High-density lipoprotein cholesterol raising: does it matter?

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Purpose of review

Cardiovascular disease (CVD) is the leading cause of morbidity and premature mortality in Europe and the United States, and is increasingly common in developing countries. High-density lipoprotein cholesterol (HDL-C) is an independent risk factor for CVD and is superior to low-density lipoprotein cholesterol (LDL-C) as a predictor of cardiovascular events. The residual risk conferred by low HDL-C in patients with a satisfactory LDL-C was recently highlighted by the European Atherosclerosis Society. Despite the lack of randomized controlled trials, it has been suggested that raising the level of HDL-C should be considered as a therapeutic strategy in high-risk patients because of the strong epidemiological evidence, compelling biological plausibility, and both experimental and clinical research supporting its cardioprotective effects.

Recent findings

Three recent large randomized clinical trials investigating the effect of HDL-C raising with niacin and dalcetrapib in statin-treated patients failed to demonstrate an improvement in cardiovascular outcomes.

Summary

There is evidence to support the view that HDL functionality and the mechanism by which a therapeutic agent raises HDL-C are more important than plasma HDL-C levels. Future therapeutic agents will be required to improve this functionality rather than simply raising the cholesterol cargo.

Keywords

cardiovascular disease, HDL functionality, HDL-cholesterol

INTRODUCTION

The prevention and treatment of atherosclerosis have historically been limited to lifestyle modification, smoking cessation, and reduction of blood pressure and low-density lipoprotein cholesterol (LDL-C) [1–3]. Although LDL-C lowering with statins has reduced cardiovascular events significantly, a substantial residual risk of 60–70% remains [4].

Most guidelines do not address high-density lipoprotein cholesterol (HDL-C) as a therapeutic target to reduce the residual cardiovascular risk in patients with satisfactory LDL-C levels [5]. The absence of unique HDL-C raising medications has made it difficult to define the benefit of raising HDL-C, but several clinical trials have suggested potential benefit [1,6,7].

EPIDEMIOLOGY

The inverse association between HDL-C concentration and cardiovascular disease (CVD) risk was first recognized in the 1970s [8,9]. The Framingham Heart Study showed HDL-C to be an independent risk factor for CVD; an increase in HDL-C of 1 mg/dl (0.026 mmol/l) was associated with a risk reduction

of 2–3% [10,11]. The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) and Systematic Coronary Risk Evaluation (SCORE) studies found HDL-C to be a better predictor of cardiovascular events than LDL-C [12–14].

The Emerging Risk Factors and Prospective Studies Collaborations showed that the inverse relationship between HDL-C and CVD risk persisted even when LDL-C was less than 2.6 mmol/l [13,15–17], suggesting significant residual cardiovascular risk after LDL-C reduction [18]. Furthermore, high

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KEY POINTS

- HDL-C is an independent risk factor for CVD.
- HDL has a variety of cardioprotective functions in addition to its role in reverse cholesterol transport.
- Recent trials investigating the effect of HDL-C raising with niacin and dalcetrapib in statin-treated patients have failed to demonstrate an improvement in cardiovascular outcomes.
- HDL-C is not a reliable biomarker of HDL function.
- Future therapeutic agents targeting HDL may be required to improve its functionality rather than simply raising concentrations.

HDL-C (>1.7 mmol/l) seems to be cardioprotective even when LDL-C is greater than 5.7 mmol/l [19].

In the US Physicians' Health Study, low total cholesterol did not protect against myocardial infarction (MI) in the presence of low HDL-C [13,20]. Moreover, up to 55% of patients hospitalized with CVD have HDL-C less than 1.0 mmol/l on admission [1,21].

The Monica Risk, Genetics, Archiving and Monograph (MORGAM) Project showed an association between higher HDL-C levels and up to a 20% risk reduction for stroke [22]. This inverse relationship suggests that, in addition to inhibiting chronic inflammation, HDL may act to reduce the acute inflammation implicated in cerebrovascular events.

Although Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) found that HDL-C did not predict first nonfatal MI and stroke in patients already on high-dose statin treatment [23], a recent meta-analysis reported that statin monotherapy did not alter the correlation between HDL-C level and cardiovascular risk [24]. HDL-C in patients receiving statins also predicted major cardiovascular events in the Treating to New Targets (TNT) study cohort [13,25]. This is important because some studies have reported that nearly 80% of statin-treated patients have low HDL-C levels [26].

Low HDL-C appears to be of greater importance in patients at high cardiometabolic risk and is amongst the factors that currently favour a decision to further reduce LDL-C levels [27,28]. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study showed an increased number of cardiovascular events in diabetic patients with persistently low HDL-C and high triglyceride levels, despite a mean LDL-C less than 2.1 mmol/l [29,30].

The secondary prevention Veteran Affairs High-Density Lipoprotein Intervention Trial (VA-HIT)

demonstrated that events could be reduced in patients with low HDL-C – the beneficial effect of gemfibrozil was related to increases in HDL-C but not changes in triglycerides or LDL-C [31]. The Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6 – HDL and LDL Treatment Strategies in Atherosclerosis (ARBITER 6-HALTS) study also suggested that raising HDL-C should be the next therapeutic target [32,33].

HDL HETEROGENEITY

Although HDL-C levels are a strong biomarker for assessing CVD risk, they do not predict either HDL functionality or composition [34]. HDL metabolism and therapeutic targets are summarized in Fig. 1 [35,36[■],37].

Plasma HDL is a heterogeneous collection of small discoid and spherical particles that are functionally diverse and differ in composition, size and electrophoretic mobility [38]. HDL particles can be separated by sequential ultracentrifugation into large, light, lipid-rich HDL2 and small, dense, protein-rich HDL3 [39]. HDL2 and HDL3 can be further subfractionated by nondenaturing polyacrylamide gradient gel electrophoresis into five distinct subpopulations of decreasing size: HDL2b, HDL2a, HDL3a, HDL3b and HDL3c [38].

These HDL subfractions may have different functional properties, but attempts to clarify their effects on cardiovascular risk have led to inconclusive results [13]. Population studies suggest that HDL2 is more cardioprotective than HDL3, but HDL3 has been reported to be superior in its capacity to inhibit vascular cell adhesion molecule 1 (VCAM-1) expression in endothelial cells [40]. The distinct anti-inflammatory properties of HDL2 and HDL3 may be related to differences in their protein and phospholipid concentrations rather than their size [41].

Identification of subclasses of HDL displaying specific biological functions may lead to their use as biomarkers for cardiovascular risk or in the assessment of novel HDL-targeted therapies [42]. Promising biomarkers of HDL functionality and cardiovascular risk include plasma myeloperoxidase (MPO), paraoxonase-1 (PON1) [43,44], apolipoprotein A-I (apoA-I), lecithin-cholesterol acyltransferase (LCAT), lipoprotein phospholipase A2, serum amyloid A (SAA) and apolipoprotein J [36[■],45].

HDL FUNCTIONS

Discoid lipid-poor HDL particles promote cholesterol efflux from subendothelial macrophages and

FIGURE 1. HDL assembly begins with the secretion of apolipoprotein A-I (apoA-I) in the liver and intestine. Nascent discoid lipid-poor HDL particles are formed by the extracellular acquisition of other apolipoproteins, lipid and phospholipids. HDL is continually remodelled by plasma and cell surface enzymes in processes mediated by ATP-binding cassette subfamily G member 1 (ABCG1), hepatic lipase, endothelial lipase, cholesteryl ester transfer protein (CETP), and phospholipid transfer protein. Interaction between HDL and the cell membrane mediated by scavenger receptor-B1 (SR-B1) promotes the hydrolysis of intracellular cholesteryl ester (CE) to form free cholesterol and its passage to the cell membrane, which it crosses to be incorporated into preβ HDL and smaller HDL₃ particles directly or via SR-B1 and ATP-binding cassette transporter A1 (ABCA1). The removal of CE from HDL is attenuated by CETP and hepatic SR-B1. rHDL, reconstituted HDL. Adapted with permission [35].

foam cells [46], via interactions with ATP-binding cassette transporter A1 (ABCA1), after esterification by LCAT. The enzyme PON1 enhances cholesterol efflux [47]. Subsequently, HDL particles deliver their cholesterol to the liver directly, via scavenger receptor-B1 (SR-B1), or indirectly, via transfer to very low-density lipoprotein (VLDL) or LDL particles by the action of cholesteryl ester transfer protein (CETP) [43]. These apoB-containing lipoproteins are taken up by the liver via the LDL receptor [10]. Facilitating the efflux of excess cholesterol from macrophages in the arterial wall and its return to the liver for excretion in the bile and faeces is the best known of HDL's cardioprotective functions [42]. This process of cholesterol clearance is known as reverse cholesterol transport (RCT) [48].

Recently, a variety of other HDL functions have been described (Fig. 2) [36[•], 49–58, 59[•]].

The increased expectation that modification of HDL might reduce CVD risk through these pleiotropic effects seems confounded by the recent reports from genetic and pharmacological studies suggesting that higher levels of plasma HDL-C are not associated with decreased CVD risk [60^{••}].

HDL DYSFUNCTION

HDL dysfunction is suggested by the observation that high HDL-C levels do not always protect against CVD [61]. HDL can undergo modification in structure and composition to become dysfunctional in conditions associated with systemic inflammation and oxidative stress [62, 63]. Dysfunctional HDL is proinflammatory and contains oxidized phospholipids and lysophospholipids, as well as proinflammatory proteins, such as SAA and ceruloplasmin. The genesis of dysfunctional HDL has been attributed

FIGURE 2. Circulating LDL must be modified by glycation or oxidation before its uptake by macrophages in the arterial wall is rapid enough to excite foam cell formation and inflammation. HDL can inhibit this atherogenic modification *in vitro*. Both spherical HDL from human plasma and discoidal rHDL have been shown to inhibit vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) expression. These anti-inflammatory effects appear to be mediated primarily by apoA-I, with a smaller contribution from phospholipids and through activation of ABCA1-dependent signalling pathways. Other anti-inflammatory effects include inhibition of the reactive oxygen species/nuclear factor kappa B signalling pathway and inhibition of monocyte activation and adhesion to the endothelium by downregulating the expression of monocyte chemoattractant protein-1. Some of HDL's anti-inflammatory effects are thought to be because of PON1 and phospholipase A2 associated with it. HDL contributes to the maintenance of vascular endothelial function through the SR-BI-dependent induction of endothelial nitric oxide synthase and enhanced prostacyclin synthesis. HDL also inhibits endothelial cell apoptosis and promotes re-endothelialization after injury by preserving the viability of phagocytic macrophages and promoting cholesterol efflux. The antithrombotic activities of HDL include the inhibition of platelet activation and aggregation, activation of protein C and S, reduced von Willebrand factor levels, and actions on tissue factor and factors X, Va and VIIIa. More recently, HDL has been shown to have a potential role in diabetes pathophysiology and its complications. ABCA1, ATP-binding cassette transporter A1; rHDL, reconstituted HDL.

to oxidation, chlorination or nitration of apoA-I through nonenzymatic glycation, homocysteinylolation, and reactions with metal ions, peroxy and hydroxyl radicals, aldehydes, MPO-generated oxidants, elastase, lipoxygenase, and phosphorylase A2 [42]. Dysfunctional HDL may promote the transfer of lipid hydroperoxides to apoB-containing lipoproteins and actually promote the VLDL and LDL oxidation required for atherosclerotic lesion

formation [61]. Proinflammatory HDL-C has been associated with increased carotid intima-media thickness and an increased risk for adverse clinical outcomes [64]. HDL from patients with coronary artery disease does not prevent LDL oxidation [65]. On the other hand, raising the level of functional HDL particles by increasing their hepatic production or by HDL infusion results in atheroprotective effects [37].

HDL function can be measured *in vitro* [66]. The capacity of HDL-C to promote cholesterol efflux from macrophages is a recognized metric of HDL function and has recently been shown to have a strong inverse relationship with both carotid intima-media thickness and the presence of angiographically confirmed coronary artery disease, independent of HDL-C levels [67^{***},68]. Determining HDL function may identify patients with normal or low HDL-C at high risk of CVD. Future therapeutic agents targeting HDL may be required to improve its functionality rather than simply raising its cholesterol cargo [36^{***}].

GENETICS

Common genetic variants associated with HDL-C, but not other lipoprotein traits, were not associated with MI in a recent Mendelian randomization study [60^{***}], suggesting that raising HDL-C pharmacologically will not necessarily translate into a reduced cardiovascular risk.

The antiatherogenic action of apoA-I is well established [69]. Mutations of *ApoA-I* could explain the functional heterogeneity of HDL particles [13]. Several genetic syndromes with reduced HDL-C and apoA-I are not associated with an increased risk of premature CVD [42]. Heterozygosity for the Milano or Paris mutations of the *ApoA-I* gene, despite HDL-C less than 0.5 mmol/l, does not confer early CVD risk [70]. Deficiency of plasma LCAT does not increase CVD risk despite HDL-C less than 0.4 mmol/l [71]. Tangier disease, caused by mutations in the ABCA1 transporter gene, in which HDL and apoA-I concentrations are virtually undetectable, is not associated with the increase in CVD expected from such an extreme phenotype [43]. Genetic deficiency of CETP increases HDL-C but would also be expected to impair RCT [72]. The mechanism by which HDL-C is increased is critical in determining whether it reduces atherosclerosis. Thus, increases in HDL-C through downregulation of SR-B1 by oestrogens and CETP activity modulation by CETP inhibitors may not reduce cardiovascular risk.

LIFESTYLE MODIFICATION

Lifestyle interventions have been shown to be effective in increasing HDL-C levels and decreasing cardiovascular risk [13]. Most current guidelines for the management of dyslipidaemia in patients with low HDL-C levels recommend a change in lifestyle, focussing on smoking cessation, regular exercise, weight loss, dietary modifications and modest alcohol consumption [73]. In patients

already on statin therapy, these dietary and lifestyle changes can raise HDL-C levels by an additional 5–10% [74]. A Mediterranean-style diet rich in fruits and vegetables and high in polyunsaturated fats improves the anti-inflammatory properties of HDL, decreases LDL-C, increases HDL-C and reduces cardiovascular events [75]. A low glycaemic index carbohydrate diet has been shown to improve HDL-C, glycaemic control and inflammatory markers [76]. Weight loss achieved through exercise may be more effective at raising HDL-C concentrations than dieting [77], but it is again difficult to attribute the reduction in cardiovascular risk to increases in HDL-C alone [78]. Smoking cessation increases HDL-C by 3–5.6% without changes in LDL-C, total cholesterol or triglyceride levels. It also favours RCT, decreases CETP and can reduce oxidative stress by improving endothelial function [79]. Moderate alcohol consumption can increase HDL-C by as much as 12% [15]. It remains unclear how much this contributes to the reduced incidence of CVD with moderate consumption of alcohol [80,81]. Alcohol may interfere with CETP activity, reducing the transfer of cholesteryl ester from HDL [15].

CURRENT THERAPIES

Lipid-lowering treatment with hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) can achieve a relative risk reduction for CVD of 25–40% [73,82], which is accepted to be secondary to LDL-C reduction, but may also be related to increases in HDL-C or HDL functionality. Statins can increase HDL-C by 5–15% [83], with a comparable increase in apoA-I levels. A Study To Evaluate the Effect of Rosuvastatin on Regression of Coronary Atherosclerosis (ASTEROID) suggested that statin-induced reductions in atheroma volume are because of increases in HDL-C in addition to reductions in LDL-C. In the Lipoprotein and Coronary Atherosclerosis Study (LCAS), fluvastatin reduced angiographic progression in patients with low HDL-C levels significantly compared with those with high HDL-C levels [84]. Statins increase HDL-C by activating peroxisome proliferator-activated receptor- α (PPAR- α), increasing the expression of apoA-I and apoA-II [85]. They may also increase HDL-C by reducing hepatic CETP expression and, thus, CETP-dependent transfer of cholesterol from HDL to VLDL. As statins lower MPO levels, they may also preserve HDL function by creating a less inflamed environment [86]. There is also some evidence that PON1 activity may be augmented by atorvastatin [87].

If concomitant hypertriglyceridaemia is present, most guidelines recommend consideration of a

fibrate [1]. The hallmarks of fibrate therapy are a 30–50% reduction in plasma triglyceride levels and a 10–15% increase in HDL-C levels [88,89]. Despite this, the beneficial effect of fibrates on all-cause and cardiac mortality remains controversial [89]. Fibrates act as PPAR- α agonists. They also increase HDL-C by reducing the CETP-dependent transfer of cholesterol from HDL to apoB-containing lipoprotein particles. Their effect on lipid modification, however, does not appear to be consistent [31,90].

Bile acid sequestrants and cholesterol uptake inhibitors such as ezetimibe reduce cholesterol absorption. They have minimal effects on HDL-C. Omega-3 fatty acids reduce triglycerides in a dose-dependent manner, but their effect on cardiovascular events appears to be independent of HDL [91].

NIACIN (NICOTINIC ACID)

The interest in raising HDL-C has brought renewed focus on the oldest and most effective agent in increasing HDL-C. Niacin was first integrated in clinical practice in the 1960s, when it was the first lipid-modifying agent shown to have an effect on cardiovascular endpoints [18]. Despite promising results, high rates of intolerance and adverse effects have precluded its widespread use.

Niacin increases HDL-C by 23%, and reduces LDL-C by 20% and triglyceride levels by 40% [28]. In a recent meta-analysis of 11 randomized controlled trials, a therapeutic strategy including niacin was shown to reduce major coronary events by 25%, stroke by 26%, and all cardiovascular events by 27%. The cardiovascular benefit of niacin appeared to be greater in patients with diabetes and metabolic syndrome despite mild adverse effects on glucose levels [92].

Although a number of trials (Table 1) have demonstrated benefit from adding niacin to other lipid-lowering drugs [7,33,93–96], it is difficult to attribute the benefit of niacin to its HDL-C-raising properties as opposed to its ability to lower LDL-C. Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes (AIM-HIGH) showed no benefit from adding niacin to simvastatin [1] although it is considered to be underpowered and have other design flaws [97]. Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE), the largest study of niacin ever undertaken, showed no benefit of adding niacin and laropiprant (Tredaptive) to simvastatin, but did demonstrate significant side-effects [98]. Although HPS2-THRIVE had no cutoff

for HDL-C and LDL-C was low at less than 2 mmol/l before randomization, no type of patient has yet been identified who benefitted from treatment [99].

FUTURE AGENTS

Interest in the inhibition of CETP was stimulated by a 1985 publication describing a Japanese population in which a low-activity genetic variant of CETP was associated with elevated HDL-C and relatively low rates of CVD [1].

The first oral CETP inhibitor to be assessed in major clinical trials was torcetrapib. Despite promising results in phase I and II studies, increases in HDL-C of 72% and decreases in LDL-C of 25% and triglycerides of 9%, the large-scale phase III Investigation of Lipid Level Management to Understand its Impact in Atherosclerosis Events (ILLUMINATE) trial was terminated early because the torcetrapib and atorvastatin group experienced increased all-cause mortality and cardiovascular events compared with recipients of atorvastatin alone [100]. This has been attributed to CETP-independent angiotensin–aldosterone activation with adverse effects on blood pressure. However, CVD rates were lower in torcetrapib-treated patients whose HDL-C increased above the median [101]. HDL isolated from torcetrapib-treated patients showed normal or enhanced promotion of cholesterol efflux [102].

The second CETP inhibitor to progress to phase III studies was dalcetrapib, which associates differently with CETP and has no angiotensin–aldosterone-stimulating or hypertensive effects. Disappointingly, the dal-OUTCOMES (efficacy and safety of dalcetrapib in patients with recent acute coronary syndrome) trial showed no effect from dalcetrapib on cardiovascular events, despite raising HDL-C by 25% [103]. Dalcetrapib was discontinued from clinical development in 2012 following the second prespecified interim analysis of primary end-point events (death from coronary heart disease, nonfatal myocardial infarction, ischaemic stroke, unstable angina or cardiac arrest with resuscitation).

A third agent, anacetrapib, has greater effects on HDL-C and LDL-C. Like dalcetrapib, it does not appear to cause hypertension or have any other ‘off-target’ effects. At present, there is no evidence to suggest any harm from complete CETP inhibition with anacetrapib (or its modulation with dalcetrapib) [104,105]. The phase III study Determining the Efficacy and tolerability of CETP Inhibition with Anacetrapib (DEFINE) examined its effect in high-risk patients already on statin therapy [104]. Anacetrapib reduced LDL-C by 40% and increased HDL-C

Table 1. Trials investigating the effect of adding niacin to other lipid-lowering agents

Trial	Year	Participants	Treatment arms	Study design	Outcome
Coronary Drug Project (CDP)	1975, 1986	8341 men with previous myocardial infarction	Oestrogen vs. dextrothyroxine vs. clofibrate vs. niacin vs. placebo	Randomized, placebo-controlled trial; endpoints recurrent nonfatal MI at 6 years and total mortality at 15 years	Niacin significantly decreased nonfatal recurrent myocardial infarction at 6 years and total mortality at 15 years
Cholesterol Lowering Atherosclerosis Study (CLAS)	1987	162 nonsmoking men aged 40–59 years with previous coronary bypass surgery	Colestipol + niacin vs. placebo	2-year randomized, placebo-controlled, angiographic trial	43% reduction in LDL-C; 37% elevation of HDL-C; atherosclerosis regression in 16.2% of colestipol–niacin treated vs. 2.4% placebo treated
Familial Atherosclerosis Treatment Study (FATS)	1990	146 men with apolipoprotein B levels >125 mg/dl, documented coronary artery disease, and family history of vascular disease	Lovastatin + colestipol vs. niacin + colestipol vs. placebo	2 1/2-year randomized, double-blind study; arteriography at baseline and after treatment	LDL-C decreased by 25% and HDL-C increased by 38%; coronary lesion progression seen in 39%
HDLAtherosclerosis Treatment Study (HATS)	2001	160 patients with coronary disease, low HDL-C and normal LDL-C	Simvastatin + niacin vs. vitamins vs. simvastatin + niacin + antioxidants vs. placebo	3-year double-blind trial; endpoints arteriographic evidence of change in coronary stenosis and first cardiovascular event	Frequency of clinical endpoint 24% with placebo; 3% with simvastatin–niacin; 21% in antioxidant group; 14% in simvastatin–niacin + antioxidants
Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER)	2004 2006	167 patients with known CHD and HDL-C <1.16 mmol/l on statin (ARBITER 2) 130 patients completing ARBITER 2 (ARBITER 3)	Extended release niacin vs. placebo	Randomized placebo-controlled trials; primary endpoint change in carotid intima-media thickness at 12 (ARBITER 2) and 24 months (ARBITER 3)	HDL-C increased from 1.01 to 1.22 mmol/l; progression of atherosclerosis slowed by 68% (ARBITER 2); HDL-C increased from 1.02 to 1.26 mmol/l; additional regression of carotid intima-media thickness of 0.041 mm
Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6 – HDL and LDL Treatment Strategies in Atherosclerosis (ARBITER 6-HALTS)	2010	315 patients with coronary heart disease or equivalent with LDL-C <100 mg/dl and HDL-C <55 mg/dl while receiving stable statin treatment	Ezetimibe vs. extended-release niacin	14-month randomized study; primary endpoint change in carotid intima-media thickness	Terminated early on basis of prespecified interim analysis showing superiority of niacin over ezetimibe on change in carotid intima-media thickness

CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction.

Table 2. HDL-modifying drugs in development

Class	Mechanism of Action	Examples	Developer	Status
CETP inhibitors	Inhibit CETP to increase circulating HDL-C and lower LDL-C	Torcetrapib	Pfizer	Discontinued 2006
		Dalcetrapib	Hoffmann-La Roche	Discontinued 2012
		Evacetrapib	Lilly	Phase III trial ACCELERATE to present in 2015
		Anacetrapib	Merck	Phase III trial REVEAL to present in 2017
ApoA-I mimetics	Stimulate cholesterol efflux from macrophages via ABCA1 and associate with HDL to induce pre β HDL formation	D-4F	Novartis	Phase II trials
Stimulator of apoA-I gene transcription	Increases apoA-I, pre β HDL, and HDL functionality	RVX-208	Resverlogix	Phase I trials
Liver receptor X (LXR) agonists	Activate RCT	DMHCA	Wyeth	Phase I trials
rHDL	Infusion of reconstituted or recombinant HDL particles	ApoA-I Milano–phospholipid complex	The Medicines Company	Phase II trials
		Wildtype apoA-I–phospholipid complex	Cerenis Therapeutics	Phase II trials

ABCA1, ATP-binding membrane cassette transporter A1; ACCELERATE, Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition With Evacetrapib in Patients at a High-Risk for Vascular Outcomes; apoA-I, apolipoprotein A-1; CETP, cholesteryl ester transfer protein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RCT, reverse cholesterol transport; REVEAL, Randomized Evaluation of the Effects of Anacetrapib Through Lipid-modification.

by 138%. Cardiovascular outcomes are currently being investigated [91[■]]. Although the development of dalcetrapib has been discontinued, a fourth CETP inhibitor, evacetrapib, is in development [106].

Drugs in development are shown in Table 2 [91[■],103[■],106–113].

CONCLUSION

Lowering LDL-C has been the primary focus in lipid modification for the prevention and treatment of atherosclerosis [2]. The ARBITER 6-HALTS study and others implied that raising HDL-C should be the next target to ameliorate the progression of CVD [32], but increases in HDL-C may not result in the cardiovascular benefit suggested by prospective observational studies [114]. To date, HDL-based therapy to reduce the residual risk of CVD remains a largely unfulfilled promise [115]. Although raising the level of functional HDL particles either by increasing their hepatic production or by HDL infusion appears promising [37], there is limited evidence that any of the clinical endpoints measured to date (plaque volume and inflammatory state of

macrophages) are correlated with decreased events [116].

There is increasing evidence that HDL-C levels are not necessarily directly correlated to HDL particle function [117]. As we understand the structural components of HDL and exact roles of each component in HDL function, traditional lipid panel studies will likely be superseded by assays of HDL function or measurement of biomarkers associated with dysfunctional HDL [42]. There remains cautious optimism that CETP inhibition may be a viable option to reduce cardiovascular risk, but the concern that the inhibition of CETP might lead HDL to become dysfunctional has not yet been fully allayed.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 492–493).

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