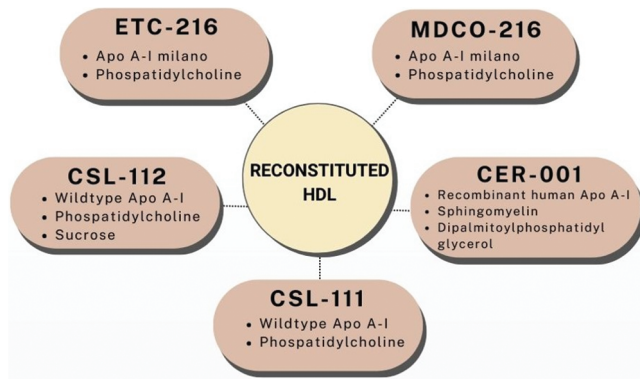


FIGURE 6. The five main reconstituted HDL preparations. Apo, apolipoprotein; HDL, high density lipoprotein.

failed to trigger plaque regression in patients with acute coronary syndrome (Nicholls *et al.*, 2018).

CER-001 is another rHDL made of recombinant human apo A-I, sphingomyelin (SPM), and dipalmitoylphosphatidyl glycerol. CER-001 increased cholesterol efflux, promoted plaque regression and decreased inflammation in animal studies (Tardy *et al.*, 2014). Nevertheless, in a clinical trial, CER-001 failed to promote plaque regression 6 weeks after administration (Tardif *et al.*, 2014). Similarly, CER-001 could not promote plaque regression in patients with acute coronary syndrome 10 weeks after administration in

combination with statins (Nicholls *et al.*, 2018). CSL-111 is a rHDL which contains wild type apo A-I and phospholipids. It was capable of reducing inflammation and improving post-ischemic heart function in mice (Richart *et al.*, 2019; Bhushan *et al.*, 2012, 2014). Nevertheless, CSL-111 could not achieve plaque regression and increased markers of liver damage in humans (Tardif *et al.*, 2007). To avoid these adverse outcomes, a new formulation called CSL-112 was developed. It contains wild type apo A-I, POPC and sucrose serving as a stabilizing agent. CSL-112, when administered, demonstrated an augmentation in cholesterol efflux from macrophages (Diditchenko *et al.*, 2013). Furthermore, it was shown to achieve plaque correction in two human clinical trials (Tardif *et al.*, 2007; Waksman *et al.*, 2010). A mayor phase III clinical trial is presently underway (Korjian *et al.*, 2023). Fig. 6 shows the main rHDL preparations.

The principal rHDL-based therapies enumerated earlier exhibit notable distinctions in their composition, dosing regimens, pharmacokinetic profiles, and pharmacodynamic properties. Numerous multifaceted factors could underlie the ineffectiveness of certain of these therapies. Initially, the study duration might have been insufficient to yield meaningful results. Additionally, the dosage employed might have been inadequate to achieve the desired therapeutic effect, or the frequency of administration may not have been sufficient. Furthermore, it is well-established that oxidative

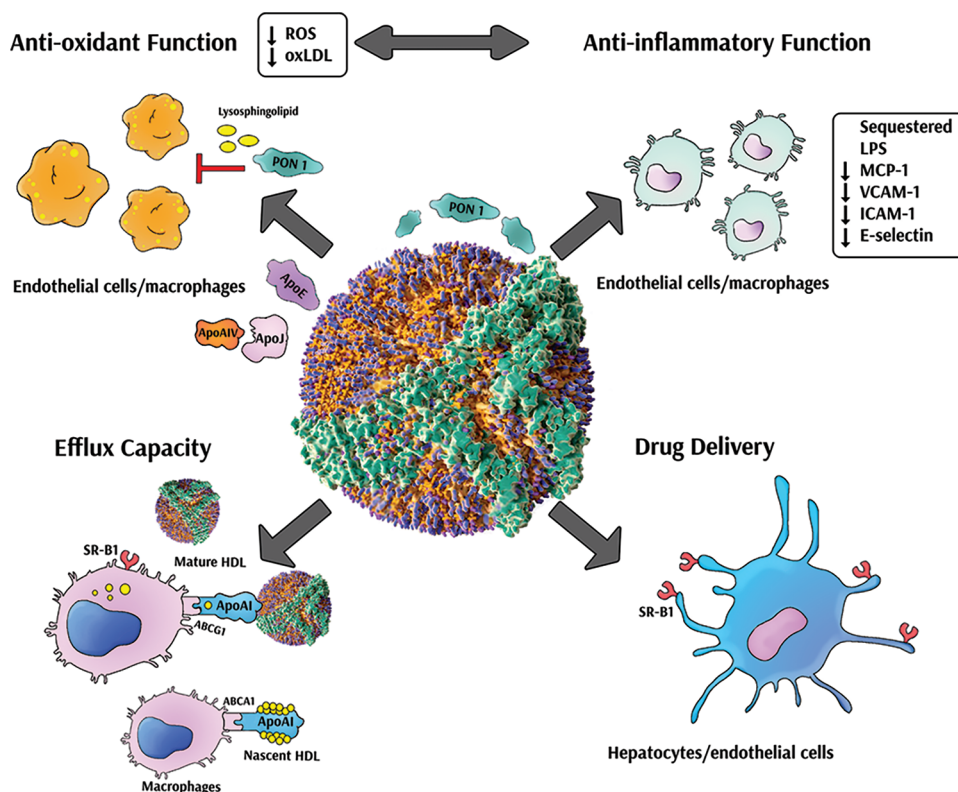


FIGURE 7. Multiple properties of reconstituted high density lipoproteins. Reconstituted high density lipoproteins (rHDL) present several atheroprotective effects. Some rHDL present potent antioxidant activity leading to reduced radical oxygen species (ROS) production in cells and decreased oxidized LDL (oxLDL) formation. Furthermore, rHDL can inhibit the secretion of cytokines and adhesion molecules in different cell types. In addition, rHDL have remarkable capacity to promote cholesterol efflux and reverse cholesterol transport. Finally, rHDL represent an efficient vehicle for drug delivery to multiple target cells. PON 1, paraoxonase 1; apo, apolipoprotein; LPS, lipopolysaccharide; MCP-1, monocyte chemoattractant protein 1; VCAM-1, vascular cell adhesion molecule 1; ICAM-1, intercellular adhesion molecule 1; ABCA1, ATP binding cassette subfamily A1; ABCG1, ATP binding cassette subfamily G1; SRB1, scavenger receptor class B type 1.

THERAPIES	CHOLESTEROL EFFLUX	ANTI-INFLAMMATORY ACTIVITY	ANTI-OXIDANT ACTIVITY
NIACIN	+	+	NO EVIDENCE AVAILABLE
CETP INHIBITORS	+	NO EVIDENCE AVAILABLE	NO EVIDENCE AVAILABLE
PCSK9 INHIBITORS	? *	? *	NO EVIDENCE AVAILABLE
RECOMBINANT LCAT	+	+	NO EVIDENCE AVAILABLE
STATINS	+ / = **	NO EVIDENCE AVAILABLE	+ / = **
PIOGLITAZONE	+	NO EVIDENCE AVAILABLE	+
METFORMIN	+	+	+
APO A-I MIMETICS	+	+	+
RECONSTITUTED HDL	+	+	NO EVIDENCE AVAILABLE

FIGURE 8. Action of different therapies on HDL functionality. CETP, cholesteryl ester transfer protein; PCSK9, proprotein convertase subtilisin/kexin type 9; LCAT, lecithin:cholesteryl acyl transferase; apo, apolipoprotein; HDL, high density lipoprotein. *Controversy in different studies. Need of a deeper understanding of the mechanisms involved. **Depends on the statin employed.

stress and inflammation have the capacity to modify the composition and functionality of HDL, potentially compromising its atheroprotective properties following administration (Huang *et al.*, 2020). A recent meta-analysis which included studies carried out in both humans and animal models showed that HDL/apo A-I replacement therapy was not associated with decreases in atheroma volume in humans, but it did associate with changes in lesion area in mice (Abudukeremu *et al.*, 2021). The authors conclude that further studies are necessary to explain the differences between animals and humans.

An important factor that could affect rHDL performance is the type of apo A-I employed. Indeed, in recent years, different formulations of rHDL which employ synthetic apo A-I mimetics instead of naturally occurring apo A-I have been developed. One of these preparations employs the aforementioned 18 A peptide, known for its antioxidant capacity (Hogarth *et al.*, 2003). Other rHDL preparations have included the 5A peptide and have shown promising results in animal models by triggering plaque regression (Schwendeman *et al.*, 2015; He *et al.*, 2021). One preparation which has received much attention is etc-642, which includes the mimetic 22A, specifically engineered to activate LCAT. This preparation was shown to greatly increase HDL-C levels in dyslipidemic patients (van Capelleveen *et al.*, 2014). In a recent study, authors tested the ability to promote cholesterol efflux and esterification of 3 of these preparations and found that the mimetics with the highest capacity to promote both steps of RCT *in vitro* could no replicate those results *in vivo* (Yuan *et al.*, 2023). These findings underscore the significance of both

pharmacodynamics and pharmacokinetics in determining the effectiveness of rHDL formulations. Similar to apo A-I mimetics, a main disadvantage of rHDL is the need to be administered intravenously, which could affect patient adherence (Huang *et al.*, 2020).

In recent years, rHDL preparations have received great interest as delivery mechanisms for drugs and different biomolecules (Huang *et al.*, 2020). Indeed, rHDL can efficiently deliver drugs to macrophages and atherosclerotic plaques. In mice, rHDL was capable of efficiently deliver simvastatin to atherosclerotic plaques, leading to a decrease in inflammation, plaque regression and an increase in the half-life of statins (Duivenvoorden *et al.*, 2014). Moreover, rHDL particles have been developed for the delivery of antisense nucleotides and small interference RNA (Raut *et al.*, 2018; Lacko *et al.*, 2015). Fig. 7 shows the main properties of rHDL preparations.

Concluding Remarks and Future Perspectives

LDL-C levels have historically been the target for therapies aimed at reducing CVD risk. Nevertheless, despite the remarkable reductions in LDL-C levels achieved with drugs such as statins and PCSK9 inhibitors, significant residual risk persists. On the other hand, therapies aimed at increasing HDL-C have, for the most part, failed to achieve CVD reduction. When added together, these facts have made HDL functionality a therapeutic target of the utmost interest. Indeed, several drugs described in the present review have shown promising results in enhancing HDL functionality. Fig. 8 shows the main drugs capable of

enhancing HDL functionality. These drugs include molecules already approved for human use, such as statins and niacin, and, particularly, compounds currently undergoing development such as several apo A-I mimetics and rHDL preparations. Indeed, there are currently over 150 mimetic peptides at some stage of development, in addition to several rHDL preparations. These therapies show promising potential to specifically improve HDL functionality. Moreover, rHDL has the added benefit of notably improving drug delivery to the intended organ/tissue, enhancing therapeutic response. Nevertheless, pharmacogenomic data on these drugs is still scarce and further studies on the effect genetic variants have on their efficacy are needed. Moreover, studies analyzing ethnic differences in the response to these drugs are lacking and minorities are underrepresented. More genetic studies are necessary to establish a better therapeutic alternative both on a population and on an individual level. Nevertheless, evidence is strong and future therapeutic strategies should incorporate HDL functionality as a main target of interest, seeking a balance between these new parameters and traditional quantitative markers such as HDL-C, in order to achieve a better assessment of CVD risk and its management. Finally, the focus on HDL functionality could extend the benefits of these drugs beyond CVD management and into the treatment of several other illnesses, such as cancer, endocrine disorders, and autoimmune diseases.

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