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Niacin Therapy, HDL Cholesterol, and Cardiovascular Disease: Is the HDL Hypothesis Defunct?

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Abstract

High-density lipoprotein cholesterol (HDL-C) has been shown in epidemiologic studies to be associated with cardiovascular (CV) risk and thus significant efforts have been focused on HDL-C modulation. Multiple pharmaceutical agents have been developed with the goal of increasing HDL-C. Niacin, the most widely used medication to raise HDL-C, increases HDL-C by up to 25 % and was shown in multiple surrogate end point studies to reduce CV risk. However, two large randomized controlled trials of niacin, AIM-HIGH and HPS2-THRIVE, have shown that despite its effects on HDL-C, niacin does not decrease the incidence of CV events and may have significant adverse effects. Studies of other classes of agents such as cholesteryl ester transfer protein (CETP) inhibitors have also shown that even dramatic increases in HDL-C do not necessarily translate to reduction in clinical events. While these findings have cast doubt upon the importance of HDL-C modulation on CV risk, it is becoming increasingly clear that HDL function-related measures may be better targets for CV risk reduction. Increasing ApoA-I, the primary apolipoprotein associated with HDL, correlates with reduced risk of events, and HDL particle concentration (HDL-P) inversely associates with incident CV events adjusted for HDL-C and LDL particle measures. Cholesterol efflux, the mechanism by which macrophages in vessel walls secrete cholesterol outside cells, correlates with both surrogate end points and clinical events. The effects of niacin on these alternate measures of HDL have been conflicting. Further studies should determine if modulation of these HDL function markers translates to clinical benefits. Although the HDL cholesterol hypothesis may be defunct, the HDL function hypothesis is now poised to be rigorously tested.

Keywords

HDL-C; Niacin; Cardiovascular disease; HDL function

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Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent All studies by the authors involving animal and/or human subjects were performed after approval by the appropriate institutional review boards. When required, written informed consent was obtained from all participants.

Conflict of Interest P Mani declares no conflicts of interest.

What Is the Connection Between HDL and Cardiovascular Disease?

Cardiovascular disease is the leading cause of death worldwide, accounting for almost seven million deaths yearly. Patients with high levels of low-density cholesterol (LDL-C) are at increased risk of cardiovascular disease [1], and lowering LDL-C using HMG-CoA reductase inhibitors, popularly known as statins, has become the primary target to reduce risk of atherosclerotic cardiovascular disease (ASCVD). While LDL-C modulation does lead to significantly decreased risk of cardiovascular events, there are still a substantial number of patients who have incident cardiovascular events despite adequate control of LDL-C [2–8]. This has prompted a search for alternative targets to reduce residual cardiovascular risk after achieving target LDL-C levels.

Low levels of high-density lipoprotein cholesterol (HDL-C) have been shown to be an independent risk factor for ASCVD in several large epidemiologic studies. The Framingham Heart Study first associated low HDL-C (<40 mg/dl in men and <50 mg/dl in women) with adverse cardiovascular events [9], and later studies have shown that cardiovascular risk decreases 2–3 % per 1 mg/dl increase in HDL-C [10]. Given the high prevalence of low HDL-C levels, estimated in one European study as present in 33 % of men and 40 % of women [11], HDL-C has emerged as a popular target for cardiovascular risk reduction in the past several years and has been incorporated into important risk stratification models including the American ASCVD risk algorithm [12•] and the European SCORE model [13].

How Can We Modulate HDL-C?

In light of the physiologic and epidemiologic data supporting a role for HDL-C in reducing cardiovascular risk, there has been significant interest in ways to increase HDL-C. Lifestyle modifications, including smoking cessation, exercise, and weight loss, are effective ways to increase HDL-C. It has been shown in one study that HDL-C falls by 20 % 6 hours after smoking and that this effect persists at 24 hours [14]. Intense exercise can also modestly raise HDL-C levels [15–17], especially in patients with metabolic syndrome or type 2 diabetes. Alcohol consumption can also slightly increase HDL-C levels [18], though this effect is less than that achieved with smoking cessation.

Although non-pharmacologic therapy can be used to slightly increase HDL-C, patients with low HDL-C will likely not significantly raise levels without medical treatment. Unfortunately, the process of identifying an effective HDL-C-raising medication has been challenging. Statins, including high-intensity statins such as atorvastatin and rosuvastatin, have been shown to increase HDL-C by only 5–15 % [8, 19, 20]. Patients on statin therapy who have low HDL-C are still at higher risk of events than those with higher HDL-C [21], highlighting the need for targeted HDL therapeutics. Fibrates, primarily used to reduce serum triglycerides, also increase HDL-C by 10–15 % [22, 23], with demonstrated clinical benefits among those with low HDL-C [24–26]. The incremental benefit of adding fibrates in statin-treated patients remains unclear.

Nicotinic acid, or niacin, has been the most widely used medication to raise HDL-C levels, increasing HDL-C by 16 to 25 % [23, 27]. The Coronary Drug Project was the first randomized controlled trial to assess the efficacy of niacin. Among men with previous

myocardial infarction (MI), niacin versus placebo had no effect on all-cause mortality but resulted in a 14% reduction in cardiovascular death, 26% reduction in strokes and transient ischemic attacks, and 11 % decreased mortality at 15-year follow-up, 9 years after termination of the trial [28, 29]. Studies subsequently followed showing the effectiveness of niacin and statin combination therapy. The HDL-Atherosclerosis Treatment Study (HATS) assessed low-dose simvastatin use with niacin in patients with ASCVD and low HDL-C. Patients treated with simvastatin and niacin had a 26 % increase in HDL-C as well as substantial reductions in LDL-C and triglycerides, leading to a significant decrease in angiographic atherosclerosis compared to those in the control arm and up to 90 % decrease in coronary events compared to placebo [30]. The Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER 2) study also showed that niacin in combination with a statin led to stabilization of carotid intima-media thickness (CIMT), a validated surrogate cardiovascular end point, over 12 months, while patients treated with statin alone saw significant progression of CIMT. The study also showed a non-significant suggestion of trend toward greater reduction in cardiovascular events in patients treated with statin/niacin combination therapy compared to those treated with statin alone [31]. The ARBITER 6-HDL and LDL Treatment Strategies in Atherosclerosis (ARBITER 6-HALTS) trial compared niacin to ezetimibe in statin-treated patients with a primary end point of change in mean CIMT. Niacin was found to induce regression of CIMT and was superior to ezetimibe [32]. These surrogate end point studies led to widespread use of niacin to increase HDL-C for a number of years, until more recent studies with hard outcomes cast doubt on the efficacy and safety of niacin.

The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial assessed if the addition of extended-release niacin to intensive statin therapy would reduce the risk of events in patients with established ASCVD and atherogenic dyslipidemia with well-controlled LDL-C (Table 1) [33••]. The double-blind, randomized trial was conducted at 92 centers in the USA and Canada. Eligible patients were older than 45 years with established cardiovascular disease (stable coronary, cerebrovascular, carotid, or peripheral arterial disease) and low HDL-C (<40 mg/dl in men or <50 mg/dl in women), high triglycerides (150–400 mg/dl), and LDL-C <180 mg/dl if not on a statin at the start of the study. Patients were initially treated with open-label simvastatin plus niacin, and those who were able to tolerate at least 1500 mg of niacin without significant side effects ($n=3414$) were randomized in a 1:1 fashion to receive niacin 1500–2000 mg plus simvastatin ($n=1718$) or placebo (with a 50-mg dose of niacin to allow for blinding) plus simvastatin ($n=1696$). Simvastatin was titrated to achieve an LDL-C of 40–80 mg/dl, and ezetimibe was used at 10 mg if required. The primary end point was composite of the first event of death from coronary disease, non-fatal myocardial infarction (MI), ischemic stroke, >23 hour hospitalization for ACS, or symptom-driven coronary or cerebral revascularization. Mean age of patients was 64 years, 85.2 % were male, 92.2 % were white, 34 % had diabetes, 71.4 % had hypertension, and 81 % had metabolic syndrome at baseline. Most patients were taking a statin at entry (94 %), with a median LDL-C of 71 mg/dl, median HDL-C of 35 mg/dl, and median triglycerides of 161 mg/dl.

The AIM-HIGH trial was halted early after a planned interim analysis suggested futility. Those assigned to the niacin group achieved significant improvement in multiple lipid parameters, including decrease in LDL-C (13.6 % compared to 7.6 % in the placebo group), decrease in median triglycerides (30.8 % compared to 9.9 % in the placebo group), and increase in HDL-C (25 % compared to 11.8 % in the placebo group). The primary end point occurred in 16.4 % of patients in the niacin group and 16.2% of patients in the placebo group (hazard ratio 1.02, 95 % confidence interval (CI) 0.87–1.21, $p=0.80$). There was an increased risk of ischemic stroke as the first event in patients in the niacin group (27 patients [1.6 %] vs. 15 patients 0.9 %], p value not reported); however, 8 of the 27 strokes in the niacin arm occurred between 2 months and 4 years after discontinuation of niacin. Analysis of all patients who had ischemic strokes, whether first or otherwise, again showed a non-significant but consistent trend toward increased risk of stroke in the niacin group (29 vs. 18 patients, hazard ratio (HR) 1.61, 95%CI 0.89–2.9, $p=0.11$). Given this lack of efficacy of niacin in improving cardiovascular outcomes, the study was terminated early after 3 years of follow-up.

The Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) study assigned over 25,000 patients with known vascular disease on statin therapy to receive extended-release niacin with laropirant (used to reduce facial flushing) versus placebo (Table 1) [34•]. This double-blind, randomized trial was conducted at 245 sites in the UK, Scandinavia, and China. Participants included men and women aged 50 to 80 with a history of MI, cerebrovascular disease, peripheral artery disease, or diabetes with evidence of symptomatic coronary disease. Unlike AIM-HIGH, there were no inclusion/exclusion criteria based on lipid parameters. All participants underwent a run-in period on simvastatin with or without ezetimibe to achieve total cholesterol of less than 135 mg/dl and then received escalating doses of niacin plus laropirant for 7–10 weeks. If they did not have clinically significant adverse effects, they were randomized to 2 g of niacin plus 40 mg of laropirant or matching placebo. The primary end point was the first major vascular event, defined as major coronary event, stroke, or coronary or non-coronary revascularization. The baseline mean LDL-C was 63 mg/dl, and mean HDL-C was 44 mg/dl. Patients in the niacin group had an average decrease in LDL-C of 10 mg/dl, average increase in HDL-C of 6 mg/dl, and average decrease in triglycerides of 33 mg/dl compared to placebo. Similar to AIM-HIGH, the study showed that despite favorable changes in HDL-C and other lipid parameters, there was no significant reduction in major vascular events with niacin (13.2 % in niacin arm vs. 13.7 % in the placebo group; HR 0.96, 95 % CI 0.90–1.03, $p=0.29$). There were also no significant differences in separate components of major vascular events including stroke. A significant 10 % reduction in rate of arterial revascularization was noted in the niacin group. However, assignment to the niacin arm was associated with significantly increased adverse effects, including gastrointestinal, musculoskeletal, infectious, and serious bleeding complications, worsened glycemic control amongst diabetics and non-diabetics (55%proportional increase in disturbances of diabetes control and 32 % proportional increase in diabetes diagnosis in the study group), and even a trend toward increased risk of death (6.2%in study group vs. 5.7%in placebo group, HR 1.09, CI 0.99–1.21, $p=0.08$). Given the adverse side effects noted, this trial was also stopped early, with median follow-up time of 3.9 years. The authors concluded that treatment with niacin-laropirant does not

reduce the risk of major vascular events but does increase the risk of serious adverse events, and thus, the use of niacin should be weighed against the potential risks observed.

These two large randomized, controlled, event-driven trials have cast doubt on the efficacy of adjunctive therapy with niacin in addition to statin therapy and have dramatically curtailed the use of niacin. The subjects enrolled in the studies had well-controlled lipids on statin therapy, with median baseline LDL-C of 71 mg/dl in AIM-HIGH and mean 63 mg/dl in HPS2 and median baseline-HDL-C of 35 mg/dl in AIM-HIGH and mean 44 mg/dl in HPS2-THRIVE [33•, 34•]. These subjects likely do not reflect the population whose lipid-modifying therapy would be intensified in clinical practice, and thus, the generalizability of the results must be considered. Other limitations of the trials should also be noted [35, 36]. For example, a higher number of patients in the AIM-HIGH placebo group than in the niacin group were on high-dose statin (24.7 % of control patients on simvastatin 80 mg vs. 17.5 % of study group patients) or ezetimibe (21.5 % of control patients vs. 9.5% of study group patients) in order to keep LDL-C levels equivalent. The control group in AIM-HIGH also received a small dose of niacin to fully blind patients to the side effect profile. The unexpected increase in HDL-C of almost 10 % in the AIM-HIGH control group led to a difference in achieved HDL-C levels of only 4 mg/dl between the two groups, which likely had an impact on the negative findings in an already somewhat underpowered study. In HPS2-THRIVE, the control group did not receive laropiprant, a prostaglandin D(2) receptor-1 antagonist administered with niacin in the study group to reduce flushing. In animal studies, it has been shown that prostaglandin D(2) receptor-1 deletions increase aneurysm formation and accelerate atherogenesis and thrombogenesis [37], but the effect of prostaglandin D(2) receptor-1 antagonism in humans is unclear. Despite these limitations, in the setting of the significant adverse effects seen with niacin, its role now should likely be limited to patients who cannot tolerate statins or who require aggressive reduction in triglycerides and non-HDL-C.

Cholesteryl ester transfer protein (CETP) inhibitors are a potentially exciting addition to HDL-C-raising therapies and initially held great promise to be the most potent HDL-modulating class available. CETP promotes the exchange of cholesteryl esters from HDL to apolipoprotein B-containing lipids (LDL and VLDL) while concurrently exchanging triglycerides from VLDL and LDL back to HDL, leading to smaller, lipid-poor HDL particles (Fig. 1). Inhibition of CETP thus markedly increases HDL-C concentration. In animal studies, cholesterol-fed rabbits receiving a CETP inhibitor demonstrated twofold increase in HDL-C, 50 % decrease in non-HDL-C, and 70 % decrease in atherosclerosis [38]. Unfortunately, these findings have not been reproducible in humans. The Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events (ILLUMINATE) study, the first randomized controlled trial of CETP inhibitors, compared patients on high-intensity statin alone to those on high-intensity statin plus torcetrapib. The study showed that while torcetrapib raised HDL-C by over 60 % and reduced LDL-C by 20 %, it led to an increase in adverse cardiovascular events and all-cause mortality [39]. Furthermore, in the Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation (ILLUSTRATE) follow-up study, torcetrapib had no benefit on coronary atherosclerosis progression as measured by intravascular ultrasound [40]. The lack of efficacy of torcetrapib was

confounded by its aldosterone-like blood pressure-raising effect (an off-target toxicity not associated with other CETP inhibitors), which may partially explain the results of the ILLUMINATE trial. However, the dal-OUTCOMES trial, which studied dalcetrapib versus placebo, was also prematurely halted for lack of efficacy [41]. Some have postulated that CETP inhibitors are mechanistically flawed because they create large, dysfunctional HDL particles, similar to patients with CETP deficiency who have HDL particles which are less effective in reverse cholesterol transport [42]. However, this does not necessarily appear to be the case, as the patients who achieved the highest levels of HDL-C on torcetrapib actually demonstrated regression in coronary plaque volume [43]. Other studies have also shown that larger HDL particles are not associated with coronary atherosclerotic progression by intravascular ultrasound [44] and that HDL particles which are created or increased with CETP inhibition are active in cholesterol efflux [45]. It remains unclear why CETP inhibitors have been ineffective in reducing cardiovascular events despite significant increases in HDL-C. The ongoing studies of anacetrapib and evacetrapib, however, have demonstrated some promise. Anacetrapib increases HDL-C by 130–140 % and decreases LDL-C by 40 % and seems to demonstrate a trend toward lowering cardiovascular events in the Determining the Efficacy and Tolerability of CETP Inhibition with Anacetrapib (DEFINE) trial [46]. Anacetrapib is currently being further evaluated in the Randomized Evaluation of the Effects of Anacetrapib Through Lipid-modification (REVEAL) trial. Evacetrapib increases HDL-C 100–130 % along with a 22–35 % decrease in LDL-C without safety issues [47] and is being tested in the Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition with Evacetrapib in Patients at a High-Risk for Vascular Outcomes (ACCELERATE) trial. The clinical outcomes associated with REVEAL and ACCELERATE will likely determine the future of CETP inhibitors.

The most direct way to modulate HDL is with the use of HDL or ApoA-I mimetics. A variant apolipoprotein called ApoA-I Milano was found in a small group of people in Italy who had marked longevity and reduced risk for atherosclerosis despite very low HDL-C levels. It was found that due to this mutation in ApoA-I, these subjects had increased effectiveness of reverse cholesterol transport and resistance to HDL catabolism [48]. Five weekly infusions of a recombinant ApoA-I Milano-phospholipid complex called ETC-216 in post-ACS patients resulted in a 4.2 % decrease in atheroma volume from baseline using intravascular ultrasound [49]. Despite these compelling results, bringing recombinant HDL infusions to market has been challenging. Several intravenous HDL mimetics are currently in development but have not yet reached the public.

Are There Any Other Useful Measures of HDL?

While doubt has been cast on the role of HDL-C as a target for therapy, there is growing evidence that there are other measures of HDL that may be more closely linked with cardiovascular events.

The biochemical mechanisms underlying the relationships between HDL and cardiovascular risk are complex. The primary atheroprotective role of HDL is in reverse cholesterol transport (RCT), which allows for the excretion of excess cholesterol from peripheral tissues via the bile and feces (Fig. 1). Cholesterol efflux is the first critical step of the RCT pathway

and is the mechanism by which macrophages in the vessel wall secrete cholesterol outside cells [50]. Lipid-poor apolipoprotein A-1 (ApoA-1) is secreted from the liver and intestine and interacts with ATP-binding cassette (ABC) transporter A-1 (ABCA-1) on hepatocytes and macrophage foam cells in atheromatous plaques, leading to efflux of free cholesterol and phospholipids. Free cholesterol in the resulting nascent HDL is esterified in the presence of lecithin/cholesterol acyltransferase (LCAT), leading to the formation of mature HDL. Mature HDL then acts as an acceptor for ABCG-1-mediated cholesterol efflux from macrophages. Cholesteryl ester transfer protein (CETP) mediates the exchange of HDL cholesteryl ester for triglycerides in Apo-B-containing lipoproteins such as LDL. Mature HDL particles can deliver cholesterol to the liver by the hepatic scavenger receptor type B1 (SR-B1) which can then be secreted into bile, completing the RCT pathway [50, 51].

In addition to its role in cholesterol excretion, HDL also has many other less-recognized functions, including anti-inflammatory, anti-oxidant, and vasoprotective properties. Antiinflammatory properties of HDL include regulation of the expression of certain cytokines, such as macrophage TNF and endothelial cell IL-1 and MCP-1, as well as protection against endotoxins [50]. HDL protects against the oxidation of LDL, largely due to the enzyme arylesterase/paraoxonase-1 (PON-1), which is transported with HDL in the plasma and functions to reduce highly atherogenic oxidized LDL particles [52]. Furthermore, HDL is able to interact with endothelial cells via the SR-B1 receptor and promote nitric oxide production [53] and endothelial cell migration for vessel repair [54, 55], allowing for the prevention of plaque growth and thrombosis formation in vessels. These functions, in addition to RCT, help prevent accumulation of endovascular atheromatous plaques.

The principal function of HDL is to promote cholesterol efflux, which can be measured ex vivo using standard cell lines expressing the receptors critical for efflux incubated with blood products from subjects. It has been shown that while HDL-C and ApoA-I levels influence cholesterol efflux capacity, they account for less than 40 % of the observed variation [56•]. Strong inverse relationships have been noted between efflux capacity and prevalent CIMT and angiographic coronary disease, even after adjustment for HDL-C and ApoA-I [56•]. Recently, it was shown that baseline cholesterol efflux capacity is inversely associated with incidence of cardiovascular events in the Dallas Heart Study [57•]. These results confirm that while HDL-C may not be an effective therapeutic target, measures of HDL functionality still hold promise as HDL markers of cardiovascular risk.

The effect of niacin on measures of HDL functionality has been assessed in several studies. Niacin increases SR-B1 and ABCG-1 mediated cholesterol efflux capacity [58–60], but not ABCA-1 mediated efflux [60, 61]. These findings appear to be closely related to increases in HDL-C and shifts toward larger particles, which are more likely to participate in efflux via SR-B1, rather than changes in inherent particle functionality. Studies which assessed the effect of niacin on cholesterol efflux in statin-treated patients have been negative [61, 62], suggesting that the addition of niacin provides no benefit with regard to cholesterol efflux when patients are already on a statin. Furthermore, while niacin does not impair antiinflammatory properties of HDL, it does not appear to augment them either [58]. In summary, while niacin does seem to improve cholesterol efflux capacity via certain

pathways, this is likely only the result of the shift in HDL subclasses induced by niacin, and this effect is negated when patients are on statin therapy.

ApoA-I, the primary apolipoprotein associated with HDL, likely better reflects HDL functionality than HDL-C levels. Unlike ApoB-containing lipids such as LDL or VLDL, each HDL particle can have varying amounts of ApoA-I on its surface, regardless of its cholesterol content. Lipid-poor ApoA-I is the main driver of ABCA-1-mediated cholesterol efflux and thus plays a crucial role in cholesterol clearance. A meta-analysis of eight statin trials which included over 38,000 patients showed that higher HDL-C and ApoA-I levels were associated with reduced risk of major cardiovascular events, even in those with very low LDL-C levels. Interestingly, the analysis showed that while increases in ApoA-I were associated with reduced risk of cardiovascular events, increases in HDL-C were not [63•].

Niacin monotherapy has been shown to increase ApoA-I in small trials [59, 60]. In AIM-HIGH, however, niacin was not effective in modulating ApoA-I, as ApoA-I levels increased to only 131 mg/dl in the niacin group, compared to 127 mg/dl in the statin plus placebo group [33••]. The effects of statin and niacin combination therapy on ApoA-I are not clear, with some studies finding significant increases in ApoA-I [64–66], but others having no effect [33••, 67]. While niacin may have some benefit on ApoA-I levels beyond statin monotherapy, specific therapeutics targeted to increase ApoA-I functionality should be studied.

HDL particle concentration (HDL-P) is a more comprehensive assessment of HDL subspecies than HDL-C and is potentially more representative of HDL functionality, as it weighs both nascent and mature HDL particles equally. Lower HDL-P has been shown in multiple large studies to predict incident cardiovascular events and coronary heart disease death independent of traditional risk factors including HDL-C and to be superior to HDL-C in predicting cardiovascular disease even after accounting for LDL particle measures [57•, 68–73]. On the other hand, HDL subclass or size parameters are not independently associated with CVD risk after accounting for LDL particle and HDL-P levels [70, 74].

The effect of niacin on HDL particle size and concentration has been well studied. It has consistently been shown that niacin shifts the HDL subclass distribution toward larger HDL particles [60, 75–77]. The effects of niacin on HDL-P are less clear. Some studies show a favorable effect of niacin plus statin on HDL-P versus statin monotherapy [71, 72], while other studies of niacin either as monotherapy or in combination with statins show no benefit [67, 78]. Unfortunately, the lack of efficacy of niacin in reducing cardiovascular events will likely curtail enthusiasm for conduct of further studies to definitively assess the impact of niacin on HDL-P, but the effect of other established and new therapeutic agents on HDL-P should be studied.

Is the HDL Hypothesis Defunct?

The last several years have raised significant doubt about the role of raising HDL-C on cardiovascular risk reduction. With the failure of niacin and two CETP inhibitors, many now believe that targeting HDL *cholesterol* is no longer appropriate. However, measures of HDL functionality, rather than cholesterol content, have proven to be more robustly associated

with clinical outcomes and deserve further investigation. The HDL *function* hypothesis is gaining traction as a more direct interrogation of the actions of HDL on the vascular system. Further studies should focus on therapies that target HDL function as measured by parameters such as ApoA-I, HDL-P, and cholesterol efflux and whether improvements in HDL function will translate into clinical benefit. While the HDL cholesterol hypothesis may have faced too many hits to recover, the HDL function hypothesis is gaining steam and holds promise as a means to reduce cardiovascular risk.

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Fig. 1. Reverse cholesterol transport. *LCAT* lecithin/cholesterol acyltransferase, *CETP* cholesteryl ester transfer protein, *FC* free cholesterol, *CE* cholesterol ester, *TG* triglycerides, *LDL-R* LDL receptor

Table 1

Summary of AIM-HIGH and HPS2-THRIVE trials

	AIM-HIGH [33]	HPS2-THRIVE [34]
Patients	3414 patients—1718 niacin and 1696 placebo. Patients with established ASCVD and well-controlled LDL-C on statin	25,673 patients—12,838 niacin + laropiprant, and 12,835 placebo. Patients with history of MI, cerebrovascular disease, peripheral artery disease, or diabetes with symptomatic coronary disease
Exclusions	Hospitalized within 4 weeks for ACS/ revascularization or stroke within 8 weeks	Hepatic, renal, muscular, or other disease. On medication that could interact with study drug. Higher-intensity LDL-lowering regimen than simvastatin 40 mg plus ezetimibe 10 mg
Primary end point/ follow-up period	First event of death from coronary disease, non-fatal MI, ischemic stroke, >23-h hospitalization for ACS, symptom-driven coronary or cerebral revascularization. 3 years	First major vascular event (major coronary event, stroke, or coronary/non-coronary revascularization). 4 years
Outcome	No difference in primary end point (HR 1.02, 95 % CI 0.87–1.21, $p=0.80$)	No difference in primary end point (HR 0.96, 95 % CI 0.90–1.03), $p=0.29$)
Adverse effects	Trend toward increased risk of ischemic stroke	Worsened glycemic control amongst diabetics, increased incidence of diabetes, GI, musculoskeletal, infectious, and serious bleeding complications. Trend toward increased risk of death
Effect on HDL-C	Increased by 25 %	Increased by 6 mg/dl
Effect on LDL-C	Decreased by 13.6 %	Decreased by 10 mg/dl
Effect on triglycerides	Decreased by 30.8 %	Decreased by 33 mg/dl