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HDL: To Treat or Not To Treat?

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Abstract Several studies have shown an inverse relationship between HDL cholesterol (HDL-C) levels and the risk of cardiovascular disease. Low HDL-C levels are commonly present in subjects with diabetes, metabolic syndrome, or obesity. These observations have suggested that increasing HDL concentrations might help in decreasing the cardiovascular disease risk. However, despite initial positive results, some recent data from clinical trials with HDL-raising therapies failed to confirm this hypothesis; in addition, data from Mendelian randomization analyses showed that nucleotide polymorphisms associated with increased HDL-C levels did not decrease the risk of myocardial infarction, further challenging the concept that higher HDL-C levels will automatically translate into lower cardiovascular disease risk. Differences in the quality and distribution of HDL particles might partly explain these findings, and in agreement with this hypothesis, some observations have suggested that HDL subpopulation levels may be better predictors of cardiovascular disease than simple HDL-C levels. Thus, it is expected that increased HDL-C levels may be beneficial when associated with an improvement in HDL function, suggesting that pharmacological approaches able to correct or increase HDL functions might produce more reliable clinical benefits.

Keywords High-density lipoprotein · Residual cardiovascular risk · Mendelian randomization · HDL-raising drugs · HDL quality · HDL quantity

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Introduction

Low levels of HDL cholesterol (HDL-C) are common in patients with a high cardiovascular risk, including those with acute coronary syndrome [1]. Reduced HDL-C levels are also common in obese subjects and patients with metabolic syndrome. Epidemiological studies have clearly shown that low HDL-C levels contribute to cardiovascular disease risk [2], and several clinical trials showed an inverse relationship between HDL-C levels and cardiovascular disease risk [2–6]. The analysis of four prospective studies revealed that each 1 mg/dL increment in HDL-C concentration is associated with a 2 % decrease in cardiovascular disease risk in men and a 3 % decrease in women [2].

This solid base of evidence [7, 8•], supported by extensive experimental and preclinical research [9, 10], led to the "HDL hypothesis," prompting research toward the development of HDL-related therapies with the aim of raising HDL-C levels and reducing the burden of atherosclerotic-related disorders.

In the last few years, data from Mendelian randomization analyses revealed that nucleotide polymorphisms associated with increased HDL-C levels in the population did not

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decrease the risk of myocardial infarction, despite a 13 % reduction expected from the increased HDL-C levels [11••]. Similarly, a genetic score combining 14 variants exclusively related to HDL-C showed no association with myocardial infarction risk [11••], further challenging the concept that higher HDL-C levels will automatically translate into lower cardiovascular disease risk. Furthermore, in the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial, niacin significantly increased HDL-C levels, but the trial was stopped because of the lack of efficacy [12]; a similar fate occurred for dalcetrapib, which in the dal-OUTCOMES trial, despite increasing HDL-C levels, showed a lack of clinically meaningful efficacy [13].

All these observations softened the enthusiasm for research into pharmacological tools linking HDL to cardiovascular diseases (CVDs). The aims of this review are to summarize the available evidence supporting or challenging the "HDL hypothesis," to discuss critically conditions where the functional properties of HDL and the subpopulation distribution rather than simply HDL-C levels should be considered, and to present the foremost therapeutic approach with drugs improving HDL function/levels.

HDL and CVDs, 50 Years of Research

Relationship of HDL-C Levels and CVD

Low plasma levels of HDL-C have been associated with increased cardiovascular risk [3, 14, 15] and represent an independent risk factor [16]. This independent relationship is maintained even after correction for other risk factors, including high triglyceride levels, diabetes, and obesity. The recommended HDL-C levels are greater than 40 mg/dL for men and greater than 50 mg/dL for women; a 1 mg/dL HDL-C increase is associated with significant coronary heart disease (CHD) risk reduction of 2 % in men and 3 % in women [2]. Low HDL-C levels are a common trait in the population, and represent a general lipoprotein abnormality in patients with metabolic syndrome, diabetes mellitus, and coronary artery disease [17–19].

Statin therapy, by reducing LDL cholesterol (LDL-C) levels, significantly reduces cardiovascular disease risk in both primary and secondary prevention [20–25]; nevertheless, statin-treated patients who reach very low levels of LDL-C still exhibit a residual cardiovascular disease risk if their HDL-C levels are low [17]. Moreover, statin-treated patients with low HDL-C levels have a higher incidence of major cardiovascular events compared with patients with higher HDL-C levels [26].

Several studies have shown an inverse relationship between HDL-C levels and cardiovascular disease risk (Table 1). In the Framingham Heart Study, the rate of CHD events is higher in patients with low HDL-C levels, independently of LDL-C levels [27]; in agreement, the Prospective Cardiovascular Munster (PROCAM) study showed that patients with HDL-C levels above 35 mg/dL had a 70 % reduced risk of developing CHD over 6 years compared with patients with HDL-C levels below 35 mg/dL [6]. The inverse relationship between HDL-C levels and cardiovascular disease risk has been supported by trials showing that pharmacological intervention to increase HDL-C levels had beneficial effects on major cardiovascular events in patients with established CHD and low HDL-C levels [28–32], atherosclerotic lesion regression being one major mechanism accounting for the observed benefits [33–36].

However, several studies failed to show a favorable effect of increasing HDL-C levels (Table 2). Two large studies failed to show reduction of the incidence of major cardiovascular events in patients treated with fibrates, despite a significant increase of HDL-C levels [29, 37]. Treatment with cholesteryl ester transfer protein (CETP) inhibitors yielded negative results: torcetrapib significantly increased HDL-C levels, but induced an increased risk of both cardiovascular events and death from any cause [38], probably due to an off-target toxicity of this drug independent of CETP inhibition [39]; dalcetrapib, which lacks the off-target effects of torcetrapib [40], despite causing an increase of HDL-C levels, failed to provide benefits to the patients, leading to the termination of the trial for futility [13]. Similarly, the AIM-HIGH trial was stopped early owing to lack of incremental clinical benefit of niacin added to statin therapy during 3 years' follow-up in patients with established CVD, despite the positive effect on lipid profile, including a rise in HDL-C levels [12].

HDL-Related Therapies and CVD

Nicotinic acid has broad lipid-modulating actions and for many years has been the principal available therapy, in addition of fibrates, which raises HDL-C levels. Following nicotinic acid therapy, HDL-C levels increase in a dose-dependent manner by up to approximately 25 %, whereas a reduction in both LDL-C levels (by 15–18 %) and triglyceride levels (by 20–40 %) was observed. Nicotinic acid is unique in lowering lipoprotein (a) levels by up to 30 %. It is therefore primarily used in subjects with low HDL-C levels as typical of mixed hyperlipidemia, hypertriglyceridemia, or familial combined hyperlipidemia, but may also be used in subjects with insulin resistance (type 2 diabetes and metabolic syndrome). Nicotinic acid has multiple beneficial effects on serum lipids and lipoprotein. In fact, nicotinic acid induces hepatic production of apolipoprotein A-I (apoA-I) and HDL [41]; furthermore, it inhibits HDL particle uptake and catabolism in the liver [42]. Nicotinic acid reduces hepatic VLDL and triglyceride secretion by several mechanisms: it decreases the flux of fatty acid from adipose tissue to the liver (due to the inhibition

Table 1 HDL and cardiovascular disease: epidemiological and genetic studies

Studies	Findings	References
General population	Subjects with low HDL-C levels had higher CAD risk The power of prediction decreases as LDL levels decrease	[6, 14, 27]
CHD subjects	High HDL-C levels were associated with the presence of dysfunctional HDL particles	[70]
Obese women	Presence of dysfunctional HDL in obese subjects	[78]
Type 1 diabetes	Linear decrease of CAD incidence with increasing HDL-C levels in men; in women, CAD incidence increased at HDL-C levels below 47 mg/dL and above 80 mg/dL	[73]
CETP deficiency	High levels of HDL-C due to CETP deficiency associated with lower prevalence of CHD in some studies but with increased risk of cardiovascular disease in others	[79–83]
IDEAL study	HDL-C levels directly correlated with occurrence of major cardiovascular events	[71]
ApoA-I_{Milano} variant	Carriers have very low HDL-C plasma levels without increase in IMT	[84]
Gene score associated with HDL-C	Genetic variants associated with increased HDL-C levels were not associated with reduced MI risk	[11••]
Mendelian randomization study	SNPs increasing HDL-C levels did not result in reduced ischemic heart disease risk	[11••]

apoA-I apoliprotein A-I, *CAD* coronary artery disease, *CETP* cholesteryl ester transfer protein, *CHD* coronary heart disease, *HDL-C* HDL cholesterol, *IMT* intima–media thickness, *MI* myocardial infarction, *SNPs* single-nucleotide polymorphisms

of hormone-sensitive lipase activity) [43]; it inhibits triglyceride formation in the liver (by inhibition of diacylglycerol acyltransferase); it increases apolipoprotein B catabolism, resulting in reduction in the levels of VLDL cholesterol and LDL-C.

Nicotinic acid may be used in combination with statins as a therapy for combined hyperlipidemia. Nicotinic acid is currently used mostly as an extended-release form. In patients with established CHD, the addition of extended-release niacin to statin therapy results in the stabilization of carotid intima–media thickness (CIMT), in contrast to the significant CIMT progression experienced by patients receiving statin monotherapy despite their having a mean baseline LDL-C level of 90 mg/dL [36]. CIMT regression was highly correlated with the degree of HDL-C level increase [33, 35].

Niacin use is limited by cutaneous flushing, a bothersome adverse effect. Flushing is the leading cause of discontinuation of therapy, estimated at 25–40 % or more [44, 45], and is mediated by prostaglandin D_2, a potent vasodilator. Prostaglandin D_2 binds to DP1 receptors in the skin. Extended-release niacin is associated with a lower frequency, intensity, and duration of flushing than immediate-release niacin [96-98]. Therefore, an antagonist of the DP1 receptor (laropiprant) which inhibits cutaneous flushing and significantly improves the tolerability of niacin by over 50 % was developed [46, 47]. Although the drug was approved for the treatment of patients with dyslipidemia in 2008, data from the AIM-HIGH trial showed that the addition of niacin to statin therapy did not induce an incremental benefit in patients with established CVD, low levels of HDL-C at the baseline, and

Table 2 Interventional studies with HDL-raising drugs

	Findings	References
Studies with positive results		
Helsinki Heart Study	Gemfibrozil increased HDL-C levels and reduced CHD risk	[85]
VA-HIT	Gemfibrozil increased HDL-C levels and reduced the risk of major cardiovascular events	[28]
BIP, FIELD	Fibrates increased HDL-C levels but did not reduce cardiovascular risk	[29, 86]
ACCORD Lipid	Fenofibrate reduced cardiovascular risk only in a subgroup of patients with low HDL-C and high TG levels	[30]
Meta-analysis of niacin trials	Niacin significantly reduced the composite end points of any CVD events (cardiac death, nonfatal MI, ACS, stroke, revascularization procedure) and major CHD events (nonfatal MI, cardiac death)	[87]
Studies with negative or neutral results		
ILLUMINATE (torcetrapib)	72 % increase in HDL-C level. Increased risk of cardiovascular events and death from any cause	[38]
dal-OUTCOMES (dalcetrapib)	31-40 % increase in HDL-C level. No reduction in the risk of recurrent cardiovascular events	[13]
AIM-HIGH (extended-release niacin)	25 % increase in HDL-C level. No incremental clinical benefit from the addition of niacin to statin therapy	[12]
HPS2-THRIVE (extended-release niacin)	No significant reduction of the combination of coronary deaths, nonfatal MI, strokes, and revascularizations compared with statin therapy	[48]

ACS acute coronary syndrome, *CHD* coronary heart disease, *CVD* cardiovascular disease, *MI* myocardial infarction, *TG* triglyceride

levels of LDL-C at the target (below 80 mg/dL) [12] (Table 2). Two years ago, the results from the Heart Protection Study 2—Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE), after nearly 4 years of follow-up, showed that the combination (extended-release niacin/laropiprant) did not significantly reduce the risk of the combination of coronary deaths, nonfatal myocardial infarction, strokes, and coronary revascularizations compared with statin therapy, but it did significantly increase the risk of nonfatal but serious side effects [48]. This prompted the European Medicines Agency to suspend the authorization for use of niacin/laropiprant (Table 2). Thus, there is presently insufficient evidence from clinical trials to recommend HDL-targeted therapy for additional event reduction. However, there is no reason for suspending the use of niacin as an adjuvant therapy for reducing atherogenic lipoprotein burden in patients who have not reached their risk-stratified LDL-C and non-HDL-C targets.

What Has Emerged in the Last 5–10 Years Challenging the HDL Hypothesis?

Observational and epidemiological studies have consistently shown that plasma levels of HDL-C are inversely associated with CVD risk. Despite this, it is still unknown whether this class of lipoproteins is causally associated with cardiovascular protection or if these particles are not directly involved in the disease. Recent clinical trials and genetic studies have focused on this aspect, pointing out the importance of better understanding of the role of HDL-C in cardioprotection, in order to exploit the pharmacological potential of HDL-C-raising drugs in the treatment of CVDs.

Mendelian Randomization, Myocardial Infarction, and HDL

The major shortcoming that affects epidemiological studies is the presence of confounding factors that are difficult to control for and measure accurately. For this reason, epidemiological observations should be validated by data from randomized controlled trials. One alternative method is represented by a Mendelian randomization approach based on the availability of genetic traits specifically associated with the variable of interest [49]. The advances in genetics and the identification by a genome-wide screening approach of genetic variants associated with the lipid profile made it possible to apply this approach to the study of the effects of the different lipid factors on CVD risk. Specifically, the possible causal effect of plasma HDL-C levels on cardiovascular outcome has recently been studied using different single-nucleotide polymorphisms (SNPs) in genes that specifically modulate HDL-C metabolism, without interfering with other CVD risk factors. Recently Voight et al. [11••] used one SNP in the endothelial lipase gene (*LIPG* Asn396Ser) [50] and a genetic score calculated by combining 14 SNPs exclusively associated with HDL-C plasma levels to assess the impact of HDL-C on the risk of myocardial infarction (Table 1). *LIPG* Asn396Ser SNP was investigated in a total of 20,913 myocardial infarction cases and 95,407 controls; the subjects investigated have been enrolled in 14 case–control studies and six cohort studies. Carriers of the 396Ser *LIPG* gene variant (2.6 % frequency) showed higher HDL-C levels, ranging from 0.08 to 0.28 mmol/L per copy of the Ser allele in the four prospective cohort studies investigated. Other CVD risk factors, such as plasma LDL-C levels, triglyceride levels, systolic blood pressure, body-mass index, risk of type 2 diabetes, fasting glucose concentration, fibrinogen concentration, plasma C-reactive protein concentration, waist-to-hip ratio, and small LDL particle concentration, were not associated with *LIPG* Asn396Ser genotype. Given the association between HDL and myocardial infarction, the inherited increases in HDL-C levels in 396Ser carriers are expected to decrease the risk of myocardial infarction by 13 % [odds ratio (OR) 0.87, 95 % confidence interval (CI) 0.84–0.91]. However, the *LIPG* 396Ser variant was not associated with reduced risk of myocardial infarction in a meta-analysis of all six cohort studies (OR=1.10, 95 % CI 0.89–1.37, p=0.37), and the result was further confirmed in a meta-analysis that combined all prospective and case–control studies (OR=0.99, 95 % CI 0.88–1.11, p=0.85). These observations were reinforced by testing the relevance of two different sets of SNPs emerging from a genome-wide association study [51]. Thirteen genetic variants specifically affecting LDL-C plasma levels and 14 SNPs exclusively linked with HDL-C plasma levels were selected and combined in two groups, and for both a genetic score was calculated. A one standard deviation (SD) increase in LDL-C concentration due to genetic score was associated with the risk of myocardial infarction (OR=2.13, 95 % CI 1.69–2.69), in agreement with epidemiological observations (OR=1.54, 95 % CI 1.45–1.63, for a one SD increase in plasma LDL-C concentration), whereas a one SD increase in HDL-C concentration due to genetic score was not associated with the risk of myocardial infarction (OR=0.93, 95 % CI 0.68–1.26, p=0.63). These observations show that increased HDL-C plasma levels do not unequivocally translate into cardiovascular protection, and prompt a careful reconsideration of the role of HDL-C in CVD.

HDL and Residual Risk in High-Risk Patients

HDL-C plasma levels are a key determinant of cardiovascular disease risk in the general population. In contrast, the relevance of HDL-C as an independent predictor of the residual cardiovascular disease risk in high-risk patients treated with aggressive statin therapy is debated. In this field the results of clinical trials are

contrasting. In the PROVE IT-TIMI 22 trial, high-risk patients receiving high-dose statin therapy after acute coronary syndrome were enrolled and were monitored for 4 months for the recurrence of nonfatal acute coronary events or cardiovascular death. In this trial, the "on treatment" plasma levels of HDL-C and apoA-I did not provide any significant incremental prediction of residual cardiovascular disease risk [52]. Similar results were obtained in the low-risk population enrolled in the primary-prevention JUPITER trial. In patients treated with rosuvastatin, the association between "on-treatment" HDL-C plasma levels, divided by quartiles, and cardiovascular risk was null [hazard ratio (HR) 1.03, 95 % CI 0.57–1.87, $p=0.97$], whereas in the placebo-treatment arm of the population, HDL-C plasma levels were inversely related to vascular risk [53]. In a post hoc analysis of the TNT trial, the relationship between HDL-C plasma levels, divided by quintiles, and the incidence of cardiovascular events did not reach statistical significance ($p=0.05$) when patients treated with atorvastatin at 80 mg/day were considered (HR 0.81, 95 % CI 0.58–1.14) [54]. A similar finding was obtained in the recent Second Manifestation of Arterial Disease (SMART) study: low HDL-C levels were associated with increased cardiovascular disease risk only in patients with clinically manifest vascular disease that was untreated or was treated with the usual dose of lipid-lowering drugs; in contrast, in patients treated with intensive lipid-lowering therapy and exhibiting optimal LDL-C levels, low HDL-C levels were not a risk factor for recurrent vascular events [55••].

In contrast, a meta-analysis of 20 large trials found an independent inverse association between low HDL-C plasma levels and cardiovascular disease risk among statin-treated patients, with no modification by statin therapy [56]. This finding is in agreement with the recent results of a post hoc analysis from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial. In this population characterized by stable ischemic heart disease receiving optimal medical therapy, there was a significant inverse relationship between HDL-C levels and cardiovascular disease risk that persisted after intensive therapy with statins and was more prominent in patients achieving LDL-C levels below 70 mg/dL [57••].

The type or intensity of statin therapy does not explain this discrepancy; perhaps the "simple" measure of HDL-C levels may not represent the correct approach to define the real role of HDL in CVD, suggesting that the evaluation of HDL functions might provide additional information on residual cardiovascular risk.

The Failure of Torcetrapib and Dalcetrapib

CETP is an enzyme involved in the transfer of cholesteryl esters from HDL to LDL and VLDL; this process results in a reduction in the levels and remodeling of HDL particles and in an increase of LDL and VLDL levels. Furthermore, CETP transfers triglyceride from VLDL or LDL to HDL, resulting in the formation of triglyceride-enriched HDL, which is easily hydrolyzed by hepatic lipase, leading to triglyceride-rich small HDL particles that are cleared more rapidly from the circulation [58]. Under pathological conditions, including atherosclerosis, CETP activity is increased; moreover, in humans, CETP deficiency results in increased HDL-C levels. Together, these observations led to the concept that CETP inhibition is a powerful tool to increase HDL-C levels, decrease LDL-C and VLDL cholesterol levels, and reduce the development of atherosclerosis [59].

The first CETP inhibitor developed, torcetrapib, despite causing a 72 % increase in HDL-C levels, was withdrawn because of an increased risk of cardiovascular events and death from any cause in the Investigation of Lipid Levels Management to Understand Its Impact in Atherosclerotic Events (ILLUMINATE) trial [38] (Table 2). Retrospectively, this effect was attributed to an off-target effect of torcetrapib such as the raising of systolic blood pressure by an average of 5.4 mmHg [60], an effect associated with the stimulation of aldosterone synthesis via pathways independent of CETP inhibition [38, 61]. The possibility that CETP inhibition per se could generate larger cholesterol-enriched HDL with impaired cholesterol efflux potential was also proposed [60]. However, this was not confirmed by in vitro studies. Among the three newer compounds, dalcetrapib, anacetrapib, and evacetrapib, with different potency toward CETP inhibition (evacetrapib>anacetrapib>dalcetrapib) and apparently lacking the off-target effects of torcetrapib, two remain under development, whereas development of dalcetrapib was halted recently.

The decision to stop development of dalcetrapib was based on interim analysis of the dal-OUTCOMES trial which showed that dalcetrapib, in acute coronary syndrome patients, failed to demonstrate a significant reduction in the incidence of cardiovascular adverse events [13] (Table 2). In contrast to the earlier CETP inhibitor torcetrapib, no safety concerns were reported. In addition, the dal-VESSEL study showed that dalcetrapib reduced CETP activity and increased HDL-C levels without affecting nitric oxide dependent endothelial function, blood pressure, or markers of inflammation and oxidative stress [62], whereas the dal-PLAQUE study demonstrated some beneficial vascular effects of the drug, including reduction in total vessel enlargement over 24 months [63].

Although the results have been disappointing, the pursuit of an extensive program of clinical trials and basic research to develop dalcetrapib has provided new information on the biology of HDL in both human and animal models, and on CETP inhibition as a viable therapeutic target for raising levels of HDL-C. Two other CETP inhibitors that raise HDL-C levels to a greater extent than dalcetrapib and also

significantly lower LDL-C levels remain under development (anacetrapib and evacetrapib). Data on clinical outcomes are warranted to understand whether CETP inhibition remains a relevant strategy for reducing the risk of CVDs.

HDL: To Treat or Not To Treat?

It is still unclear whether the pharmacological increase of HDL-C levels has or does not have beneficial effects on cardiovascular disease risk, as conflicting results have been obtained from human clinical studies. For example, in the AIM-HIGH trial, no clinical benefits from the addition of niacin to statin therapy during a 36-month follow-up period were observed, despite favorable changes in lipid profile, including a significant increase in HDL-C levels [12]. A possible explanation could be related to the fact that niacin alters the composition of HDL particles and not the total particle number, by reducing the number of small cholesterol-poor HDL particles and increasing the number of large cholesterol-enriched HDL particles [64, 65]. From this point of view, niacin is not an HDL-increasing drug [64]. Several pieces of evidence suggest that increasing HDL-C levels without increasing the particle number may not result in clinical benefits; on the other hand, the VA-HIT trial showed that gemfibrozil reduced the incidence of CHD events, despite a modest rise in HDL-C levels, probably due to the increase in the number of HDL particles as a result of increased numbers of small HDL particles [66].

It will be highly relevant to discover whether the CETP inhibitors in development, in addition to being able to increase HDL-C plasma levels, can improve HDL function and/or HDL subclass distribution in patients with CVD. Anacetrapib has been shown to increase the number of large HDL particles [67] as well as the number of small pre-ß particles [68], with data suggesting that this drug might also improve HDL function [69].

Quality of HDL Versus Quantity: Epidemiological and Clinical Evidence

Although several epidemiological observations have shown an inverse correlation between plasma levels of HDL-C and the incidence of coronary artery disease, some recent observations have challenged this relationship. Differences in the quality of HDL particles might partly explain these discrepancies, and in agreement with this hypothesis, some observations have suggested that HDL subpopulation levels may be better predictors of CVD than simple HDL-C levels [7].

Several conditions, including dyslipidemia, have been associated with altered HDL composition and functionality [8•]; in addition, in patients with established CHD, subjects with high HDL-C levels carry dysfunctional proinflammatory HDL particles, and statin treatment resulted in the restoration of the anti-inflammatory properties of HDL [70]. These findings suggest that carrying a high concentration of dysfunctional HDL-C may be more unsafe than low HDL-C levels. According to this hypothesis, the analysis of two studies revealed that very high plasma HDL-C levels and very large HDL particles are associated with increased cardiovascular disease risk [71]. Similarly, the ability of HDL to trigger cholesterol efflux from macrophages, a measure of HDL function, was inversely associated with subclinical atherosclerosis and coronary artery disease, and was independent of the HDL-C level [72]. Finally, among patients with long-standing type 1 diabetes, high HDL-C levels (above 80 mg/mL), due to increased levels of small HDL3 particles, were associated with increased risk of coronary artery disease in women [73]. Together, these observations reinforce the concept that HDL function might be more relevant than HDL-C levels.

Novel Pharmacological Approaches Targeting HDL

The pharmacological approaches related to HDL biology which are under development are mainly aimed at investigating the potential effect not only on HDL-C levels but also on HDL function. It is expected that an increase in HDL-C levels can be beneficial when associated with an improvement in HDL function. The first category includes two CETP inhibitors (anacetrapib and evacetrapib) which are currently being tested in phase III trials. Ultimately, the benefits of each of these novel CETP inhibitors must be determined through prospective, randomized, clinical outcome trials. Although CETP inhibitors were developed on the premise that they would increase HDL-C levels more than any therapy currently available, the possibility that the benefit may still be largely due to the incremental lowering of LDL-C levels observed with the more potent inhibitors should be considered for the transfer of these drugs into clinical practice [74].

The main areas under development include the investigation of HDL mimetics. The rationale is based on the possibility of mimicking the first phase of the HDL life cycle and promoting cholesterol efflux, mainly from cholesterol-loaded cells in the vascular wall such as macrophages and foam cells. To this aim, lipid-poor apoA-I–phospholipid complexes have been extensively studied in preclinical models and preliminary studies in humans. Different approaches are under investigation and include CSL-111, CER-001, and MDCO216. A second approach to improve HDL function is represented by small peptides designed to mimic apoA-I function. At least 22 apoA-I mimetics are under development [75]; however, with the exception of D4-F, the other peptides require parenteral administration and, in humans, data on efficacy,

tolerability, and safety, including autoantibody generation, are lacking. Other approaches include the infusion of delipidated HDL, the use of antisense oligonucleotide inhibitors which can increase HDL-C levels by inhibiting ABCA-1 degradation [76, 77•], and the infusion of recombinant lecithin cholesterol acyltransferase, which could favor cholesterol efflux to HDL and improve HDL maturation.

Conclusions

Recently, several clinical outcome trials, including AIM-HIGH, HPS2-THRIVE, and dal-OUTCOMES, have indicated that increasing HDL-C levels does not simply translate into a cardiovascular benefit. This was shown mainly in patients already receiving highly effective statin treatment; is it possible that this would have blunted any possibility to see additional effects? Compared with LDL metabolism, HDL biology is more complicated, with several HDL subclasses and a maturation cycle that requires the action of several players, including hepatic and peripheral cells as well as different enzymes. It is therefore reasonable that a step forward in HDL pharmacology should be undertaken by considering approaches that improve HDL function rather than simply affecting HDL-C levels; furthermore, it should be taken into consideration that patients other than those enrolled so far in clinical studies would benefit from HDL-raising drugs. The dichotomy of HDL-triglycerides is well known, and the possibility that HDL represent a stable biomarker of general health status which reflects better changes in plasma triglyceride levels should also be considered. However, also drugs directly affecting triglyceride levels failed in some trials to show an additional benefit on cardiovascular mortality [37]. Again this supports the possibility that patients other than those receiving statin therapy would benefit from drugs affecting HDL-C or triglyceride levels. Future pharmacological approaches influencing HDL should be investigated with a more focused hypothesis on HDL biology taking into account the new compelling evidence for the critical role of HDL in other conditions such as immune-related responses.

Compliance with Ethics Guidelines

Conflict of Interest Angela Pirillo, Gianpaolo Tibolla, and Giuseppe Danilo Norata declare that they have no conflict of interest. Alberico Luigi Catapano has received personal fees from AstraZeneca, Angen, and Aegerion, grants from Eli-Lilly, Mediolanum, Sanofi, Rottapharm, and Recordati, and grants and personal fees from Genzyme and Merck.

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- •• Of major importance

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