

# HDL therapies — past, present and future

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**Abstract:** For a number of years, high-density lipoprotein (HDL) has been recognized to have an athero-protective role by promoting reverse lipid transport, a process facilitating the cholesterol efflux from atherosclerotic plaques in the artery wall and its elimination by the liver via biliary excretion.

On the contrary, low-density lipoprotein (LDL) particles carry cholesterol to the organs and tissues where it can be used to produce hormones or maintain cell metabolism. When an imbalance develops, as a result of either an excess level of cholesterol associated with LDL (LDL-C) or a less effective cholesterol elimination by HDL (HDL-C), this causes an excess of cholesterol to be transported to the tissues and promotes the deposition of cholesterol. This often occurs in the artery walls, particularly in the coronary arteries. There is no approved medical treatment for directly suppressing or treating the atherosclerotic plaque once it is formed. Epidemiological studies have shown that the risk of developing cardio-vascular disease (CVD) is higher in patients with low levels of HDL-C regardless of LDL-C levels, even in patients optimally treated with LDL-C-lowering therapies. These data highlight that low HDL-C and low HDL particle number is an important target of therapies aiming to reduce the residual risk of CVD.

**Keywords:** high-density lipoprotein, low-density lipoprotein, apolipoprotein A-I, atherosclerosis, cholesterol, P2Y receptors

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## 1. Introduction

The main cholesterol transporters in the blood are lipoproteins, especially low-density lipoprotein (LDL) and high-density lipoprotein (HDL) particles. LDL particles carry cholesterol to the organs and tissues where it can be used to produce hormones, maintain cell metabolism or be metabolized into, for example, biliary acids. HDL particles take excess cholesterol from the tissues by a pathway called reverse lipid transport (RLT), and carry it to the liver for either storage, recycling or elimination<sup>[1]</sup> (Figure 1). An HDL is a complex containing apolipoprotein (apo) A-I and phospholipids bound together to form a nanoparticle synthesized in the liver or the bowel. The newly synthesized complex (called a pre- $\beta$  HDL particle<sup>[2]</sup>) comprises a negatively charged nascent disc-shaped particle of several nanometers in

diameter. In the circulation, the empty nascent pre- $\beta$  HDL particle captures cholesterol and other lipids and transforms into a spherical particle, known as mature HDL (Figure 2).

In young healthy individuals, the production and elimination of cholesterol are in equilibrium. However, with increasing age and rich diet, an imbalance often develops, as a result of either an excess level of cholesterol associated with LDL (LDL-C) or a less effective cholesterol elimination by HDL (HDL-C). This imbalance causes an excess of cholesterol to be transported to the tissues and promotes the deposition of cholesterol. This may occur throughout the tissues of the body, but often occurs in the artery walls, particularly in the arteries that supply the heart muscle<sup>[3]</sup>. The resulting cholesterol deposits can cause potentially life-threatening complications, such as vascular

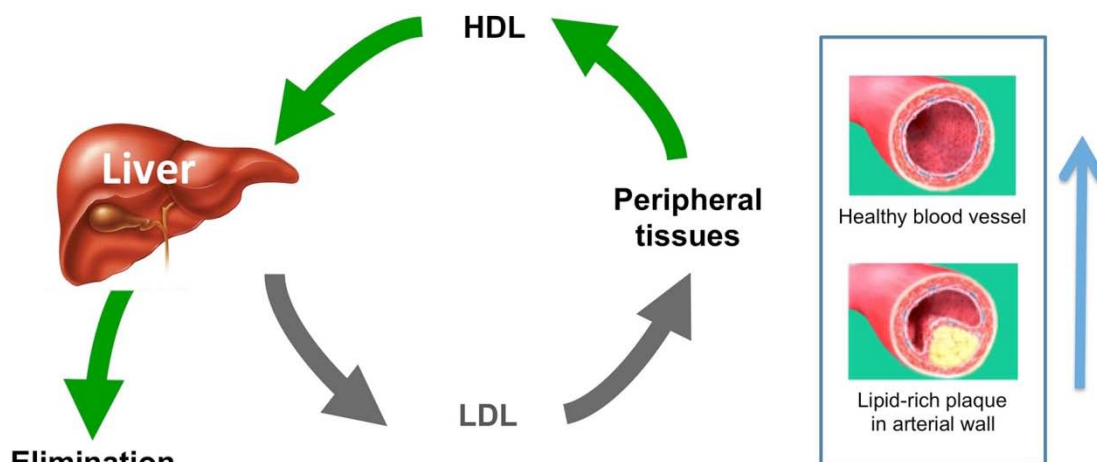


Figure 1 Cholesterol cycle.

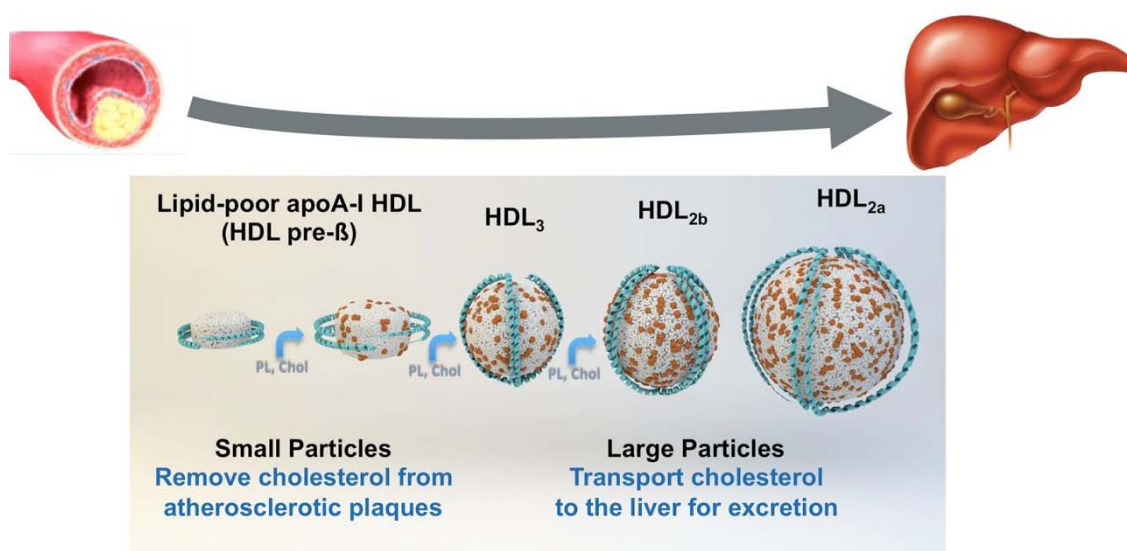


Figure 2 HDL maturation pathway.

inflammation and the formation of atherosclerotic plaques, which may stenose or narrow the arteries causing chest pain on exertion or even at rest. The unexpected rupture of a plaque can result in sudden obstruction of these arteries, leading to acute coronary syndrome (ACS), unstable angina pectoris or a myocardial infarction (MI), and could be fatal. Despite secondary prevention measures, including drugs such as aspirin and other antiplatelet agents, beta-blockers, angiotensin converting enzyme (ACE) inhibitors and statins, the cardiovascular event recurrence rate in post-ACS patients remains high, particularly within the first few weeks post the initial ACS event. This highlights the significant unmet medical need in this patient group.

The process of cholesterol accumulation takes place

over many years, even decades, and individuals may remain asymptomatic for long periods of time despite developing significant risk of cardiovascular disease (CVD). The imbalance in cholesterol regulation may be exacerbated by other CVD risk factors including gender, hypertension, smoking, diabetes, obesity, genetic predisposition, physical inactivity and a high-fat diet<sup>[4]</sup>. Consequently, a healthy low-fat diet, especially low in saturated fats, not smoking, physical activity and reduced stress are among public health recommendations to lower the risk of CVD<sup>[5]</sup>.

There is no approved medical treatment for directly suppressing or treating the atherosclerotic plaque once it is formed. Mechanical removal of the atherosclerotic plaques (rotatory atherectomy) or restoring the artery diameter by using a stent may be performed.

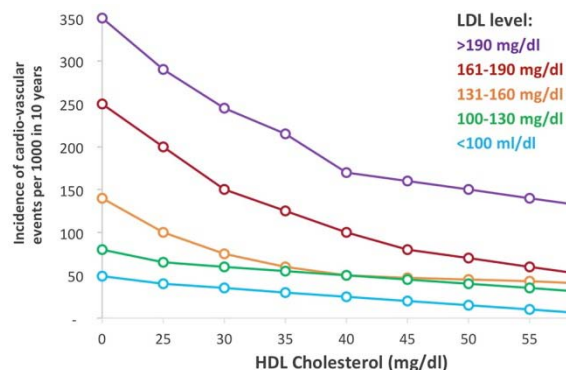
However, these invasive methods only treat the disease locally, while other vessels may also be loaded with plaque. These local procedures cannot treat a disease such as atherosclerosis, which is systemic and marked by accumulation of cholesterol in all vessel walls, with multiple plaques in several vascular beds. Atherosclerotic disease is treated indirectly by reducing cholesterol levels in the blood. Current medical recommendations for the treatment of excessive cholesterol include pharmacotherapy with LDL-C-lowering agents such as statins, inhibitors of PCSK9 preventing LDL receptor elimination (proteolysis), bile-acid sequestering resins and intestinal cholesterol absorption inhibitors. These aim to reduce LDL-C levels in the circulation, with the long-term goal of limiting or preventing continued accumulation of cholesterol in the vessel walls. These preventative strategies have proven efficacy for reducing CVD events by one third, and have become the standard of care recommended by health authorities for the treatment of CVD risk.

An important limitation of LDL-C-lowering therapies is that, in most patients, treatment is initiated around age of 30 to 40 years, when cholesterol has already been accumulating in their vessel walls for decades. In addition, these treatments have only a modest effect on regression of the atherosclerotic plaque<sup>[6]</sup> which is only achieved when very low levels of LDL-C (< 70 mg/dL) are attained with high doses of the most potent statins administered for several years. Such low LDL-C levels are often not attainable either because of the increased risk of side effects at higher doses or because of poor compliance with long-term treatment<sup>[7]</sup>. The recent results of the clinical trial IMPROVE-IT, conducted in patients who had experienced an ACS, demonstrated the difficulty in achieving further CVD risk reduction with intensive LDL-C lowering. In this study, long-term combination therapy (ezetimibe plus simvastatin for 7 years) to achieve an additional LDL-C reduction of 15–20% compared with simvastatin alone, resulted in only a small reduction (2%) in absolute risk of the primary endpoint of CVD death, nonfatal MI, unstable angina, coronary revascularization or stroke (32.7% and 34.7%, respectively)<sup>[8]</sup>.

The findings of IMPROVE-IT<sup>[9,10]</sup>, and those of other LDL-C-lowering studies, have highlighted that despite the one-third reduction in risk with LDL-C lowering, CVD risk remains high in patients whose LDL-C levels are below target level. Consequently, many patients who have a CVD event present with relatively “normal” LDL-C levels. There is a still a

significant unmet medical need for addressing the remaining two-thirds of CVD risk<sup>[11]</sup>. This presents an opportunity for new therapies, which may directly eliminate atherosclerotic plaque, to reduce the risk of CVD. Recently, PCSK9 inhibitors, monoclonal antibodies directed against PCSK9 enzyme, were approved to treat high risk patients with CVD. They are very effective in lowering LDL-C on top of standard of care, and safety and effect on CV outcome are currently being evaluated in long term studies. It is however unlikely that the CVD risk will be completely abolished as the cause for atherosclerotic plaque is multifactorial and LDL lowering has limited effect on already present plaques.

One factor that contributes to the residual risk of CVD is cholesterol imbalance resulting from a defect in cholesterol elimination by HDL particles rather than by an “excess” of cholesterol transported by LDL particles. The protective role of HDL particles has been demonstrated in several epidemiological studies (FRAMINGHAM, MONICA, and PROCAM). These studies have shown that the risk of developing CVD is higher in patients with low levels of HDL-C regardless of LDL-C levels, even in patients optimally treated with LDL-C-lowering therapies (Figure 3)<sup>[12,13]</sup>. Other large-scale studies have demonstrated that the level of apoA-I (the main protein in HDL particles) represents a better predictive factor of CVD events. Recently, the number of HDL particles rather than the amount of HDL-C was demonstrated to be more relevant to protect against CVD (MESA trial<sup>[14]</sup>) including in patients treated with statins (JUPITER trial<sup>[6]</sup>). These studies are part of a large body of clinical evidence demonstrating the cardio-protective role of HDL (in particular the number of HDL particle) and the value



**Figure 3.** CVD risk predicted versus HDL-C and LDL-C levels in the PROCAM study. Data were from 7152 males between 35–65 years of age. The total of coronary events in 10 years was of 406<sup>[13]</sup>.

of low HDL-C levels for predicting elevated CVD risk at the individual patient level<sup>[15–18]</sup>. For example, low levels of HDL-C (e.g., < 0.90 mmol/L or 35 mg/dL) are associated with a particularly elevated risk of death due to CVD, corresponding to 4.1-fold increased risk in men and 3.1-fold in women<sup>[17]</sup>.

These data highlight that low HDL-C and low HDL particle number are important targets of therapies aiming to reduce the residual risk of CVD.

## 2. Strategies for Managing Patients with Low HDL-C

Therapeutic treatment options for managing patients with low HDL-C levels and low HDL particle number are currently limited, although several compounds targeting HDL are currently in clinical development.

Increasing the number of functional HDL particles represents an important therapeutic approach for the next major advance in treating atherosclerosis. There are two main strategies for increasing functional HDL. The first approach is to use HDL mimetic therapy based on administration of small, empty and functional pre- $\beta$  HDL particles to increase the overall transport capacity for cholesterol, and thereby increase its elimination. The second strategy is focused on the use of small molecules to increase the number of HDL particles. Recently, activation of the P2Y<sub>13</sub> receptor (P2Y<sub>13</sub>R) has been shown to directly increase the uptake of HDL-C by the liver facilitating elimination of lipids. Consequently, P2Y<sub>13</sub>R agonists have potential for improving RLT.

### 2.1 Therapies that Increase the Number of Functional HDL

#### 2.1.1 HDL Mimetics

During the last two decades, several attempts have been made to develop an HDL mimetic capable of inducing regression of atherosclerotic plaques. These treatments were mainly designed to optimize cholesterol mobilization and for treatment of patients post ACS. HDL mimetic therapy in post-ACS patients should increase cholesterol transport via the RLT pathway by providing an additional capacity to eliminate cholesterol by infusing pre- $\beta$  HDL particles and thus to reduce atherosclerotic plaques throughout the body vessels. The elimination of cholesterol accumulated in the vessel wall, especially during the acute phase of increased vulnerability to cardiovascular recurrence post-ACS, has the potential to result in a rapid and

significant reduction in atherosclerotic plaques, and stabilization of the lesions leading to less recurrent events.

The importance of using/creating functional HDL particles was highlighted recently by the report by Voight *et al.*<sup>[19]</sup> showing that the sole increase in the HDL-C in humans, will not necessarily improve the protection against myocardial infarction<sup>[19]</sup>. Standard assays to evaluate LDL-C and HDL-C quantify the cholesterol content within the respective lipoprotein fractions which only indicates the distribution of cholesterol in different lipoprotein particles at a given time. However, these measures do not indicate if the lipoprotein particles are functional and actively transferring cholesterol to the liver for elimination. Both LDL particles (LDL-p) and HDL particles (HDL-p) vary in their content of cholesterol, and thus determining the number of lipoprotein particles may be more predictive than estimating the cholesterol concentration in assessing the cardiovascular risk. This hypothesis was supported by the data from the Framingham offspring study on LDL-C<sup>[20]</sup> and more recently for HDL-C in the MESA (Multi-Ethnic Study of Atherosclerosis) trial<sup>[14]</sup>. This report demonstrated a more consistent inverse association between cardiovascular endpoints and HDL-p compared with HDL-C. These findings suggest that a direct quantification of the concentration of HDL-p may be more useful to define the cardiovascular risk and to evaluate novel HDL-directed therapies which could modulate such lipoprotein particles metabolism<sup>[21]</sup>.

The first randomized trial of HDL infusion in humans examined the effects of intravenous administration of recombinant apolipoprotein (apo) A-I<sub>milano</sub> (a naturally occurring mutated form of human apoA-I with Arg-173 to Cys substitution) in a complex with synthetic phosphatidylcholine (ETC-216). This apoA-I<sub>milano</sub> complex produced a significant reduction over baseline in coronary atherosclerosis as measured by intravascular ultrasonography (IVUS)<sup>[22]</sup>. Another study, using purified apoA-I from human plasma combined with soybean phosphatidylcholine (CSL-111), showed significant improvements in the plaque characterization index and coronary score on quantitative coronary angiography in humans<sup>[23]</sup>. This observation, was confirmed in a trial in which atherectomy to excise plaque was performed on the superficial femoral artery of patients ( $n = 10$ ) with claudication. Significant improvement of the lipid content, the macrophage size and inflammation markers of the plaques were ob-



served after a single infusion of CSL-111 80 mg/kg<sup>[24]</sup>. Recently, three clinical trials have examined the effects of CER-001, a negatively charged lipoprotein complex consisting of phospholipid and recombinant human apoA-I that mimics the structure and function of natural HDL. Infusion of CER-001 was observed to improve carotid wall thickness of patients with familial hypercholesterolaemia<sup>[25]</sup> and those with hypo-alphalipoproteinaemia<sup>[26]</sup>. CER-001 also improved coronary plaque burden measured by IVUS at the lowest tested dose (3 mg/kg) versus baseline and versus placebo in post-ACS patients<sup>[27,28]</sup>. The results of studies with CER-001 are reviewed elsewhere<sup>[29]</sup>.

### 2.1.2 Small-molecule HDL-increasing Therapies

There have been several attempts to increase the HDL-C levels using pharmacological intervention. HDL-C levels have been reported to be increased upon chronic administration of fibrates in animals and also in humans<sup>[30]</sup>. Niacin is the only drug that has been available for patients to raise HDL-C<sup>[31]</sup>. However, recent data from large clinical trials with niacin did not show any significant improvement in the cardiovascular risk over statins, commonly used for lipid management<sup>[32]</sup>.

#### (1) RVX-208

RVX-208 (Resverlogix Corp) induces the synthesis of apoA-I by selectively binding to the bromodomains of bromo and extraterminal (BET) transcriptional regulators<sup>[33]</sup>. In ASSERT, a Phase II study involving 299 patients, RVX-208 administered over 12 weeks failed to meet its primary endpoint (i.e., the percent change in ApoA-I from baseline for each treatment arm compared to placebo) and did not increase HDL by the magnitude expected. The highest dose of RVX-208 (300 mg/day) increased apoA-I by only approximately 4.5% and HDL by approximately 7%. In addition, a number of RVX-208-treated patients experienced elevations in transaminases, a marker of liver injury, to at least three times above the upper limit of normal, compared with no rise in the placebo group<sup>[34]</sup>.

Recent findings of the Phase II(b) trial, ASSURE, indicate that RVX-208 does not appear to induce regression of atherosclerotic plaque. This study examined the effect of treatment on plaque regression in 324 high-risk CVD patients over 6 months. The study did not meet its primary endpoint, namely a 0.6% change in percent atherosclerotic volume (PAV) as determined by IVUS<sup>[35]</sup>. In a post-hoc analysis of this study, regression of atherosclerotic plaque as meas-

ured by the change from baseline in PAV0(75%) and total atherosclerotic volume (TAV;  $-6.3 \text{ mm}^3$ ) was observed in patients with high levels of C-reactive protein (CRP) treated with RVX-208. The comparison with placebo was not reported. When data on major adverse cardiovascular events (MACE) from both ASSURE and another RVX-208 Phase II study, SUSTAIN<sup>[36]</sup>, were combined ( $n = 499$ ), the rate of MACE in patients treated with RVX-208 ( $n = 331$ ) was lower compared with patients receiving placebo ( $n = 168$ ; 6.74% vs 15.09%;  $p = 0.02$ )<sup>[37]</sup>. Furthermore, in patients with CRP greater than 2.0 mg/dL ( $n = 283$ ), The benefit of RVX-208 treatment appeared more pronounced and the rate of MACE was 6.42% in RVX-208-treated ( $n = 179$ ) compared with 20.53% in the placebo group ( $n = 104$ ;  $p = 0.007$ ).

A Phase III study of RVX-208 (BETonMACE) has recently been initiated. This multi-center, double-blind, randomized, parallel-group trial will compare treatment with RVX-208 100 mg twice daily for up to 104 weeks compared with placebo in high-risk type 2 diabetes mellitus patients with coronary artery disease (CAD). The primary endpoint is the time to first occurrence of MACE.

#### (2) CETP Inhibitors

Agents in the “-cetrapib” class increase HDL-C by inhibition of cholesteryl ester transfer protein (CETP), a protein that plays a key role in modulating the exchange of cholesteryl esters (CE) and triglycerides. There is intense debate in the scientific community about whether inhibition of CETP, which increases cholesterol content and therefore the size of the HDL particle by enhanced CE transfer via LDL particles, is actually effective at improving the RLT pathway and ultimately resulting in plaque regression. Some experts contend that the HDL particles becomes so overloaded with cholesterol by this mechanism that the “constipated” particles become non-functional and are no longer able to unload cholesterol in the liver. Several agents in this class have been examined in clinical trials, three agents failed to show reduction of CV outcome and only anacetrapib and Dezima 001 (also initially named TA-8995) remain in late stage clinical development.

Torcetrapib (Pfizer) was developed for use in combination with atorvastatin. Torcetrapib decreased LDL-C levels by approximately 15% and increased HDL-C levels by 50–100% depending on the dose. A limiting adverse effect of torcetrapib was a significant rise in

blood pressure. The compound was tested in a large Phase III study, ILLUMINATE, to examine its impact on atherosclerotic events<sup>[38]</sup>. Despite increasing HDL-C and reducing LDL-C, the combination of atorvastatin and torcetrapib increased rather than decreased MACE compared with atorvastatin alone. The trial was terminated prematurely due to increased cardiovascular events and mortality in the torcetrapib arm. Other clinical studies and follow-up analyses clarified that the observed adverse cardiovascular events were compound specific and that pursuing further clinical development with other compounds was possible.

Dalcetrapib was developed by Roche after being licensed from Japan Tobacco. It produced relatively modest effects on the lipid profile in Phase II studies. dal-PLAQUE, a Phase II imaging study of dalcetrapib in patients with, or at high risk of, coronary heart disease (CHD) showed only a modest decrease in plaque volume after 24 months<sup>[39]</sup>, smaller than that achieved with high-dose statin treatment over the same time period. Development of Dalcetrapib was halted in 2012 following an interim analysis that concluded the Phase III trial, dal-OUTCOMES as dalcetrapib failed to show a reduction in the rate of cardiovascular events compared with placebo<sup>[40]</sup>.

Anacetrapib (Merck) is currently in Phase III clinical development. The results of a Phase II study with anacetrapib, DEFINE, were published in 2010<sup>[41]</sup>. At 24 weeks, anacetrapib decreased LDL-C by 40% and increased HDL-C by 138% in patients with, or at risk of, CHD, who were already treated with a statin. There was no significant difference in blood pressure between the patients treated with anacetrapib versus placebo. REVEAL, a large-scale clinical study is currently ongoing and Merck plans to submit its marketing authorization request in 2015 or 2016. The important finding that anacetrapib accumulates in adipose tissues due to the strong intrinsic lipophilicity of the component was reported recently. Although no specific safety findings have been noted so far, this observation may have substantial implications on its future clinical development.

Evacetrapib (Lilly) was in Phase III development until very recently. Data from a 400-patient Phase II trial designed to assess the impact on efficacy (LDL-C and HDL-C) and safety, of adding different doses of the compound to standard statin doses were reported in 2011<sup>[42]</sup>. In this study, evacetrapib was tested for 12 weeks, alone or in combination with simvastatin 40 mg/day, atorvastatin 20 mg/day or rosuvastatin 10 mg/day in patients with elevated LDL-C or a low level

of HDL-C. Evacetrapib alone produced a dose-dependent increase in HDL-C from 53.6% to 128.8% and a decrease in LDL-C of between 13.6% and 35.9%. When given in combination with a statin, Evacetrapib produced increases in HDL-C of 78.5% to 88.5% and decreases in LDL-C of between 11.2% and 13.9% compared with statin monotherapy. The Phase III trial, ACCELERATE, was a multi-center, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of evacetrapib in participants ( $n = 12,095$ ) with high-risk atherosclerotic CVD. The primary outcome measure was time to first occurrence of cardiovascular death, MI, stroke, coronary revascularization, or hospitalization for unstable angina. The study was terminated recently on the advice of the independent data monitoring committee because of a lack of efficacy in the interim analysis. The failure of this trial raises the question of whether lack of efficacy for reducing CVD events is a class effect of these compounds. This study raised also the question about the validity of measuring cellular cholesterol efflux capacity as a predictive marker of CVD risk as both dalcetrapib and evacetrapib increase cellular cholesterol efflux capacity but failed to reduce CVD risk. Such results also raised the concern that the LDL-C lowering (on top of statin therapy — see above) is not always linked to CVD risk.

TA-8995 is a less lipophilic compound that was licensed from Mitsubishi Tanabe Pharma by Dezima, a Dutch biotechnology company. Positive effects of this compound on HDL-C were recently reported from a small Phase II(b) study as 364 patients were enrolled. At week 12, LDL cholesterol levels were reduced in a dose-dependent manner between 27.4% to 45.3% at the 10 mg dose. LDL cholesterol levels were reduced by 68.2% in patients given 10 mg TA-8995 plus atorvastatin, and by 63.3% in patients given rosuvastatin plus 10 mg TA-8995. A daily dose of TA-8995 increased HDL cholesterol levels between 75.8%, up to 179.0%. In patients receiving 10 mg TA-8995 and 20 mg atorvastatin HDL cholesterol levels increased by 152.1% and in patients receiving 10 mg TA-8995 and 10 mg rosuvastatin by 157.5%. No serious adverse events or signs of liver or muscle toxic effects were recorded<sup>[43]</sup>.

## 2.2 Therapies that Directly Increase Removal of Lipids by the Liver

### P2Y<sub>13</sub>R Agonists

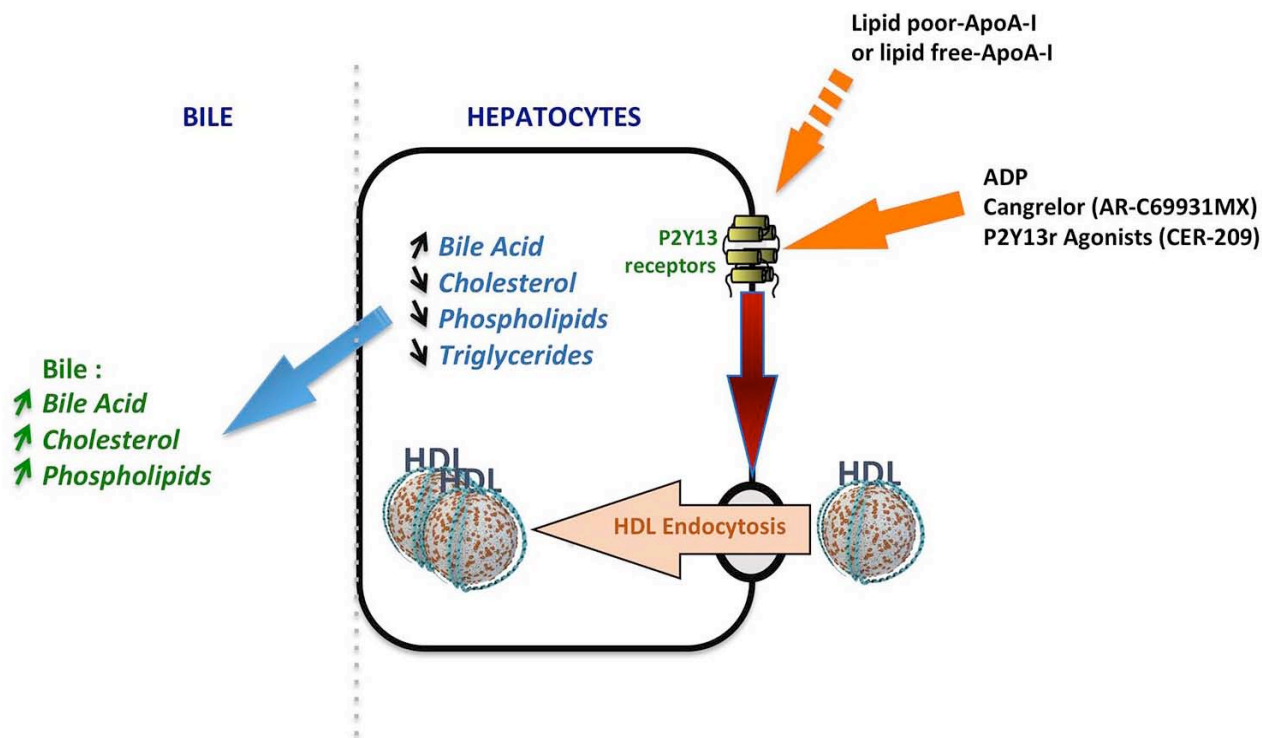
The discovery of F<sub>1</sub>-ATPase and the P2Y<sub>13</sub>R in the

liver, which regulates recognition of HDL-C, added to our understanding of HDL metabolism and identified new therapeutic targets for treating atherosclerosis. Indeed, a nucleotidase activity of ectopic F1-ATPase subunit presents at the cell surface of hepatocytes, allows the hydrolysis of ATP to ADP which in turn stimulates the P2Y13R resulting in the uptake of the HDL by the cells<sup>[44,45]</sup>. The P2Y13R receptor belongs to the well-known family of the P2Y receptors, which includes P2Y12R, target of successful platelet anti-aggregation drugs.

*In vitro* and *in vivo* tests have demonstrated the increased HDL-C uptake by liver cells (hepatocytes) upon stimulation of the activity of HDL receptors in the liver and hence increasing the RLT by promoting HDL recognition by the liver. This causes a decrease in the circulating HDL-C levels (mature HDL particles loaded with cholesterol) and leads to increased elimination of cholesterol in the feces, which should have a beneficial effect on atherosclerosis by reducing further cholesterol accumulation. Instead of “pushing” the cholesterol to the liver by increasing the number of HDL particles transporting cholesterol, as with HDL

mimetics, increasing P2Y13R activity would result in better “traction” of HDL-C being “pulled out” of the body by the increased activity of the liver receptors (Figure 4). Another potential benefit of this increase in P2Y13R activity is an improvement in overall liver metabolism because the increased cholesterol flow to the liver would be accompanied by an increase in gallbladder secretion of cholesterol and lipids. This, in turn, translates into a decrease in triglycerides and cholesterol levels in the serum and in the liver<sup>[46]</sup> and would result in a “healthier” liver.

Preclinical studies of the P2Y13R agonist, CER-209, have shown that it increases elimination of mature HDL particles loaded with cholesterol, and this effect is accompanied by a compensation in the synthesis of HDL, resulting in an increase in the number of small circulating HDL particles. In an atherosclerosis model in rabbits, 4 weeks of treatment with CER-209 induced a 30% regression of atherosclerotic plaques in the aorta as assessed by measuring the cholesterol content of the artery, and this was confirmed by immunohistological analysis<sup>[46]</sup>.



**Figure 4.** Hepatic P2Y13R receptor pathway. Lipid-free-apoA-I would bind to the ectopic F1-ATPase complex presents at the cell surface and induce local and transient ADP production which by stimulating the P2Y13R will in turn stimulate the HDL endocytosis. Consequently, lipids elimination will be increased in the bile. Some agonist of the P2Y13R were already described such as ADP, the ATP modified compound Cangrelor® (AR-C69931MX) or CER-209 an new class of P2Y13R agonists.

### 3. Conclusion

A residual risk of CVD remains in patients with LDL-C levels below recommended targets. Low HDL-C levels are associated with an increased risk of CVD. Therefore, targeting the removal of cholesterol from the body by increasing the number, or functionality, of HDL particles is an important therapeutic goal.

HDL mimetic therapy is based on infusion of small empty and functional pre- $\beta$  HDL particles to increase the overall transport capacity for cholesterol, thereby increasing cholesterol elimination. HDL mimetic therapy was mainly designed as acute post-ACS therapy. Studies have shown improvement in atherosclerotic plaque burden assessed by vascular imaging with infusion of HDL mimetics.

Small molecule HDL therapy promotes RLT by raising the number of HDL particles. It has potential as post-ACS therapy and also as a long-term treatment for the prevention of CVD. Most of the Phase III studies of small molecule HDL therapies, either CETP inhibitors or RXV-208, have been designed to examine the long-term effects of treatment. This is a tacit indication that these classes will more likely demonstrate benefit only over long-term chronic use; i.e. the primary effect is a gradual slowing of the progressive accumulation of cholesterol that will become manifest only over a substantial period of time. The lack of efficacy for reducing CVD event rate in Phase III studies of CETP inhibitors performed to date has called in to question the effectiveness of this mechanism of increasing HDL-C and decreasing LDL-C.

In contrast with compounds that increase the number of HDL particles, P2Y<sub>13</sub>R agonists improve RLT by increasing the uptake of cholesterol by hepatocytes, thereby promoting elimination of accumulated cholesterol and also facilitating the elimination of lipids in the bile. The preclinical data on P2Y<sub>13</sub>R agonists support their potential as pharmacological therapy for atherosclerotic disease and liver disease such as NAFLD (Non-Alcoholic Fatty Liver Disease) and NASH (Non-Alcoholic Steato-Hepatitis).

### Conflict of Interest and Funding

No conflict of interest has been reported by the author.

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