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Review

Drugs Targeting High-Density Lipoprotein Cholesterol for Coronary Artery Disease Management

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ABSTRACT

Many patients remain at high risk for future cardiovascular events despite levels of low-density lipoprotein cholesterol (LDL-C) at, or below, target while taking statin therapy. Much effort is therefore being focused on strategies to reduce this residual risk. High-density lipoprotein cholesterol (HDL-C) is a strong, independent, inverse predictor of coronary heart disease risk and is therefore an attractive therapeutic target. Currently available agents that raise HDL-C have only modest effects and there is limited evidence of additional cardiovascular risk reduction on top of background statin therapy associated with their use. It was hoped that the use of cholesteryl ester transfer protein (CETP) inhibitors would provide additional benefit, but the results of clinical outcome studies to date have been disappointing. The results of ongoing trials with other CETP inhibitors that raise HDL-C to a greater degree and also lower LDL-C, as well as with other emerging therapies are awaited.

RÉSUMÉ

Beaucoup de patients demeurent exposés à un risque élevé d'événements cardiovasculaires malgré des taux de cholestérol à lipoprotéines de basse densité (cholestérol LDL) correspondant au taux cible ou étant en dessous de ce taux durant la prise de statines. Par conséquent, de nombreux efforts sont axés sur les stratégies pour réduire ce risque résiduel. Le cholestérol à lipoprotéines de haute densité (cholestérol HDL) est un excellent prédicteur inverse et indépendant du risque de maladie coronarienne et, par conséquent, une cible thérapeutique attrayante. Les agents actuellement disponibles qui augmentent le cholestérol à HDL n'ont que des effets modestes dont les preuves d'une réduction additionnelle du risque cardiovasculaire associé à leur utilisation, en plus du traitement de base par statines, sont limitées. On espérait que l'utilisation des inhibiteurs de la protéine de transfert des esters de cholestéryle (PTEC) fournirait des avantages additionnels, mais les résultats d'études cliniques actuelles ont été décevants. Les résultats d'essais en cours utilisant d'autres inhibiteurs de la PTEC qui augmentent le cholestérol HDL à un niveau supérieur et qui abaissent aussi le cholestérol LDL ainsi que d'autres nouveaux traitements sont attendus.

Statin therapy has been shown to lower low-density lipoprotein cholesterol (LDL-C) by approximately 25%-50% with a corresponding 24%-40% relative risk reduction in cardiovascular (CV) events in trials of both high and lower risk patients.¹⁻¹² Nonetheless, many patients remain at substantial risk for future CV events¹³; thus, additional effective therapies are needed. Multiple epidemiologic studies have shown that low levels of high-density lipoprotein cholesterol (HDL-C) are a significant predictor of CV risk, even after adjustment for other risk factors including LDL-C,¹⁴⁻¹⁹ and HDL-C is an important contributor to global cardiometabolic risk.²⁰ A strong, inverse association has been shown

between HDL-C levels and coronary heart disease (CHD), such that every 0.03 mmol/L increment in HDL-C is associated with a significant 2%-3% reduction in the risk of future CHD and a 3%-5% decrement in CV disease (CVD) mortality.¹⁶ Furthermore, there is clinical trial evidence that the association between low HDL-C levels and increased CV risk is present even in statin-treated patients with "optimized" LDL-C levels.²¹ Thus, HDL-C holds potential as a therapeutic target.

HDL-C plays a central role in reverse cholesterol transport (RCT), the process by which excess cholesterol is removed from peripheral tissues including vascular macrophage foam cells and transported to the liver for excretion into bile (see Fig. 1).²²⁻²⁴ Other, less appreciated, antiatherogenic properties of HDL-C have been described including antioxidant and anti-inflammatory effects, inhibition of endothelial cell adhesion molecule expression, prostacyclin stabilization and increased nitric oxide production.²⁴⁻²⁷

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See page xxx for disclosure information.

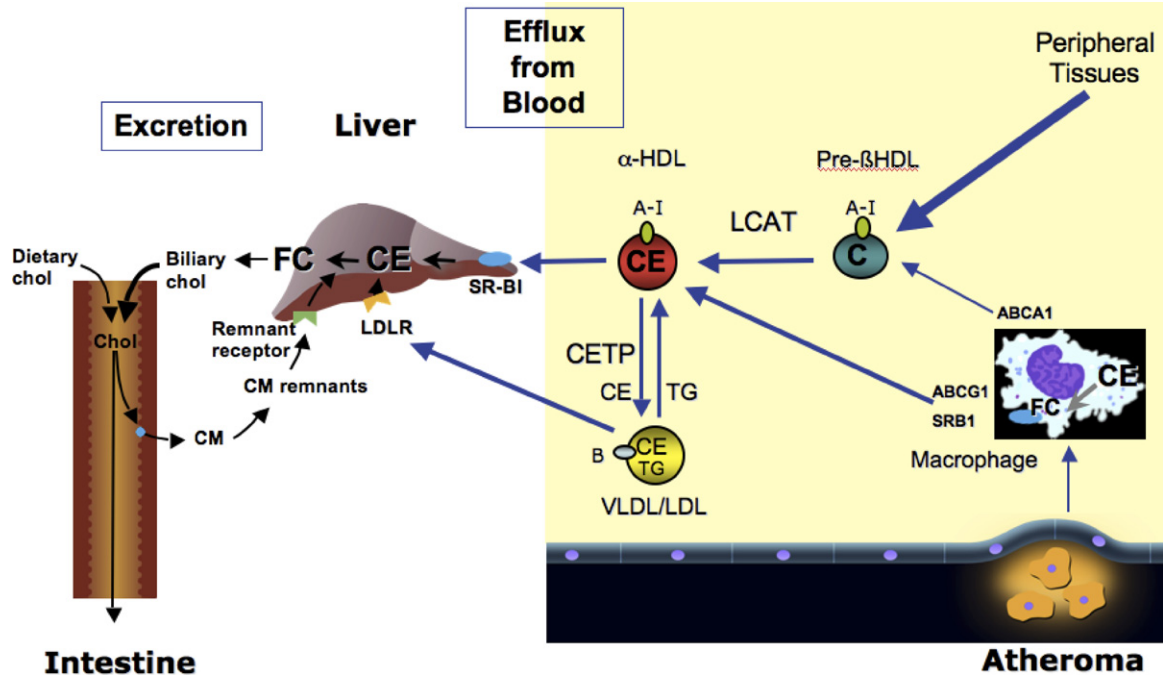


Figure 1. Overview of reverse cholesterol (Chol) transport (RCT). In RCT, ATP-binding cassette transporter 1 (ABCA1) mediates cholesterol efflux from cells to pre- β HDL to form nascent HDL. α HDL can also transport cholesterol out of cells by binding to the ATP-binding cassette sub-family G member 1 (ABCG1) transporter or scavenger receptor class B type 1 (SR-B1) receptor. Mature HDL cholesterol forms when free cholesterol (FC) is esterified to cholesterol esters (CE) by lecithin-cholesterol acyltransferase (LCAT). CE and FC can be taken up directly by the liver via SR-B1 for biliary excretion or conversion to bile acids. Cholesterol ester transfer protein (CETP) mediates the transfer of CE from HDL cholesterol particles to apolipoprotein B-containing particles, including very-low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) cholesterol particles, in exchange for triglycerides (TG). VLDL can be transformed into LDL, and LDL particles bind to hepatic LDL receptors (LDLR), thereby providing an indirect method for cholesterol delivery to the liver. CM, chylomicron; HDL, high-density lipoprotein.

HDL-C may also reduce the risk of thrombosis by inhibiting platelet activation and aggregation.²⁸ Thus, strategies that raise HDL-C may be protective against atherosclerosis through mechanisms beyond RCT.

Nonpharmacologic strategies including aerobic exercise, dietary modification, weight loss, smoking cessation, and moderate alcohol consumption can have a modest impact on HDL-C, in the order of 3%-15%²⁹ and remain a mainstay of therapy. This review will focus on currently available classes of medications that increase HDL-C levels, as well as emerging agents, most notably the cholesteryl ester transfer protein (CETP) inhibitors, for which large CV outcome trials are ongoing. While niacin, fibrates, and to a lesser extent statins, increase HDL-C, they also lower triglycerides and LDL-C (Table 1). As it is not possible to isolate these drugs' HDL-C-raising effects in trials of coronary artery disease (CAD) prevention, it is difficult to determine how much of the benefit derived from these agents is attributable to changes in HDL-C. Furthermore, while low levels of HDL-C have been identified as an important, independent risk factor for the development of CVD, considerable controversy exists regarding the need for pharmacologic treatment of low HDL-C levels, as to date there is a lack of definitive clinical trial evidence demonstrating improvement in CV outcomes with therapeutic increases in HDL-C, particularly in the setting of effective statin therapy.

HDL-C and the Risk of Myocardial Infarction

In a mendelian randomization study, a genetic variant (LIPG Asn396Ser) associated with substantial increases in HDL-C levels (0.14 mmol/L higher; $P = 8 \times 10^{-13}$), but similar levels of other lipids and nonlipid risk factors compared to noncarriers, did not alter the risk of myocardial infarction (MI) (odds ratio [OR], 0.99; 95% confidence interval [CI], 0.88-1.11; $P = 0.85$).³⁰ Furthermore, a 1 SD increase in HDL-C due to genetic score was not associated with risk of MI (OR, 0.93; 95% CI, 0.68-1.26; $P = 0.63$), though from observational studies such an increase would be expected to be associated with reduced risk (OR, 0.62; 95% CI, 0.58-0.66). In contrast, genetic polymorphisms related to plasma LDL-C were consistently associated with an increased risk of MI concordant with that estimated from observational epidemiology. These results challenge the assumption that therapeutic increases in HDL-C should uniformly translate into reduced risk of MI.

HDL as a Predictor of Residual Risk in Statin-Treated Patients

In the simvastatin-treated group of the Scandinavian Simvastatin Survival Study (4S), changes in LDL-C and HDL-C from baseline correlated with reduction in the risk of major CV events, although the relationship with LDL-C was more important.^{31,32} Furthermore, in a pooled analysis of 4 statin trials, modest increases in HDL-C levels with statin therapy corre-

Table 1. Currently available HDL-C-raising agents

Class	Specific agents	HDL-C effects	Other lipid effects	Adverse effects
Niacin	Generic niacin (nicotinic acid) Extended-release niacin (Niaspan [Abbott Laboratories, North Chicago, IL])	↑ 15%-35%	↓ LDL-C 5%-25% ↓ TG 20%-50%	Flushing Pruritis Upper GI symptoms: nausea, vomiting, dyspepsia Hepatotoxicity Hyperglycemia Hyperuricemia
Fibrates	Bezafibrate Fenofibrate Gemfibrozil	↑ 6%-20%	↓ LDL-C 0-20% (but can also result in paradoxical increases, especially in those with ↑ TG) ↓ TG 20%-50%	Dyspepsia Gallstones Hepatotoxicity Myopathy Risk of rhabdomyolysis when combined with statins (gemfibrozil only)
Statins	Atorvastatin Fluvastatin Lovastatin Pravastatin Rosuvastatin Simvastatin	↑ 5%-15%	↓ LDL-C 18%-55% ↓ TG 7%-30%	Myalgias, myositis, rhabdomyolysis (rare) Elevated liver enzymes, hepatotoxicity

C, cholesterol; GI, gastrointestinal; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides.

lated independently with regression of coronary atherosclerosis, although the relationship with improved clinical outcomes remains unknown.³³ In a post hoc analysis of subjects with stable CAD in the Treating to New Targets (TNT) trial, HDL-C, both as a continuous variable and according to quintiles, was shown to be a significant inverse predictor of major CV events across the entire study cohort, even after adjusting for baseline risk factors.²¹ In a regression analysis to determine the interaction between HDL-C and LDL-C levels in patients receiving statins, the predictive role of HDL-C was less marked but still achieved borderline significance ($P = 0.05$). Five-year rates of CV events were 25% lower among those with HDL-C levels in the highest quintile compared with those in the lowest quintile (hazard ratio [HR], 0.75; 95% CI, 0.6-0.95). Even in statin-treated patients who achieved low LDL-C levels (<1.8 mmol/L), the effect of HDL-C on outcomes remained significant (HR, 0.61; 95% CI, 0.38-0.97). The difference in CV risk between the highest and lowest quintile did not, however, reach significance in those allocated to receive high-dose statin therapy with atorvastatin 80 mg daily (HR, 0.81; 95% CI, 0.58-1.14).

In contrast with the above findings, a meta-regression analysis including 108 randomized trials involving almost 300,000 subjects at risk for CV events showed no association between treatment-associated changes in HDL-C and risk ratios for CHD events, or total mortality, when adjusted for changes in LDL-C.³⁴ Furthermore, a relationship was not observed in the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial of CV prevention in lower risk subjects with a baseline LDL-C less than 3.4 mmol/L and a high-sensitivity C-reactive protein of 2 mg/L or more.¹² In the placebo-treated subjects, both HDL-C and apolipoprotein (apo)A1 concentrations were strongly inversely related to vascular risk, both at baseline and on-treatment.³⁵ In contrast, these relationships were attenuated and no longer significant among the 8900 patients who received rosuvastatin 20 mg daily and achieved a mean on-treatment LDL-C of 1.4 mmol/L. Of note, subjects in the JUPITER trial had lower CV

risk that those in 4S or TNT, which might explain the discrepant findings.

Niacin

Of the currently available lipid modifying agents, niacin has the greatest HDL-C-raising effect and also effectively decreases triglycerides. Niacin was introduced as a lipid-lowering agent in the mid-1950s. Evidence of its benefit in the secondary prevention of CHD dates back to the Coronary Drug Project, a placebo-controlled multicentre trial of several lipid-lowering drugs in which 1119 male patients with a proven previous MI were randomized to receive niacin.³⁶ Despite adherence problems due to side effects such as flushing and gastrointestinal irritation, the niacin-treated group had a lower incidence of definite nonfatal MI compared with placebo but no significant reduction in mortality after the initial 6 years of follow-up. This became significant in the subsequent 9-year extended follow-up, in which there were 11% fewer deaths in the group previously randomized to niacin ($P = 0.0004$).³⁷

The Familial Atherosclerosis Treatment Study (FATS) evaluated the impact of 2 intensive lipid-lowering strategies compared with conventional therapy on coronary arteriography in men with established coronary atherosclerosis and high levels of apoB (≥ 1.25 mmol/L).³⁸ Patients in the intensive groups received colestipol with either lovastatin or niacin, while those in the conventional arm received placebo, with colestipol added if their LDL-C was elevated. Conventional treatment resulted in frequent progression of coronary disease (46%), infrequent regression (11%), and a substantial number of CV events (11 events in 10 of 52 patients). By comparison, more intensive therapy halved the frequency of progression, tripled that of regression, and reduced the frequency of CV events by 73% ($P = 0.01$). Multivariate analysis indicated that the increases in HDL-C correlated independently with regression of coronary lesions. Although smaller in numbers, the 10-year follow-up study reported a 13.5% reduction in CV events and 18.5% reduction in total mortality ($P < 0.05$), in those patients treated with aggressive triple-drug therapy.³⁹ When an-

other end point, carotid intima-media thickness, was evaluated in statin-treated patients with or at high risk for CAD, the **Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6 (ARBITER 6)** trial was terminated prematurely after 14 months as the use of extended-release niacin caused significant regression of carotid intima-media thickness compared with ezetimibe.⁴⁰ The incidence of major CV events, although very few in number, was lower in the niacin group than in the ezetimibe group (1% vs 5%; $P = 0.04$), though this was a secondary end point.

In the 3-year double-blind **HDL-Atherosclerosis Treatment Study (HATS)** trial, 160 subjects with CAD, low HDL-C levels (<0.91 mmol/L in men, <1.03 mmol/L in women), and "normal" LDL-C levels (≤ 3.75 mmol/L) were randomized to receive simvastatin plus niacin alone or in combination with antioxidants, antioxidants alone, or placebo.⁴¹ The use of simvastatin plus niacin was associated with a 42% reduction in mean LDL-C levels, a 26% increase in HDL-C levels, a small but significant regression in arteriographic evidence of coronary stenosis, and a significant, 90% relative risk reduction ($P < 0.01$) in a prespecified composite end point which included death from coronary causes, confirmed MI or stroke, and revascularization due to worsening ischemic symptoms.

Combination therapy: niacin and statin

Many of the trials discussed above were conducted prior to the routine use of intensive statin therapy and other disease-modifying interventions such as antiplatelet therapy, β -blockers and renin-angiotensin system inhibitors, which have had a profound effect on our ability to prevent recurrent CV events. Results of the recently published **Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH)** trial, question the utility of adding niacin to raise low levels of HDL-C (mean at baseline approximately 0.9 mmol/L) in statin-treated patients with target LDL-C levels (<1.8 mmol/L).⁴² In this large, multicentre trial of patients with established CVD and atherogenic dyslipidemia, all participants received simvastatin 40 to 80 mg per day plus ezetimibe 10 mg per day, if needed, to maintain an LDL-C of 1.03-2.07 mmol/L. Subjects were randomized to receive extended-release niacin or placebo. The trial was stopped prematurely after a mean follow-up of 3 years due to lack of efficacy. Although niacin therapy significantly increased HDL-C levels and lowered triglyceride and LDL-C levels, there was no incremental CV benefit from the addition of niacin to statin therapy. The primary outcome (a composite of death from CAD, nonfatal MI, ischemic stroke, hospitalization for an acute coronary syndrome (ACS), or symptom-driven coronary or cerebral revascularization) occurred in 16.4% of subjects in the niacin group and 16.2% of those in the placebo group (HR, 1.02; 95% CI, 0.87-1.21; $P = 0.79$). It is important to note that this study was likely underpowered to detect a decrease in CV events and had several other limitations. First, lipid-lowering medications were adjusted after randomization to optimize LDL-C levels and this may have minimized the LDL-C-lowering benefit of niacin. As well, there was a surprising 13% increase in HDL-C levels in the placebo group and therefore relatively small differences in HDL-C were observed between the 2 study arms. Furthermore, these results do not necessarily apply to those

patients whose LDL-C levels are not well controlled with statin therapy.

The much larger **Heart Protection Study 2: Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE)** study has completed recruitment of over 25,000 participants and is scheduled to conclude in 2013.⁴³ These results should clarify the utility of extended release niacin, combined with laropiprant to reduce flushing, in the prevention of major vascular events in high-risk patients who are receiving intensive LDL-C-lowering therapy with simvastatin 40 mg with or without ezetimibe, as required.

Fibrates

Fibrates have been employed for many years in the management of dyslipidemia. This class of agents act selectively on the peroxisome proliferator receptor alpha (PPAR α) receptor to reduce plasma triglycerides, reduce LDL-C, and raise HDL-C levels in the order of 6%-20%. However, outcome studies of the effect of fibrates on CV risk have yielded mixed results.

The **Helsinki Heart Study (HHS)** was a double blind, placebo-controlled trial of 4081 dyslipidemic middle-aged men without known CVD (non-HDL-C ≥ 5.2 mmol/L) to test the efficacy of gemfibrozil in the prevention of CHD.⁴⁴ Treatment with gemfibrozil caused an approximately 10% rise in HDL-C and 10% fall in LDL-C levels, associated with a 34% reduction in the incidence of CHD (95% CI, 8.2-52.6; $P < 0.02$).

Two important secondary prevention trials, the **Veterans Affairs HDL Intervention Trial (VA-HIT)**⁴⁵ and **Bezafibrate Infarction Prevention (BIP)** study⁴⁶ demonstrated the overall safety of fibrates but yielded differing results regarding their efficacy. In VA-HIT, participants had a relatively low mean baseline LDL-C level of 2.9 mmol/L; gemfibrozil raised HDL-C by 6% and decreased triglycerides by 31% and this was associated with a 22% ($P = 0.006$) reduced risk of having a nonfatal MI or death due to CHD.⁴⁵ LDL-C was unchanged throughout the study, suggesting that HDL-C is an independent risk factor for CHD. While bezafibrate also raised HDL-C levels and lowered triglycerides in the BIP study, the frequency of the primary end point (fatal or nonfatal MI or sudden death) was 13.6% on bezafibrate vs 15.0% on placebo ($P = 0.26$).⁴⁶ In a post hoc analysis, the subgroup with high baseline triglycerides (≥ 2.3 mmol/L) had a significant 39.5% reduction in the cumulative probability of the primary end point ($P = 0.02$). Of note, a third small trial of secondary prevention with only 92 participants showed a significant increase in HDL-C concentrations associated with significantly less angiographic disease progression and a 74% relative reduction in coronary events ($P = 0.019$) with bezafibrate compared with placebo, despite no net change in LDL-C.⁴⁷

The **Fenofibrate Intervention and Event Lowering in Diabetes (FIELD)** study was conducted entirely in patients with type 2 diabetes, with or without existing heart disease, and showed a nonsignificant 11% reduction in the primary outcome of coronary events ($P = 0.16$).⁴⁸ Treatment benefit may have been partly masked by higher rates of statin therapy initiation in patients allocated to placebo. Moreover, in the subgroup of patients without CVD at baseline, there was a highly significant 19% reduction in the relative risk of major CV events ($P = 0.004$). In addition to the beneficial effects on

macrovascular disease, fenofibrate is the only lipid-lowering agent that has been shown to improve microvascular complications, including rates of lower extremity amputation⁴⁹ and progression of, and need for laser treatment for, retinopathy,^{50,51} in patients with type 2 diabetes (although improvement in glomerular filtration rate has been shown in some statin trials).⁵²

A meta-analysis by Jun et al. examined the effects of fibrates on CV outcomes in 18 clinical trials of more than 45,000 participants with a broad range of baseline characteristics.⁵³ They showed a modest, but significant, 10% relative-risk reduction in major CV events ($P = 0.048$) and a 13% reduction in coronary events ($P < 0.0001$). There was no effect on the risk of stroke, all-cause, and CV mortality or sudden death. Fibrates were also associated with a 14% reduced risk of albuminuria progression and a lower risk of diabetic retinopathy. There was no significant increase in serious adverse events, including rhabdomyolysis, though increases in serum creatinine concentrations were twice as common in those on fibrate therapy. Interestingly, a subset analysis on coronary events showed that trials which included individuals with high average baseline triglyceride concentrations reported greater proportional risk reductions with fibrate therapy ($P = 0.030$), while baseline trial HDL-C concentrations did not appear to affect outcome in this analysis ($P = 0.47$). This finding is in contrast to subgroup analyses from several individual studies, which have reported greater proportional risk reductions in individuals with the lowest baseline HDL-C values.^{54,55} Unfortunately, the authors were unable to analyze the effect of both high triglycerides and low HDL-C, a common profile particularly among patients with diabetes or the metabolic syndrome who have previously been shown to derive greater benefit from fibrates.

Combination therapy: fibrate and statin

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) lipid trial was a large, multicentre trial designed to test whether combination therapy with simvastatin and fenofibrate would reduce CVD compared with statin monotherapy in patients with type 2 diabetes mellitus, at high risk for CVD.⁵⁴ The primary outcome, which was the first occurrence of a major fatal or nonfatal CV event, occurred at an annual rate of 2.2% in the fenofibrate group and 2.4% in the placebo group (HR, 0.92; 95% CI, 0.79-1.08; $P = 0.32$). Within prespecified subgroup analyses, only sex had a significant interaction with treatment, suggesting a benefit for men and possible harm for women ($P = 0.01$ for interaction). As well, there was a suggestion of heterogeneity according to baseline lipid levels such that patients with both high triglycerides (≥ 2.3 mmol/L) and low HDL-C (≤ 0.9 mmol/L) appeared to benefit more from fenofibrate compared with other patients, though this did not reach statistical significance ($P = 0.057$, with a prespecified P value for subgroups of < 0.01). Importantly, no increase in muscle-related adverse events were observed with combination therapy. To date, there is no clinical trial evidence on the effects of combination therapy with a statin and a fibrate compared with statin therapy alone in patients without diabetes.

CETP Inhibitors

CETP redistributes cholesterol esters from high-density lipoprotein (HDL) into proatherogenic very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) particles, in exchange for triglycerides, and therefore lowers plasma HDL-C levels (Fig. 1).⁵⁶ Rodents, which are naturally deficient in CETP, are relatively resistant to the development of diet-induced atherosclerosis, while rabbits, which have naturally high levels of CETP are highly susceptible. Furthermore, inhibition of CETP in cholesterol-fed rabbits reduces atherosclerosis,⁵⁶⁻⁵⁸ although caution must be used when translating results of animal models to humans. In contrast to humans with genetic CETP deficiency, however, non-HDL-C is also markedly decreased in CETP-inhibited rabbits, which might, in part, explain the species difference in atherogenicity.

Humans with CETP deficiency due to molecular defects in the CETP gene have markedly elevated plasma levels of HDL-C and apoA1.⁵⁹⁻⁶¹ However, subjects with genetic CETP deficiency have been variably reported to be either protected, or at increased risk, for atherosclerotic disease.⁶² In a small study of Japanese families with CETP deficiency, members heterozygous for a point mutation (G→A) in the splice donor site of intron 14 of the CETP gene, had increased HDL-C levels which appeared to be associated with longevity.⁶¹ However, in the Omagari region of Japan, where the intron 14 mutation in the CETP gene is exceptionally frequent, a statistically significant U-shaped relationship was identified between HDL-C levels and the incidence of ischemic changes on electrocardiograms and marked hyperalphalipoproteinemia was not associated with longevity.⁶³ In the Honolulu Heart Program, genetic CETP deficiency was an independent risk factor for CHD among Japanese-American men living in Hawaii who had intermediate HDL-C levels (1.06 and 1.55 mmol/L), though CETP deficiency was not related to CHD prevalence among men who had HDL-C levels above or below these cutoff points.⁶⁴ In the Japanese population living in Kochi Prefecture, subjects with both very high (≥ 2.06 mmol/L) and mild to moderate HDL-C elevations (1.55-2.05 mmol/L), showed a low prevalence of CHD, whether or not they had CETP deficiency.⁶⁵

A large meta-analysis showed that mutations which correlate with modest reductions in CETP mass and function (Taq1B [rs708272], 1405V [rs5882], and 629 C>A [rs1800775]), are associated with modest (4.5%) elevations in HDL-C and an approximately 5% reduction in risk for CHD.⁶⁶ In the Women's Genome Health Study, a single-nucleotide polymorphism at the CETP locus was associated with a per-allele increase in HDL-C levels of 0.08 mmol/L and a concordant 24% reduction in risk for future MI (95% CI, 0.62-0.94), which was not eliminated when adjusted for HDL-C.⁶⁷ In contrast, analysis of genome-wide association studies across tens of thousands of patients showed that common CETP polymorphisms are strongly associated with variation in HDL-C levels, but not associated with differences in CHD risk.⁶⁸ Several other studies, including a prospective analysis of participants in the Framingham Offspring Study and the Ludwigshafen Risk and Cardiovascular Health (LURIC) study in German patients undergoing coronary angiography, have shown an inverse relationship between CETP activity and risk for CV events.^{69,70} In the LURIC study, the HR for death in the lowest CETP quartile was 1.33 (1.07-1.65; $P = 0.011$)

Table 2. Comparison of CETP inhibitors

	Torcetrapib ^{72,76,82,*}	Anacetrapib ^{83,84}	Dalcetrapib ^{85,86}	Evacetrapib ⁸⁷
Key structural characteristics ⁸⁸	Trifluoromethyl-benzene derivative	Trifluoromethyl-benzene derivative	Benzenethiol moiety	Benzazepine compound
In vitro potency (CE transfer) ⁸⁹	IC ₅₀ = 13 ± 2.7 nM	IC ₅₀ = 17 ± 4.8 nM	IC ₅₀ = 1178 ± 443 nM [†]	IC ₅₀ = 26 nM [‡]
Dose in phase III clinical development	60 mg used in ILLUMINATE	100 mg daily	600 mg daily	Unknown
Increase in HDL-C	60%-100%	Approximately 140%	17%-36%	54%-129%
Decrease in LDL-C	17%-25%	Approximately 40%	Not significant	14%-36%
Adverse effects on BP, electrolytes, and aldosterone	Yes	No	No	No

BP, blood pressure; C, cholesterol; CE, cholesterol ester; CETP, CE transfer protein; ILLUMINATE, Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events trial; HDL, high-density lipoprotein; IC₅₀, concentration of compound causing a 50% inhibition of CETP activity; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein.

* Development halted in 2006.

[†] When compound preincubated with CETP and HDL donor particles for 24 hours prior to addition of VLDL/LDL acceptor particles, dalcetrapib became 26-fold more potent; IC₅₀ = 45 ± 2.1 nM.

[‡] Assessed in a separate study therefore cannot directly compare with other CETP inhibitors.

compared with patients in the highest CETP quartile, after adjustment for other CV risk factors.⁷⁰ In a 10-year follow-up analysis of CAD patients treated with statins in the **Regression Growth Evaluation Statin Study** (REGRESS), carriers of Taq1B-B2 had reduced CETP activity and higher HDL-C levels ($P < 0.001$ for both). However, each copy of the B2 polymorphism was associated with an increased risk for ischemic heart disease death and all-cause mortality of 53% and 30%, respectively ($P = 0.03$, $P = 0.04$).⁷¹ Thus, the potential therapeutic benefit of CETP inhibition in humans remains uncertain.

The first CETP inhibitor to be studied in a phase III clinical trial was torcetrapib. Early clinical experience with torcetrapib was promising, demonstrating increases in HDL-C of 60%-100% and reduction in LDL-C by approximately 20%, though small increases in blood pressure had also been observed.⁷²⁻⁷⁵ However, the **Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events** (ILLUMINATE) trial was terminated prematurely due to an unexpected increase in CV events (HR, 1.25; 95% CI, 1.09-1.44; $P = 0.001$) and total mortality (HR, 1.58; 95% CI, 1.14-2.19; $P = 0.006$).⁷⁶ This now appears to be the result of off-target effects of torcetrapib on adrenal steroid production, including increased aldosterone and cortisol, resulting in increased blood pressure and other potential adverse effects on the vasculature.⁷⁷⁻⁸⁰ These effects appear to be independent of CETP inhibition and may be mediated by L-type calcium channels.⁸¹ In the **Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation** (ILLUSTRATE) trial, treatment with torcetrapib had no overall effect on percent atheroma volume despite substantial increases in HDL-C.⁸² However, there was a significant inverse relationship between changes in HDL-C and atheroma volume such that those participants with regression had greater increases in HDL-C. In addition, participants in the highest on-treatment HDL-C quartile showed significant regression of percent atheroma volume compared with those in the lowest quartile ($-0.31 \pm 0.27\%$ vs $0.88 \pm 0.27\%$; $P = 0.001$). This suggests that increases in HDL-C levels achieved using a more selective CETP inhibitor without these off target side effects could still prove effective in the treatment of CVD.

Up until recently, there were 3 CETP inhibitors in phase 3 development: dalcetrapib, anacetrapib, and more recently, evacetrapib, however, development of dalcetrapib was terminated. Important and differentiating properties of these agents are highlighted in Table 2. To date, no formal head-to-head studies have been conducted.

In phase II clinical trials, dalcetrapib 600 mg raised HDL-C concentrations by up to 31%, without significant effects on LDL-C, triglycerides, or blood pressure, and was well tolerated.⁸⁵ The **Dalcetrapib HDL Evaluation, Atherosclerosis and Reverse Cholesterol Transport** (dal-HEART) program encompassed a number of double-blind, randomized, placebo controlled studies designed to evaluate the overall safety of dalcetrapib and to determine the effect of-raising HDL-C with dalcetrapib 600 mg daily on atherosclerotic disease progression and clinical outcomes.⁹⁰⁻⁹³ Dal-PLAQUE assessed the effect of dalcetrapib on imaging measures of plaque inflammation and plaque burden using novel noninvasive multimodality imaging including magnetic resonance imaging and 18F-fluorodeoxyglucose positron emission tomography/computed tomography.⁹⁴ Dalcetrapib use showed no evidence of harm or adverse change during 24 months and a suggestion of some antiatherosclerotic benefits. In the dal-VESSEL study, dalcetrapib had no adverse effect on the primary outcomes of blood pressure, as measured by ambulatory blood pressure monitoring at 4 weeks, or endothelial dysfunction, as measured by flow-mediated dilatation at 12 weeks, in patients with CHD or CHD risk equivalents.⁸⁶ At 36 weeks, HDL-C increased by 31% ($P < 0.001$) and triglycerides were modestly reduced by 14% compared with placebo, while no statistically significant changes were observed in LDL-C or total cholesterol. The frequency of adverse events was similar between the dalcetrapib and placebo arms of these trials.

The dal-OUTCOMES trial was designed to determine whether CETP inhibition with dalcetrapib reduces CV morbidity and mortality in about 15,600 statin-treated patients with a recent ACS.⁹² This trial was stopped prematurely after the prespecified second interim analysis due to futility. No safety concerns were apparently observed. The other studies in the dal-HEART program were also terminated.⁹⁰⁻⁹³ Although dalcetrapib did not show benefit in the dal-OUTCOMES study, it cannot yet be determined whether this was a result of

a lack of benefit of CETP inhibition on CVD, or rather because the drug is a relatively weak CETP inhibitor. Anacetrapib and evacetrapib, which are associated with much greater HDL-C raising, as well as clinically important LDL-C lowering, may still show clinical benefit.

In early studies, anacetrapib produced dose-dependent lipid-altering effects with up to a 129% increase in HDL-C and a 38% decrease in LDL-C in patients with dyslipidemia but did not significantly alter blood pressure in healthy individuals. Coadministration of anacetrapib with atorvastatin produced significant incremental LDL-C reductions compared with atorvastatin monotherapy and a similar HDL-C rise compared with anacetrapib alone.⁸³ In the **D**etermining the **E**fficacy and **T**olerability of **C**ETP **I**nhibition **W**ith **A**nacetrapib (**DEFINE**) study of patients with, or at risk for CHD, with LDL-C levels in the guideline-recommended range on statin therapy, anacetrapib produced an approximately 138% increase in HDL-C and 40% reduction in LDL-C levels and no increase in CV events relative to placebo.⁸⁴ In studies thus far, anacetrapib appears to have a good safety profile without significant effects on blood pressure, serum electrolytes or aldosterone levels.^{83,84,95} The ongoing **R**andomized **E**valuation of the **E**ffects of **A**nacetrapib **T**hrough **L**ipid-**M**odification (**REVEAL**) trial will evaluate whether anacetrapib can reduce coronary events in approximately 30,000 men and women with pre-existing vascular disease who are also receiving atorvastatin.⁹⁶

In a randomized controlled trial of 398 patients, evacetrapib monotherapy at doses of 30, 100, or 500 mg daily produced dose-dependent increases in HDL-C of 53.6% to 128.8% and decreases in LDL-C of up to 36%.⁸⁷ In pre-clinical studies, evacetrapib did not appear to have effects on blood pressure or adrenal synthesis of aldosterone or cortisol.⁹⁷ No details of ongoing trials with evacetrapib are yet available.

HDL Functionality

Increased recognition of the structural and functional heterogeneity of HDL particles has led to the understanding that antiatherogenic therapies must address not only HDL quantity but also the functional quality of resulting particles. The optimal clinical measurement of HDL to appreciate its functional benefits is as yet unclear. One such measure, cholesterol efflux capacity has a strong inverse association with both carotid intima-media thickness and the likelihood of angiographic CAD, independent of HDL-C levels.⁹⁸ Impaired HDL functionality has been reported in a variety of disease states including established CHD,⁹⁹ acute sepsis, and inflammatory states,¹⁰⁰ and metabolic irregularities such as diabetes, the metabolic syndrome, and end-stage renal disease.¹⁰¹

HDL circulates in plasma as a heterogeneous population of lipoproteins that can be separated and classified according to their size, shape, density, composition, and charge.¹⁰² Individual HDL subclasses differ in their ability to promote cholesterol efflux through distinct transporter mechanisms, as well as their nontransport related antiatherosclerotic properties. Small, lipid-poor pre- β -HDL, is the major acceptor of cholesterol effluxed from cells through the ATP-binding cassette transporter 1 (ABCA1).¹⁰² With increasing cholesterol content and particle size, HDL particles accept cholesterol from ATP-

binding cassette sub-family G member 1 (ABCG1) and scavenger receptor class B type 1 (SR-B1), rather than ABCA1.

CETP plays a major role in HDL remodelling in humans (Fig. 1). It promotes heterotypic neutral lipid transfer from HDL to apoB containing lipoprotein particles, LDL and VLDL, a potentially proatherogenic process. CETP also facilitates homotypic transfer of cholesterol esters from HDL3 to HDL2 generating larger, lower density HDL and pre- β -HDL, a potentially antiatherogenic process.¹⁰³ A proposed distinction differentiates the CETP modulator dalcetrapib, from the CETP inhibitors torcetrapib and anacetrapib, based on the putative ability of modulators to selectively inhibit heterotypic transfer between HDL and LDL/VLDL without affecting intra-HDL homotypic transfer and formation of pre- β -HDL.¹⁰⁴ In a hamster model of RCT, CETP modulation with dalcetrapib was more efficient than CETP inhibition with either anacetrapib or torcetrapib in promoting macrophage to feces RCT, while all compounds increased plasma HDL-C levels.¹⁰³ In separate clinical trials, it would appear, however, that CETP inhibition with anacetrapib leads to a greater absolute rise in HDL-C levels than dalcetrapib as well as significant reductions in LDL-C beyond statin monotherapy that are not seen with dalcetrapib. In addition, in a small study, CETP inhibition with anacetrapib, relative to niacin or placebo, led to a more dramatic increase in the ability of HDL-C to promote net cholesterol efflux from foam cells by increasing HDL concentrations and by causing increased efflux at matched HDL concentrations, suggesting enhanced particle functionality, which was more prominent at higher HDL-C concentrations.¹⁰⁵ The degree of CETP inhibition required in humans to optimally increase HDL levels and improve HDL functionality remains undetermined.

Other Emerging Therapies

Although early in development, infusion therapy, with autologous HDL or exogenously produced HDL mimetics, has shown promise in small studies conducted in the acute setting. In a clinical trial of 47 subjects with ACS, 5 weekly infusions of recombinant apoA-1 Milano-phospholipid complex was associated with a rapid, significant 4.2% regression of total atheroma volume as assessed by intravascular ultrasound, despite the short duration of treatment.¹⁰⁶

An investigational device known as the Lipid Sciences Plasma Delipidation System-2 (LS PDS-2; Lipid Sciences Inc, Pleasanton, CA) converts α HDL to pre- β -like HDL by selectively removing cholesterol from HDL in samples of plasma collected from patients by apheresis. The major pathway for cholesterol efflux from cholesterol-filled macrophages is through interaction of pre- β -HDL with the ABCA1 transporter (Fig. 1). In ACS subjects, 7 weeks of autologous delipidated HDL plasma infusions were well tolerated and resulted in increased levels of pre- β -like HDL and a nonsignificant trend toward atheroma regression.¹⁰⁷ Interestingly, the reduction in atheroma volume obtained in the short-term apoA-1 Milano and selective HDL delipidation trials was almost 2-fold that observed with 18 months of high-dose statin (80 mg atorvastatin) therapy in the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial.¹⁰⁸

In a Canadian study conducted at 17 centres, 4 weekly infusions of reconstituted HDL-C (CSL-111) did not produce

a significant change in the primary end point, percentage change in atheroma volume, but did lead to improvements in plaque characterization index and coronary score on quantitative angiography, though the clinical significance of these findings is unknown.¹⁰⁹ Although promising, further study is required in larger patient populations with longer follow-up to confirm the safety profile of these agents and determine their effect on clinical CV events.

Conclusions

Although low baseline levels of HDL-C are a powerful, independent predictor of CV risk, controversy exists as to whether HDL-C continues to predict risk in the setting of effective statin therapy. Moreover, it remains unclear whether therapeutic increases in HDL-C provide incremental benefit beyond statins alone. As such, current Canadian Cardiovascular Society guidelines for the management of dyslipidemia do not list HDL-C levels as a target of therapy (although the total cholesterol/HDL ratio is an optional secondary target). Effective strategies to further reduce residual CV risk remain an ongoing challenge. Further research may yield means of improving HDL-C both qualitatively, as well as quantitatively, with resultant beneficial effects on CV outcomes. However, given the lack of benefit observed in trials of CETP inhibitors to date, results of ongoing clinical outcome studies will be required before these agents are adopted into practice.

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