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DIABETES AND CARDIOVASCULAR DISEASE (S MALIK, SECTION EDITOR)

Role of HDL in Those with Diabetes

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Abstract Low levels of high-density lipoprotein cholesterol (HDL-C) have been associated with an increased risk of coronary heart disease in prospective population studies and clinical trials of high-risk patients treated with a low to moderate intensity statin. As a result, therapeutic targets were developed to increase concentrations of HDL-C. Subsequently, clinical trials of high-intensity statins have not supported this previously well-established association. In trials of high-intensity statin therapy, low HDL particle concentration (HDL-P) has been associated with an increased risk of future cardiovascular events. Therefore, strategies that increase HDL-C without expanding the pool of HDL-P with its rich proteome/lipidome do not seem to be an effective strategy. In this review, we discuss potential mechanisms of action for the anti-atherogenic effect of HDL and the impact of current and emerging therapies on the functional capacity of HDL-P. Finally, we discuss emerging therapies that increase the concentration and functional properties of HDL.

Keywords HDL · apoA-I · Sphingosine-1-phosphate · LDL · Triglycerides · Phospholipids · HDL particles · HDL functionality · Reverse cholesterol transport · Atherosclerosis · Niacin · Fibrates · CETP inhibitor

Introduction

Cardiovascular disease (CVD) of atherosclerotic origin remains the major cause of morbidity and mortality worldwide [1]. A landmark meta-analysis [2] including more than 90,000 patients (comprised in 14 randomized clinical trials studying statin therapy) confirmed that there was a 21 % reduction in CVD events for every 40 mg/dL of decrease in the concentration of low-density lipoprotein cholesterol (LDL-C) [2], thus, confirming the safety and effectiveness of statin-induced LDL-C reduction. Notwithstanding, despite a decrease in CVD events associated with statin therapy, a significant number of CVD events still take place, a phenomenon termed "residual risk" [3]. For instance, in stable CHD patients enrolled in Treating to New Targets (TNT) trial [4], high-dose atorvastatin (80 mg daily) was 22 % more effective than low-dose atorvastatin (10 mg daily) in reducing recurrent events. This translates into a 78 % of CVD events still taking place in spite of LDL-C levels of 78 mg/dL. In an analysis of patients with LDL-C levels <70 mg/dL, low high-density lipoprotein (HDL) cholesterol (HDL-C) levels were associated with a higher event rate in this cohort of atorvastatin-treated patients; however, these risk relationships were nonsignificant among the subset of patients randomized to atorvastatin 80 mg daily [5]. In the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, low levels of HDL-C were not associated with more events in rosuvastatin treated participants [6], but low levels of HDL particles (HDL-P) were predictive of CVD events [7••].The analysis of HDL in JUPITER suggests that the concentration of HDL particles rather than the cholesterol content of HDL particles is a more robust predictor of CVD events, and a more appropriate target for therapeutic interventions [8••]. Pharmacologic therapies that target the cholesterol content of HDL (HDL-C) vs expanding the pool of HDL-P have consistently failed to reduce CVD events. These trials suggest new approaches to HDL modifying therapies for reducing residual risk in patients treated with high-intensity statins.

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apo A-I can diffuse back to the plasma; in fact, the concentration of plasma oxTrp72 apo A-I is directly correlated with CVD, even after adjusting by HDL-C and conventional risk factors [32•].

Specifically focusing on T2DM, nonenzymatic glycation of HDL particles is one of the main mechanisms of dysfunctional HDL. Nonenzymatic glycation of apoA-I has been shown to impair all the beneficial effects of the HDL particles; (1) It reduces ABCA1-dependent cholesterol efflux [33] and the HDL-mediated activation of LCAT [33]; (2) The usual HDL-induced inhibition of endothelial VCAM-1 expression is lost in HDL from T2DM CVD patients, thus, favoring the adhesion of macrophages to activated endothelial cells [34, 35, 36•] and reducing the anti-inflammatory activity of HDL; (3) HDL from T2DM loses its vasorelaxant effects, in fact HDL isolated from T2DM patients has a reduced ability to stimulate endothelial nitric oxide production and endothelial-dependent vasodilation and to promote endothelial progenitor cell-mediated endothelial repair [37]; (4) HDL from T2DM CVD patients does not inhibit endothelial apoptosis because it fails to activate anti-apoptotic proteins while simultaneously stimulating pro-apoptotic pathways [36•]. Interestingly, these HDL activities seem to be partially restored in T2DM patients after niacin treatment [37].

There are other mechanisms explaining dysfunctional HDL in diabetes. Chronic inflammation in T2DM elevates serum amyloid A (SAA) protein [38], and SAA displaces apoA-I from the surface of HDL, thus, generating free apoA-I, which is cleared faster by the kidney. Besides, oxidative stress is enhanced in T2DM, which both reduces the levels of PON1 [39] and selectively oxidizes amino acid residues in apoA-I (such as Met, Cys, Tyr, and Lys), with the final result being a decrease in the anti-oxidant capacity of HDL particles.

The changes in lipid content also contribute to HDL dysfunction in diabetes. The altered phospholipid composition of HDL in T2DM results in an elevated sphingomyelin to phosphatidylcholine ratio, which increases HDL surface rigidity [40] (a key determinant of anti-oxidant activity of HDL) [41].

"Diabetic dyslipoproteinemia" is characterized by low levels of HDL-P, high levels of large VLDL particles, total and small oxidized LDL-P [42]. In insulin-resistant states, hypertriglyceridemia is primarily due to increased hepatic production of VLDL particles, postprandial hyperlipidemia and low lipoprotein lipase (LPL) levels. This hypertriglyceridemia enhances the CETP-mediated interchange of TG from TG-rich lipoproteins to HDL-L/HDL-VL and the subsequent TG-enrichment of HDL. Hepatic lipase has greater activity against TG and will, thus, convert large HDL particle to small HDL particles, which are also cleared more rapidly from the circulation by the kidney, thus, reducing the concentration of HDL-P. Furthermore, TG-enriched HDL are intrinsically more unstable in the circulation, with apoA-I loosely bound; in fact, the CE/TG ratio represents a key factor in determining HDL particle stability and plasma residence time. A low CE/TG ratio indicates unstable HDL particles. These intrinsically unstable HDL particles are more rapidly cleared from the circulation, further decreasing HDL-P.

Epidemiologic Evidences of the Protective Role of HDL

Since the 1960s, it has been consistently described in prospective epidemiologic studies a strong inverse relationship between HDL-C levels and CVD risk among patients with high or normal LDL-C levels (for a complete review, [11]). A "classic" study suggested that every 1-mg/dL increase in HDL-C was associated with a CHD risk reduction of 2 %–3 % in CVD events [43]. In addition, this inverse correlation between HDL-C concentrations and CVD events also seemed to remains true in the presence of low LDL-C levels [5, 44].

However, the hypothesis that HDL-C and apoA-I directly confer biological protection against atherosclerosis has never been proven. The same is true for the hypothesis that raising HDL-C or apoA-I levels will result in reduced CVD risk. In fact, several recent lines of evidence have questioned HDL-C and apoA-I as relevant therapeutic targets. First, a recent study showed that some genetic variants that raise HDL-C levels are not associated with a proportionally lower risk of myocardial infarction [45•]. Second, a subanalysis of JUPITER trial has shown that HDL-C and apoA-I were associated with reduced CVD risk among patients in the placebo arm, but that this association was lost among people on rosuvastatin 20 mg achieving very low LDL-C [6]. Third, data from population studies and from a meta-analysis have suggested that changes in HDL-C levels after initiation of lipid modifying therapy are not independently associated with CVD risk [46•, 47]. Finally, recent clinical trials have shown that HDL-C raising pharmacologic therapy increases HDL-C levels but does not reduce CVD events (eg, AIM-HIGH [48] and HPS-THRIVE for niacin, dal-OUTCOMES [49•] for dalcetrapib, ACCORD [50] for fenofibrate).

One possible explanation for this apparent inconsistency between epidemiologic studies and intervention/genetic studies is that we have been focusing specifically on a surrogate and crude measurement like HDL-C, ie, on the cholesterol content of HDL, which may not accurately reflect the beneficial properties of HDL. Thus, we should focus on more sensitive markers of HDL metabolism (eg, HDL-P), which truly reflect and are responsible for the actual beneficial effects of HDL. Several arguments support this hypothesis. First, the relationship between HDL-C and CVD risk is partially confounded by the association between low HDL-C and high levels of LDL-P. In fact, data from the Framingham Offspring Study [51] demonstrate a significant "disconnect" between LDL-C and LDL-P in patients with low HDL-C levels; this implies that a substantial portion of the excess CVD risk of

patients with low HDL-C stems from an unrecognized excess of small, dense LDL-P containing less cholesterol than normal. Second, HDL-C (and even apo A-I) are static mass-based measurement, which cannot represent a dynamic functional process such as RCT (or the anti-inflammatory, anti-apoptotic, anti-oxidant effects of HDL). In fact, only 5 % of the total cholesterol carried by HDL particles is derived from macrophage cholesterol efflux [10••], thus, HDL-C may be an insensitive method to quantify the anti-atherosclerotic properties of HDL. However, the effects of HDL are performed by the HDL-P, therefore, the concentration of HDL-P represent a direct measurement of macrophage RCT. HDL-P particles contain 2–5 molecules of apoA-I; as a consequence, the concentration of apoA-I cannot be used to quantify HDL-P.

To support this hypothesis, there is direct evidence that the concentration of HDL-P provides clinically useful information that is distinct from HDL-C. For instance, in some recent studies, HDL-P concentration has emerged as a predictor of CVD risk that may be superior to that of HDL-C both in population studies [52, 53••, 54•] and randomized, clinical trials of lipid-modifying therapies [7••, 55]. In the Multi-Ethnic Study of Atherosclerosis (MESA), HDL-C was not associated with carotid intima-medial thickness (cIMT) after adjusting by HDL-P and LDL-P; however, low HDL-P predicted higher risk of elevated carotid intima-medial thickness regardless of HDL-C level [53••], even after adjusting by LDL-P. In the JUPITER trial, even though HDL-C did not predict CV risk in statin-treated patients, HDL-P did predict CV risk in all patients (placebo and statin) and even after adjusting by HDL-C levels [7••]. This is finally confirmed in a subanalysis of Veterans Affair High-Density Lipoprotein Intervention Trial (VA-HIT) [55], HDL-VS particles (with high capacity to accept cholesterol) were predictors of CVD risk (OR 0.71, %95 CI, 0.60–0.84, $P<0.01$), whereas the risk associated with HDL-M concentration was weaker (OR 0.82 [0.70–0.96], $P<0.02$) and for HDL-L/HDL-VL particles (with low capacity to regain cholesterol) nonsignificant. Additionally, the clinical relevance of HDL-P also explains the results of the genetic analyses; different alleles in the endothelial lipase (EL) gene increase HDL-C without reducing CVD risk [45•], because mutations resulting in reduced EL activity only increases HDL-C without actually increasing HDL-P, while mutations resulting in reduced phospholipid transfer protein activity translate into reduced CVD risk because they result in increased number of HDL-P [56].

Nonpharmacologic Strategies for Increasing HDL-C

Aerobic Exercise

Regular aerobic exercise moderately increases HDL-C by about 5 % [57, 58]. There appears to exist a minimum exercise volume for a significant increase in HDL-C level that was estimated to be 900 kcal of energy expenditure per week or 120 minutes of exercise per week [58]. Exercise duration per session was the most important element of an exercise prescription, more so than exercise intensity or duration; in fact, a meta-analysis of 25 studies estimated that every 10-minute prolongation of exercise per session was associated with an approximately 1.4 mg/dL increase in HDL-C level [58]. Exercise was more effective in raising HDL-C in subject with initially total cholesterol levels >220 mg/dL or if the body mass index was under 28 [58]. In the first month of exercising the anti-inflammatory effects of HDL-C predominate; in fact after only 3 weeks of exercise, although HDL-C levels did not change, HDL-C preferentially converted to an anti-inflammatory state [59].

Weight Loss

Since obesity is the central abnormality contributing to insulin resistance, weight loss is particularly beneficial for overweight and T2DM patients [60]. In obese patients, the loss of only 1 kilogram is associated to 0.35 mg/dL increase in HDL-C concentration [61]. Since LPL levels are reduced in acute caloric restriction but are greatly increased with established weight loss [62], patients actively losing weight experience an early and transient phase of HDL-C reduction and then HDL-C levels increases proportional to weight loss when the weight is stabilized [63]. In 34 morbid obese patients, bariatric surgery was accompanied by a 20 % decrease in weight, a 14 % increase in HDL-C levels, a 42 % raise in HDL-2 (HDL-L) particles and an improvement in cholesterol efflux through ABCG1 and SR-BI [64].

Tobacco Cessation

Among nonsmokers and light, moderate, and heavy smokers, a significant dose response effect was present for HDL-C (reduction of 4.6, 6.3, and 8.9 % for light, moderate, and heavy smokers compared with nonsmokers) and apolipoprotein AI (reduction of 0, 3.7 and 5.7 % for moderate, and heavy smokers compared with nonsmokers) [65]. Tobacco cessation increases both HDL-C concentrations by 4 mg/dL in men and 6 mg/dL in women , apo A-I levels [66] and HDL-P (especially HDL-2 or HDL-L) [66], as early as 2 weeks [67].

Alcohol Intake

Moderate alcohol intake (20–40 gr daily, roughly 2 drinks in males and 1 drink in females) increases HDL-C levels by 5 %–15 % and decrease CVD risk [68, 69]. Ethanol itself seems to be the cause of this lipoprotein change, thus, all alcoholic drinks could theoretically raise HDL-C [69]. In a recent meta-analysis of more than 16,000 patients, there was a

J-shaped curve of alcohol consumption vs all-cause and CVD mortality [70] (with maximal protection at 22 gr of daily alcohol).

Diets

Diets rich in polyunsaturated free fatty acids (nuts, olive oil, and fatty fish such as salmon, trout, or sardines) increase HDL-C levels and reduce CV risk [71••]. Consumption of a saturated fat reduces the anti-inflammatory potential of HDL and impairs arterial endothelial function. In contrast, the anti-inflammatory activity of HDL improves after consumption of polyunsaturated fat [72].

Diets with low glycemic index both increase HDL-C levels [73–75] and improve HDL anti-inflammatory properties [59]. In fact, considering glycemic index as a continuous variable, we found a reduction in HDL-C concentration of –0.06 mmol/L per 15-unit increase in glycemic index in the diet [74].

The effect of these interventions is summarized in Table 1.

Pharmacologic Treatment

Statins

HDL-C increase due to statin therapy is only mild, by around 5 %–10 % and greatly depends on the statin, with rosuvastatin showing the greatest increases in HDL-C. In a double blind study with 318 patients with metabolic syndrome, rosuvastatin increased HDL-P by 15 % and HDL-C by 10 % compared with placebo and was more effective than atorvastatin in increasing both HDL-C and HDL-P [76]. Besides, while atorvastatin increased HDL-C and HDL-P to a higher extent in patients with high baseline TG levels, the effects of rosuvastatin on HDL-C and HDL-P were independent of baseline TG levels [76].

This effect is partly due to a mild increase in apo A-I synthesis [77] and a reduction in CETP activity [78]. Additionally, statin therapy seems to improve the effects of HDL on cholesterol efflux through SR-B1 but not through ABCA1. Specifically, treatment with atorvastatin was accompanied by a dose-dependent increase in cholesterol efflux from hepatoma cells, an experimental model already validated for the SR-B1 receptor [79]. Additionally, in THP-1 cells, statins increase miR33 expression, thus, reducing ABCA1 expression; in fact, in J774 cells (an experimental model validated for ABCA1 receptor), incubation with statins reduced ABCA1-mediated cholesterol efflux to HDL [80•]. However, whether such statin effects demonstrated under cell culture conditions are relevant *in vivo* remains unknown.

Fibrates

Fibrates are peroxisome proliferator-activated receptor alpha (PPAR-α) agonists. The fibrates-induced increase in HDL-C is 10 %–20 %, while the reduction in TG and LDL-C is 20 %–50 % and 10 %–20 %, respectively. We want to remark that gemfibrozil is the rare example of a raise in HDL-C (7 %) while also specifically increasing the concentration of HDL-P by 21 % [55]. Their mechanism of action is multiple [81]. Fibrates slightly increase the expression of apo A-I, ABCA1, and SR-BI. They also decrease TG (by reducing VLDL synthesis and by activating LPL), which leads to decreased CETP activity. Thus, TG reduction is an indirect way of increasing HDL-C, and the higher the baseline levels of TG, the more marked the increase in HDL-C levels.

The primary-prevention Helsinki Heart Study showed a 34 % reduction in CVD events with an 11 % increase in HDL-C [82]; the benefits were more pronounced in the

Table 1 Effects of nonpharmacologic strategies in HDL-C concentrations

Therapeutic intervention	Increase in HDL-C levels, %	Mechanism of action
Aerobic exercise	5–10	Increases HDL-VS, RCT, LPL, atheroprotective subpopulations, antioxidant activity
Tobacco cessation	5–10	Increases apoA-I and HDL-L
		Increases LCAT and RCT
		Decreases CETP
Weight loss	0.35 mg/dL per kilogram of weight lost	Increases LCAT, LPL, and RCT
Bariatric surgery	15 %	Increases HDL-L and RCT (via SR-B1 and ABCG1)
Alcohol consumption	5–15	Increases ABCA1, apo A-I, and paraoxonase
		Decreases CETP
Dietary factors	0–5	Improves LDL-C/HDL-C ratio
(n-3 PUFAs, n-6 PUFAs, low glycemic index)		Increases HDL-L, antioxidant and anti-inflammatory capacity

LPL lipoprotein lipase, *PUFA* polyunsaturated fatty acid, *RCT* reverse cholesterol transport

Modified from: Santos-Gallego CG, Torres F, Badimon JJ. The beneficial effects of HDL-C on atherosclerosis: rationale and clinical results. Clin Lipidol. 2011;6:181–208 [11]

subgroup with TG >200 mg/dL and HDL-C <42 mg/dL, in which there was a 72 % reduction in CVD event [83]. However, as LDL-C was also decreased by 11 %, those results could be attributed to LDL-C-reduction; besides, only 2.5 % of patients were diabetic. The secondary-prevention VA-HIT [84] clinical trial was the first trial ever in demonstrating that HDL-C increase reduced CVD events in patients. As LDL-C levels were identical in both study groups, the 22 % reduction in CV events could only be attributed to the gemfibrozil-mediated 6 % increase in HDL-C levels. Importantly, gemfibrozil treatment raised the concentration of HDL-P (10 %) and HDL-VS/HDL-S particles (21 %); as a matter of fact, the concentrations of these HDL-P achieved with gemfibrozil were significant, independent predictors of new CVD events (OR 0.71, 95 % CI, 0.61–0.81). We want to point out that, 25 % of patients were diabetic and gemfibrozil showed to reduce CV events in both DM patients (RR 24 [0.1–43], $P<0.05$) and non-DM patients (RR 24 [6, 7••, 8••, 9••, 10••, 11–14, 15•, 16•, 17, 18, 19•, 20–30], $P=0.009$).

The Bezafibrate Infarction Prevention (BIP, only 10 % of DM population) [85] and Fenofibrate Intervention and Event Lowering in Diabetes (FIELD, 100 % of T2DM patients) [86] clinical trials did not show a reduction in CV events in the overall study population, but fibrates reduced the primary composite end point in patients with baseline TG >200 and HDL-C <35 mg/dL. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid Trial [87] studied in 5518 T2DM patients the combination of statin and fibrate vs statin monotherapy; again, there were no significant differences in CVD events. We want to emphasize that not all fibrates are created equal; unlike gemfibrozil [55], fenofibrate has not shown to increase the concentration of HDL-P. Besides, 100 % of the population was T2DM, but surprisingly only 15 % of the patients showed diabetic dyslipoproteinemia, precisely the subgroup where fibrates have consistently proven to be more effective [87]. For a review of all the trials, see Table 2 and other publications [11].

Overall, fibrates seem to reduce total cardiovascular events, coronary events, and albuminuria progression, but they do not show any effect on total or cardiovascular mortality [88].

Niacin

Niacin (vitamin B3, at doses of 1–1.5 gr) is the most effective therapy so far for raising HDL-C. It increases HDL-C by 20 %–35 % and reduces LDL-C by 15 %–20 % and TG by 30 %–50 %, while also decreasing Lp(a). Interestingly, niacin treatment did not increase the number of HDL-P but it increased HDL-C exclusively due to an increase in the size of the HDL particles [89]. Niacin treatment also seemed to improve the cholesterol efflux, anti-inflammatory, antioxidant, vasorelaxant, and endothelial protective effects of HDL-C in diabetic patients [37, 90].

Niacin initially showed consistent benefits in randomized clinical trials with clinical endpoints and with imaging endpoints (atherosclerosis burden). For a review of all the trials, see Table 2 and other publications [11]. However, great controversy has stirred in the last year with the premature end of the seemingly definitive trials, Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes [48] (AIM-HIGH) and Heart Protection Study2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS-2 THRIVE), both showing lack of effect of niacin treatment using CVD outcomes as primary endpoints. AIM-HIGH study randomized 3300 statin-naïve patients with a 3-year follow-up to niacin or placebo (on the background of statin and ezetimibe to maintain LDL-C <80 mg/dL), but failed to demonstrate difference in CVD events between both arms. 34 % of population was diabetic, but there was no overall effect of niacin in diabetes vs nondiabetes patients.

HPS-2 THRIVE enrolled 25,673 patients (32 % of DM population) with a follow-up of 4 years to simvastatin or simvastatin+niacin/laropiprant (niacin causes flushing by binding the PGD2 receptor and laropiprant inhibits this receptor, thus, mitigating flushing), but also failed to demonstrate a difference in CVD events. Besides, the niacin arm was associated with a 3.7 % absolute excess in the incidence of diabetes complications, and a 1.8 % absolute increase in new diagnoses of diabetes (equating to a 25 % increased risk of new-onset diabetes). This study was the last nail in the coffin of niacin.

Additional hypotheses may explain the failure of niacin in this context. First and foremost, the combination of statin and niacin does not increase the number of HDL-P [89, 90]. Therefore, strategies that increase HDL-C without expanding the pool of HDL with its rich proteome/lipidome do not seem to be an effective strategy. In fact, this is corroborated because niacin treatment in AIM-HIGH raised HDL-C by 29 % but it did not improve cholesterol efflux or the HDL anti-inflammatory properties [91•], thus, providing a mechanistic hypothesis for these disappointing results. Besides, niacin treatment moderately enhances the capacity of serum HDL to promote cholesterol efflux from cholesterol-loaded THP-1 macrophages [90], however, niacin had no effect on cholesterol efflux from J774 macrophages in statin-treated patients [92], and all patients in both trials were on statins (which, as previously explained, reduce cholesterol efflux through an miR33-mediated decrease in ABCA-1 expression [80•]). Thus, the atheroprotective properties attributed to niacin may not be the same in statin-treated patients as reported for niacin monotherapy.

Table 2 Main randomized clinical trials involving HDL-C raising drugs with their clinical and imaging endpoints

Study	Drug (s)	Patients receiving treatment, no./total (%)	↑ in HDL-C Levels (%)	Follow-up Duration (yrs)	Outcomes
Nicotinic Acid					
Clinical outcomes studies					
CDP, 1975	Niacin	1119/8341 (13.4)	NR	6	Decreased (15 %) nonfatal MI
CDP Follow-up, 1986	Niacin	1119/8341 (13.4)	NR	15	Decreased (11 %) death
Stockholm, 1988	Niacin + clofibrate	279/555 (50.3)	NR	5	Decreased (26 %) death; decreased (36 %) CAD death
HATS, 2001	Niacin + simvastatin	38/160 (23.8)	26	3	Decreased (90 %) first death, MI, stroke, or revascularization
AFREGS, 2005	Niacin + gemfibrozil + cholestyramine	71/143 (49.7)	36	2,5	Decreased (13 %) composite clinical outcome of angina, MI, TIA, stroke, death, and CV procedures; decreased focal coronary stenosis (secondary outcome)
AIM-HIGH, 2011 [48]	Niacin + simva	1718/3414 (50.3)	25* (12)	3	No difference in 1° endpoint (MI, coronary death, hosp, revasc)
HPS2-THRIVE, 2013	Niacin + laropiprant	12838/25673 (50)	13	3.9	No difference in 1′ endpoint (coronary event, stroke, revasc)
Imaging studies					
CLAS I, 1987	Niacin + colestipol	94/188 (50.0)	37	2	Decreased coronary atherosclerosis
CLAS II, 1990	Niacin + colestipol	75/138 (54.3)	37	4	Decreased coronary atherosclerosis
FATS, 1990	Niacin + colestipol	48/146 (32.9)	43	2,5	Decreased coronary atherosclerosis; decreased death, MI, or revascularization (secondary outcome)
CLAS Fem, 1991	Niacin + colestipol	80/162 (49.4)	38	2	Decreased femoral atherosclerosis
CLAS IMT; 1993	Niacin + colestipol	39/78 (50.0)	38	4	Decreased carotid IMT (regression also observed at yrs 1 and 2)
SCRIP, 1994	Niacin + colestipol + gemfibrozil + lovastatin + aggressive lifestyle modification	145/300 (48.3)	12	4	Decreased coronary atherosclerosis; decreased frequency of new coronary lesion formation
ARBITER 2, 1994	Niacin + statin	87/167 (52.1)	21	1	No progression in atherosclerosis (carotid IMT)
ARBITER 3, 1996	Niacin + statin	87/167 (52.1)	23	2	Decreased carotid IMT
ARBITER 6, 2009	Niacin + statin vs ezetimibe + statin	187/336 (55.6), only 208 had follow-up study at 14 mo	18,4	14 mos	Decreased carotid IMT
Oxford Niacin Study, 2009	Niacin + statin	71	23	1	Decreased carotid wall area, as per MRI
NIA plaque (AHA, not published)	Niacin + statin	145	6	1,5	No change on carotid wall volume, as per MRI
Fibrates					
Clinical outcomes studies					
Newcastle, 1971	Clofibrate	244/497 (49.1)	NR	5	Decreased (33 %) MI
Edimburgo, 1971	Clofibrate	350/717 (48.8)	NR	6	Decreased (62 %) death; decreased (53 %) MI
CDP, 1975	Clofibrate 1,6 gr	1103/8341 (13.2)	NR	6	Nonsignificant decrease (9 %) in nonfatal MI or CAD death ($P > 0.05$)
WHO Cooperative Trial, 1978	Clofibrate 1,6 gr	5331/15 745 (33.9)	NR	5,3	Increased (47 %) death

Table 2 (continued)

Study	Drug (s)	Patients receiving treatment, no./total (%)	↑ in HDL-C Levels (%)	Follow-up Duration (yrs)	Outcomes
					Decreased (20 %) incidence of CAD (mainly due to decreased [25 %] nonfatal MI)
WHO Follow-up, 1984	Clofibrate 1,6 gr	5331/15 745 (33.9)	NR	13	Nonsignificant increase (11 %) in death ($P>0.05$)
HHS, 1987 [82]	Gemfibrozil 1200 mgr	2051/4081 (50.3)	11	5	Decreased nonfatal MI or CAD death (34 %, $P>0.02$)
VA-HIT, 1999 [84]	Gemfibrozil 1200 mgr	1264/2531 (49.9)	6	5,1	Decreased nonfatal MI or CAD death (22 %, $P=0.006$)
BIP, 2000 [85]	Bezafibrate 400 mgr	1548/3090 (50.1)	18	6,2	Nonsignificant decrease in nonfatal MI or CAD death (9 %, $P>0.24$). Significant decrease if baseline TG >200 and HDL <35 (42 %, $P=0.02$)
LEADER; 2002	Bezafibrate 400 mgr	783/1568 (46.9)	11	5	Nonsignificant decrease (4 %) in CAD and stroke ($P>0.05$)D Decreased (40 %) nonfatal MI (secondary outcome)
FIELD, 2005 [86]	Fenofibrate 200mgr	4895/9795 (50.0)	1,2	5	Nonsignificant decrease (11 %) in CAD death or nonfatal MI ($P=0.16$); 24 % decrease in nonfatal MI ($P=0.01$) Nonsignificant increase in total mortality (19 %, $P=0.22$);
ACCORD [87]	Fenofibrate	/5518 (50.0)	1.8	4.7	No decrease in primary endpoint (major CV events) neither in secondary endpoints (major coronary events, stroke, CV mortality)
Imaging studies					
BECAIT, 1996 [55]	Bezafibrate	42/92 (45.7)	9	5	Decreased progression of CAD
LOCAT, 1997 [56]	Gemfibrozil	197/395 (49.9)	21	2,7	Decreased progression of CAD
DAIS, 2001 [57]	Fenofibrate	207/418 (49.5)	8	3	Decreased progression of CAD in patients with DM
Inhibitors de CETP					
Clinical outcomes studies					
ILLUMINATE, 2007 [95]	Torcetrapib + atorvastatin	7533/15067 (50)	72	1	25 % increase in CV events ($P=0,001$); increased death (58 %).
Dalcetrapib, DAL-Outcome [49•]	Dalcetrapib + Statin	7938/15871(50)	40	1	No difference in coronary event + coronary death + stroke
Imaging studies					
ILLUSTRATE, 2007 [96]	Torcetrapib + atorvastatin	591/1188 (49.7)	61	2	No decrease in coronary atherosclerosis progression, as per IVUS
RADIANCE 1, 2007 [97]	Torcetrapib + atorvastatin	450/904 (49.8)	54	2	No decrease in carotid atherosclerosis progression by IMT

Table 2 (continued)

Study	Drug (s)	Patients receiving treatment, no./total (%)	↑ in HDL-C Levels (%)	Follow-up Duration (yrs)	Outcomes
RADIANCE 2, 2007 [98]	Torcetrapib + atorvastatin	377/752 (50)	63	1,8	No change in maximum intima-media thickness
DAL-Plaque [102]	Dalcetrapib + Statin	64/130 (49.8)	31	2	No ↓ in carotid wall (MRI) or macrophage infiltration (PET)
Therapies specifically increasing HDL-P					
Apo A-I Milano, 2003 [112]	ETC-216 (Apo A-I Milano + PL)	45/57 (78.9)	NR	5 wk	Decreased coronary atheroma volume on IVUS
ERASE, 2007 [119]	Reconstituted HDL (CSL-111)	111/183 (60.7)	NR	6 wk	No decrease in coronary atheroma volume on IVUS
Waksmann, 2011 [116]	Autologous delipidated HDL	14/28 (50)	NR	2 wk	HDL-VS increased from 5 % to 80 % Atheroma volume was reduced by 12 % (P=0.2)
ASSURE, 2014 [118]	Resverlogix	240/323 (75)	NR	26 wk	Reduction of 0.6 % in atheroma volume as per IVUS (P=0.08), which was significant if high CRP. Less vulnerability as per VH.

CAD coronary artery disease, *CRP* C-reactive protein, *CV* cardiovascular, *IMT* intima-media thickness, *IVUS* intravascular ultrasound, *MI* myocardial infarction, *MRI* magnetic resonance imaging, *PET* positron emission tomography, *TIA* transient ischemic accident, *VH* virtual histology

Modified from: Santos-Gallego CG, Torres F, Badimon JJ. The beneficial effects of HDL-C on atherosclerosis: rationale and clinical results. Clin Lipidol. 2011;6:181–208 [11]

CETP Inhibitors

Certain Japanese patients with very high HDL-C levels due to low CETP activity were reported in 1989 [93]. That led to the development of several CETP inhibitors, including torcetrapib, dalcetrapib, anacetrapib, and evacetrapib. Torcetrapib was a promising agent since it increased HDL-C by 60 % [94]. Unexpectedly, torcetrapib exhibited deleterious effects in human patients. The Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) clinical trial was the clinical outcomes trial studying in 15,067 patients (45 % DM) the effect of torcetrapib on clinical events [95], it showed a significant increase in both CVD mortality and all-cause mortality in spite of HDL-C increase of 72 % and LDL-C decreases of 25 %, while the 3 imaging studies confirmed atherosclerosis progression (both using IVUS [96] and carotid intima media thickness [97, 98]). Torcetrapib was deleterious in both DM and non-DM patients.

Two different hypotheses may explain this unexpected finding. The first theory relies in that torcetrapib increases HDL-C levels by increasing the cholesterol content within the HDL particle, not by increasing the concentration of HDL-P (thus, not expanding HDL lipidome/proteome and not augmenting the HDL-VS, the main acceptors for macrophage cholesterol efflux). The second hypothesis is that CETP inhibition strategy is safe and useful (some preliminary reports suggest that torcetrapib modestly improves the cholesterol efflux to HDL-L/HDL-VL [99, 100]), but there was unexpected off-target toxicity of the specific molecule torcetrapib. In fact, torcetrapib resulted in activation of renin-angiotensin-aldosterone system, increases in natremia, reductions in kalemia, and increases in blood pressure (in some patients up to 15 mm Hg) [95]. Moreover, other CETP inhibitors (dalcetrapib and anacetrapib) do not cause hypertension and polymorphisms in the CETP gene are concordant with HDL-C levels but not with blood pressure (ie, the hypertensive action of torcetrapib is unlikely to be due to CETP inhibition).

Dalcetrapib is the second CETP inhibitor tested in clinical trials. It increases HDL-C by 34 % [101] but it has demonstrated no improvement in CV outcomes (although it was not harmful) in dal-OUTCOMES [49•] in 15781 patients (25 % DM), no reduction of MRI-evaluated atherosclerosis in dal-PLAQUE [102] and no improvement in endothelial function as per flow-mediated dilation in dal VESSEL [103]. The effect of dalcetrapib was similar in both DM and non-DM patients. Anacetrapib increases HDL-C by 138 %, and LDL-C by 40 %, without any increase in CVD events [104], interestingly, anacetrapib treatment enhanced cholesterol efflux to HDL and the anti-inflammatory properties of HDL [90]. The Randomized EValuation of the Effects of Anacetrapib Through Lipid-modification (REVEAL HPS-3 TIMI 55) trial will be the morbidity and mortality clinical trial assessing anacetrapib

effectiveness in clinical practice in CVD patients in combination with statins. An interesting aspect of anacetrapib is the 40 % reduction in LDL-C, so it is possible that anacetrapib improves CV outcomes, but it will be difficult to demonstrate if this beneficial effect is due to the raise in HDL-C or to the additional lowering of LDL-C.

Therapies Specifically Increasing the Number of HDL-P

We have shown that strategies that increase HDL-C without expanding the pool of HDL-P do not seem to be an effective strategy to reduce CVD. Therefore, novel therapies increasing HDL-P are highly sought after.

Apo A-I Milano is a molecular variant of apo A-I characterized by the Arg(173)–>Cys substitution due to a rare point mutation (R173C), which allows for disulfide dimer formation and consequent anti-oxidant properties of thiol groups. Individuals carrying the apo A-I(Milano) mutation have very low plasma HDL-C levels (10–20 mg/dL) but paradoxically do not develop CVD, leading to the hypothesis that apo A-I(Milano) may be a more functional and beneficial variant of apo A-I [105, 106]. In experimental models, apo A-I(Milano) has demonstrated to regress atherosclerosis in mice [107] and rabbits [108], to change the atheroma plaque into a less vulnerable phenotype [108], to reduce in-stent restenosis [109] and to exhibit antithrombotic [110], and vasoprotective [111] properties. These atheroprotective effects have been successfully confirmed in human patients. First, patients immediately after acute coronary syndrome received 5 weekly injections of Apo A-IM, and intravascular ultrasound found that there was a 4.5 % plaque regression [112]. Besides, another study with injection of reconstituted HDL-C with apo A- I_{Milano} was associated with reverse coronary remodeling and reduced atheroma burden [113].

Direct infusion of rHDL (combination of apo A-I and phospholipids) has been shown to improve RCT [114] and to be endothelial protective. The effect of 4 weekly injections of reconstituted HDL was studied in 183 ACS patients (20 % DM)l [115] using surrogate endpoints (atheroma burden by intravascular ultrasound): there was no statistical significance in atheroma volume in the treatment group compared with placebo (primary endpoint) but there was significant differences compared with baseline atheroma volume (by 5 %, secondary endpoint), but with a high percentage of liver abnormalities.

A novel and promising strategy is the weekly infusions of autologous delipidated HDL. This therapy reduced plaque volume by 12 % in 28 ACS patients [116] (while placebo did increase plaque volume by 3 %). This difference was not statistically significant (P=0.2) due to the small sample size (only 28 patients). Besides, the concentration of HDL-VS increased in the delipidated arm form 5.6 % to an impressive 79.8 %, and this raise in the pool of HDL-P likely explains the impressive reduction in IVUS-determined atheroma burden [116].

Resverlogix (RVX-208) is an apo A-I upregulator because it is a BET-protein inhibitor, leading to enhanced apoA-I gene transcription and increasing, apo A-I synthesis. Resverlogix increased apo A-I mRNA expression, de novo apo A-I synthesis and nascent HDL in vitro in hepatic cells culture; resverlogix also increased serum apo A-I by 60 % and HDL-C levels by 97 % in vivo in adult green monkeys, while simultaneously increasing cholesterol efflux via ABCA1, ABCG1, and SR-BI [117]. In an initial human study with 18 healthy volunteers, RVX-208 treatment increased apo A-I by 10 %, HDL-C by 10 %, cholesterol efflux by 11 %, and HDL-VS by 42 % [117]. However, these promising results were only moderately confirmed in a subsequent study involving 299 statin-treated patients; resverlogix showed a dose-dependent increase on apo A-I levels (by 5.6 %) and HDL-C (by 3.2–8.3 %) [118]. HDL-P only increased by 5 % (HDL-VS by 4 %), which may not be enough to translate in improvements in CVD outcomes. Finally, a recent clinical trial in 324 patients with CVD and HDL-C <39 mg/dL were treated with resverlogix for 26 weeks. There was no statistically significant differences in the primary endpoint (-0.6 % change in percent atheroma volume as determined by intravascular ultrasound, P=0.08), but there was nonetheless significant reduction of atheroma in the subset of patients with high C-reactive protein and less vulnerability as per virtual histology [119].

Apo A-I mimetic peptides are 18 amino acids peptides, which do not have sequence homology with apo A-I (243 amino acids), but mimic the class A amphipathic helixes contained in apo A-I. Intravenous L-4 F inhibits lesion formation in diet-induced atherosclerosis in mice [120]. D-4 F is the same peptide as L-4 F, but is synthesized from all D-amino acids instead of L-amino acids, which confers resistance to intestinal peptidases, thereby allowing oral administration; in fact, oral D-4 F protected mice from diet-induced atherosclerosis [121]. In humans, the administration of 1 single dose of D-4 F to CVD patients improved anti-inflammatory properties of HDL [122]. To overcome the barrier of the cost of chemically synthesizing these peptides, a new variety of tomato genetically overexpressing the apo A-I mimetic 6 F has been developed [123].

Conclusions

Although effective, LDL-C lowering is not enough to completely abrogate atherosclerotic burden and CV events, therefore, strategies focusing on HDL are an attractive promise. First we explain the atheroprotective effects of HDL, both dependent of RCT and also of pleiotropic effects independent

of RCT (anti-inflammatory, anti-diabetic, antithrombotic, anti-apoptotic, vasodilating, and anti-oxidant properties). Then we explain that the relationship between HDL-C and CVD risk are partially confounded by the association between low HDL-C and high levels of LDL-P. This is the rationale to understand that the most important feature of HDL is function (dependent on the concentration of HDL-P) and not HDL-C levels (the amount of cholesterol carried by HDL-P). If we increase HDL-C without expanding the number of particles (eg, niacin in AIM-HIGH or HPS-THRIVE), CVD risk will not be reduced. Therefore, strategies that increase HDL-C without expanding the pool of HDL-P with its rich proteome/lipidome do not seem to be an effective strategy. Finally, the main strategies targeting HDL are explained, with specific focus on the present and future pharmacologic armamentarium and in the results of the main clinical trials involving HDL raising therapy through expansion of the numbers of HDL particles.

Compliance with Ethics Guidelines

Conflict of Interest Carlos G. Santos-Gallego declares that he has no conflict of interest. Robert S. Rosenson has received grant/research support from Astra Zeneca, Amgen, Hoffman-LaRoche, Sanofi-Aventis. He has been a consultant/advisor for Abbott Labs, Aegerion, Amgen, Astra Zeneca, GSK Hoffman-LaRoche, Janssen, LipoScience, Novartis, Regeneron, Sanofi-Aventis. He has equity interests/stock options in LipoScience, Medicines Company. He has received honoraria from Kowa. He receives royalties from UpToDate, Inc.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
, ••• Of major importance

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