LEADINGEDGE
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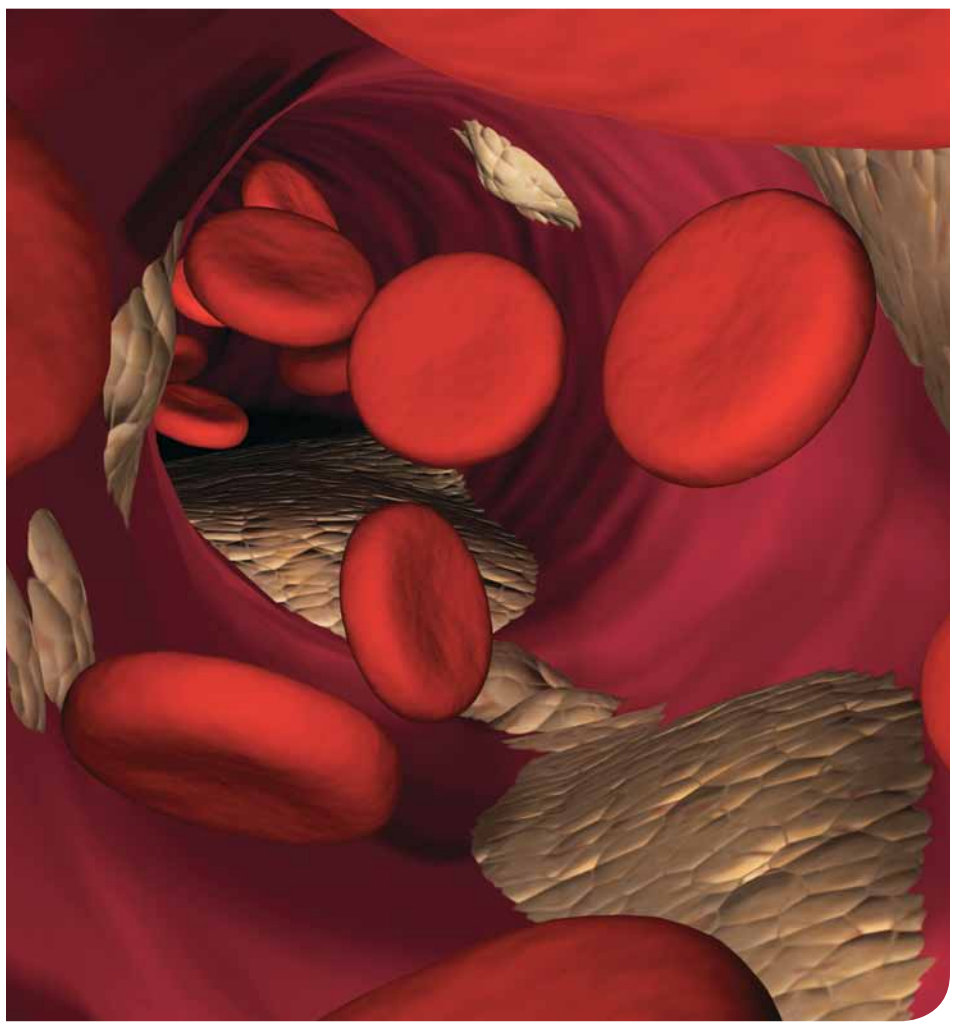
SHOULD HDL BE A THERAPEUTIC TARGET?



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The role of high-density lipoprotein (HDL) in cardiovascular disease (CVD) and protection is a subject of continued debate. Recent research findings have modified some of our previous assumptions in this area of medicine. Understanding the relative value of HDL-raising therapy is an integral component of a cardiovascular clinician's therapeutic repertoire.

The Canadian Cardiovascular Research Network invited a panel of internationally renowned researchers to present and discuss evidence surrounding the question: *Should HDL be a therapeutic target?* This issue of Leading Edge highlights these discussions.

Dr. Robert Hegele

Results of recent genetic studies have led researchers to presume that HDL is a less potent cadiovascular risk factor than LDL. Having looked closely at the evidence, I will present a counterview.

Current knowledge about the value of HDL as a predictor of cardiovascular risk and as a target of treatment falls into four basic categories:
- Epidemiologic
- Mechanistic
- Pharmacologic
- Genetic

Epidemiologic knowledge

The epidemiologic evidence for the cardiovascular benefit of HDL is perhaps the most solid and most widely appreciated.

Low-density lipoprotein (LDL) lowering has been shown repeatedly to be the platinum standard of cardioprotection. Numerous studies – both observational and also from pharmacologic studies using statins – have confirmed that degree of reduction of LDL correlates robustly with reduction of ischemic heart disease in a fairly linear pattern. Every 1% decrease in LDL results in a reduction of events. The epidemiologic relationship is very strong.

There is comparably strong epidemiological evidence in favour of the idea that HDL levels are inversely related to cardiovascular disease risk. In 16 epidemiologic studies of HDL, low levels of HDL predicted cardiovascular events even more robustly than high levels of LDL. For example, the Atherosclerosis Risk In Communities (ARIC) study stratified subjects according to quintiles of HDL. In both men and women, but especially in women, the inverse relationship between HDL levels and cardiovascular risk was robust and clear after adjusting for standard risk factors (*Figure 1*).

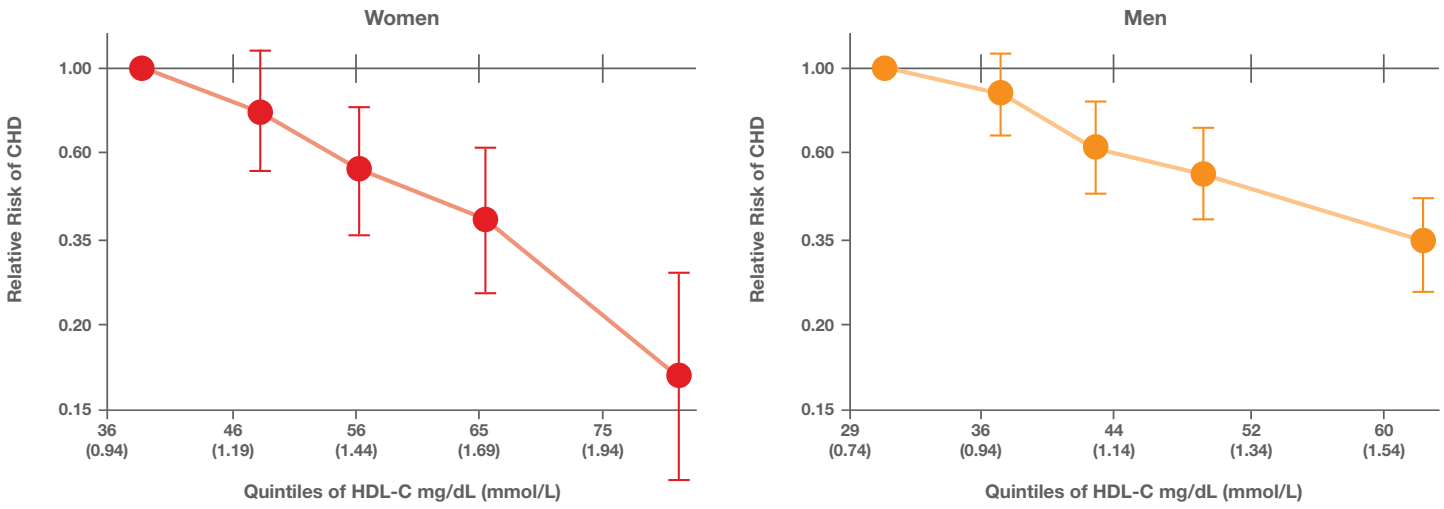
Furthermore. the recent well-designed Emerging Risk Factors Collaboration study had similar results: at all levels of non-HDL cholesterol and in all patient groups, HDL levels were inversely related to event risk. The correlation persisted after adjustment for all known risk factors.

THE BOTTOMLINE

Key concepts:

1. Several epidemiological studies have demonstrated that low HDL cholesterol levels powerfully predict cardiovascular risk.
2. Although raising HDL cholesterol has the potential to reduce residual risk, current pharmacological strategies have yielded mixed results.
3. Fibrates and Niacin are two strategies currently available that raise HDL-cholesterol. A recent meta-analysis suggests that Fibrates may reduce composite cardiovascular events by 10%. Niacin has been shown to reduce surrogate outcomes of atherosclerosis, although there are mixed clinical trial results regarding endpoint reduction.
4. Dalcetrapib and Anacetrapib are CETP inhibitors which raise HDL cholesterol through targeting reverse cholesterol transport. Unlike the first agent in the class, Torceptrapib, these compounds appear to be free of off-site pharmacological effects, and appear to be safe and well tolerated. Dalcetrapib has been demonstrated to have no adverse effect on endothelial function or plaque inflammation.
5. Large scale clinical endpoint studies, such as Dal-Outcomes and REVEAL are ongoing to evaluate these two therapies prospectively.

Figure 1: **Continuous relationship between HDL-C and CHD*† *Atherosclerosis Risk in Communities (ARIC) Study***



* Coronary Heart Disease † Adjusted for age and race
Sharrett et al. *Circulation* 2001;104:1108-1113

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The Canadian Cardiovascular Research Network (CCRN) is a not-for-profi t academic research organization that aims to foster basic, translational, clinical and population level research efforts and generate new knowledge to improve cardiovascular care in Canada. An additional mandate is to develop state-of-the-art knowledge integration platforms that feature multidisciplinary and inter-specialty collaboration focusing on the future of health care delivery, research and academia-industry interface.

Mechanistic understanding

Two major categories of mechanisms may account for HDL's cardio-protective effect:

1) Reverse cholesterol transport: off-loading of cholesterol from arterial wall macrophages, bringing cholesterol safely back into the liver where it can be excreted in bile
2) Anti-atherogenic effects such as an anti-inflammatory effect, inhibition of oxidation of atherogenic lipids in the circulation and in the arterial wall, improvement in vasoreactivity, promotion of fibrinolysis, and reduction in smooth muscle cell growth and of vascular proliferation

If HDL owes its cardioprotective effect mainly to reverse cholesterol transport, a drug that does not boost this mechanism would not be expected to yield clinical benefit. However, if HDL's anti-atherogenic effects take centre-stage, then simply raising HDL levels by any mechanism should translate to a clinical benefit because of all of the beneficial effects of HDL beyond just reverse cholesterol transport.

Not only is HDL more mechanistically complex than LDL, but structurally it is also complicated: it has many more subtypes: about 13 vs. only 3 main subtypes for LDL. Thus, raising one subtype of HDL (such as prebeta HDL-1, which many feel is the key HDL subtype involved in reverse cholesterol transport) may improve clinical outcomes, while raising another subfraction of HDL may not have any effect. Unfortunately, current clinical laboratory tests estimate HDL levels by measuring the cholesterol content in the HDL particle, but yield no information about the relative quantities and functions of these HDL subtypes.

Pharmacologic knowledge

The Cholesterol Trialists meta-analysis showed convincingly using findings from more than 20 studies on more than 100,000 patients that reduction of LDL cholesterol by 1 mmol/L reduces cardiovascular events by about 25%.

There is less compelling data about the effects relationship between "on-treatment" HDL levels and cardiovascular events. We know that in people with well-treated LDL (e.g. 1.8 mmol/L), on-treatment HDL levels are still predictive of events. For instance, subgroup analysis of the Treating to New Targets (TNT) study showed that HDL levels on treatment were a good predictor of outcomes even when LDL was lowered markedly by high-dose compared to low-dose atorvastatin. In contrast, subgroup analysis of the JUPITER study showed that for people with very low treated LDL (<1.4 mmol/L) on rosuvastatin 20 mg , HDL levels ceased to influence cardiovascular risk.

Genetic knowledge

Evidence from the genetic literature on the relationship between HDL levels and CVD risk is contradictory. For instance, there are families and populations that have either genetically high HDL or genetically low HDL. For instance, about 20 years ago, researchers discovered Japanese families with very high HDL (e.g. 2.5 mmol/L) had low rates of heart disease – a finding that spurred interest in HDL's cardioprotective role. More recently, studies of a Newfoundland family with a rare gene mutation that led to a complete absence of Apo-A1 and HDL in homozygotic individuals showed that some, but not all, mutation carriers had increased cardiovascular disease risk. Despite the mathematically infinite ratio of LDL to HDL in these individuals, some of them developed coronary heart disease (CHD), including a 26-year-old male who required coronary artery bypass surgery. The ones with CHD tend to have other risk factors, such as smoking, diabetes, and elevated LDL, and we treat them by controlling their LDL. It seems that low HDL creates "fertile ground" for other risk factors to act on.

There are four known types of genetic mutations that raise HDL to very high levels:

- Mutations causing CETP deficiency: often (though not always) decrease vascular risk
- Mutations causing hepatic lipase deficiency: associated with compositionally "bad" HDL
- Mutations causing receptor defect: no apparent effect on vascular risk
- Endothelial lipase mutation: no apparent effect on vascular risk

About 4% of Japanese people have one of two mutations that lead to CETP deficiency. This population has extremely low rates of heart disease, but the relationship between HDL and events is less clear-cut in other ethnic groups with these mutations, especially Caucasians.

On the other hand, Tangier disease, which is associated with very-low-to-absent HDL levels, is not consistently associated with increased cardiovascular risk. (It bears noting, however, that individuals with Tangier disease also have very low LDL.)

Mendelian randomization

Mendelian randomization refers to the use of genetic variants to estimate a causal effect between a modifiable risk factor and a health outcome. Mendelian randomization studies yield information about the effect of a genetic variant over an entire lifetime on a clinical outcome. These powerful studies can be likened to randomized controlled trials, but applied to genetics, with two alleles being compared (e.g. variant that raises HDL vs. normal variant) taking the place of active drug vs. placebo.

When this approach was applied to LDL, it showed that pretty much any mutation that lowers LDL lowers CVD risk, while any mutation that raises LDL also raises CVD risk. However this same approach yields quite contradictory results for HDL. For instance, an HDL-lowering mutation was discovered in about 1% of the 35,000 patients in the Copenhagen Heart study. People with this mutation have HDL levels around the 20th percentile (< 0.7 mmol/L) and very low plasma Apo-A1 levels. All other lipids are unchanged due to the mutation. Because of the very low HDL levels, one might expect that these patients would have an elevated CVD risk, but surprisingly they do not. It has been suggested that the mutation may not be severe enough. In fact, some recent data suggests that mutations leading to greater HDL reductions in Quebec are associated with increased vascular events.

The literature thus suggests that genes that affect LDL show a more robust correlation with cardiovascular outcomes than genes that affect HDL. Among the ~30 known genetic variants that increase LDL, almost every one increases cardiovascular risk. For example, the LDL-lowering PCSK9 gene variant is linked to a dramatic 88% reduction in CVD risk. By contrast, only half the HDL-raising variants influence cardiovascular risk. In brief, LDL "stacks up well" as a biomarker, while the link between HDL-raising genes and event reduction is somewhat attenuated. This is not to say these genes do not have a significant effect on risk: a close examination of the evidence reveals most of them clearly do. What seems to vary is the extent (*Figure 2*).

Figure 2: **Summary: evidence for the role of LDL, HDL and CETP in CVD and cardioprotection**

	LDL	HDL	CETP
Epidemiologic	++++	**++++**	++
Mechanistic – in vitro	++++	**++++**	++
Mechanistic – in vivo	++++	**++**	+++
Genetic – rare	++++	**++**	+/-
Genetic – common	++++	**+**	+/-
Clinical trials	++++	**++**	+/-

Dr. Lawrence Leiter

While statins significantly reduce the risk of cardiovascular events, they do not eliminate it. The remaining "residual risk" (i.e., risk remaining when LDL is at target) suggests that targeting other risk factors may yield additional benefits beyond the well-established statin effect.

The 2009 Canadian Cardiovascular Society (CCS) guidelines appropriately state that solid evidence for combination therapy is still lacking; at the same time, the guidelines suggest consideration of combination therapy in high-risk patients whose LDL is already at target. (Figure 3)

Of currently available medications, the agents that raise HDL levels the most, while also lowering triglyceride (TG) levels, include niacin and the fibrates (*Figure 4*).

Fibrate trials

In the primary prevention Helsinki Heart Study, use of gemfibrozil was associated with a significant 34% reduction in cardiovascular (CV) outcomes. The trial included patients with high LDL alone, high TG alone, and high LDL/high TG. All three groups benefited from fibrate therapy.

Figure 3: **2009 CCS lipid guidelines: optional secondary targets to reduce residual risk**

Test	Cutoff point	Intervention
TC/HDL ratio	> 4.0	**Niacin, fibrate**
Non-HDL cholesterol	> 3.5 mmol/L	**Niacin, fibrate**
Apo-B/A1	> 0.8	**Niacin, ezetimibe**
Triglycerides	> 1.7 mmol/L	**Fibrate, niacin**
hsCRP	> 2 mg/L	**Statin, ezetimibe**

TC = total cholesterol;
hsCRP = high-sensitivity C-reactive protein
Genest J et al. *Can J Cardiol* 2009;25(10):567-579.

Figure 4: **HDL-C Boosting Agents: Pros and Cons**

Agent	Pros	Cons
Niacin	↑ HDL-C 15%–35% ↓ LDL-C 5%–25% ↓ Triglycerides 20%–50%	• Flushing • Potencial hepatotoxicity • Hyperglycemia • Hyperuricemia (gout) • Upper GI distress
Fibrates	↑ HDL-C 10%–20% ↓ LDL-C 5%–20% ↓ Triglycerides 20%–50%	• Dyspepsia • Gallstones • Myopathy • Risk of myotoxicity (rhabdomyolysis) when combined with statins
Statins	↑ HDL-C 5%–15% ↓ LDL-C 18%–55% ↓ Triglycerides 7%–30%	• Myopathy • ↑ Liver enzymes • Risk of myotoxicity (rhabdomyolysis) when combined with fibrates

HDl-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol
Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *JAMA* 2001;285:2486-97.
Assman G et al. *Circulation* 2004;109(23 suppl 1):III-8–III-14.

Contrary to expectations, the group showing greatest benefit was the high-LDL group.

In the BIP secondary prevention trial, in which patients were not selected for high TG or low HDL, treatment with bezafibrate did not result in a significant reduction in events. In contrast, treatment did lead to a statistically significant benefit in the VA-HIT trial, which included patients with a high risk of myocardial infarction and low HDL. Similar benefits occurred in BECAIT, a small study of young men with premature heart disease. In all these trials, subgroups with metabolic syndrome or overt diabetes derived greater absolute and relative benefits from fibrate intervention than patients unaffected by these conditions.

The biggest study of fibrate monotherapy was FIELD, which involved about 10,000 patients with type 2 diabetes and had primary endpoints of coronary death and nonfatal MI. Treatment led to a non-significant 11% risk reduction. The trial raised concerns because, while nonfatal MI decreased significantly by 24% in the active treatment group, death from coronary heart disease increased by a non-significant 11% in the treatment group. It is hoped that ongoing analyses of the trial will eventually explain these divergent results. As a matter of interest, post-hoc FIELD subgroup analyses revealed that retinopathy rates were lower and albuminuria showed less progression/more regression in the fenofibrate-treated group.

A meta-analysis of 18 fibrate trials, involving 45,000 patients and published last year in The Lancet, linked fibrate treatment to several statistically significant benefits:

- 10% reduction in composite cardiovascular events
- 13% reduction in coronary events
- 19% reduction in nonfatal coronary events
- Reduced progression of albuminuria and retinopathy

On the other hand, treatment did not lead to significant changes in all-cause mortality or cardiac death.

ACCORD trials

The most recent fibrate trial involved about half of the 10,000 patients from the ACCORD glucose trial. Subjects, who were not selected for high TG or low HDL, received either fenofibrate or placebo on top of statin therapy. The primary endpoint of major fatal or nonfatal cardiovascular events was reduced by a nonsignificant 8% in the treatment arm, though patients with high TG and low HDL derived a greater (but still nonsignificant) numerical benefit from treatment, a finding that supports results from other studies.

By the end of the study, similar to what was observed in FIELD, HDL levels had increased by just a few percentage points in the treatment group, and thus it appears that fenofibrate does not have a large, long term, HDL raising effect. On the other hand, triglyceride (TG) levels were decreased significantly with fenofibrate treatment. LDL levels progressively fell in both arms, presumably because statin doses were increased over the course of the study as the evidence for LDL reduction in patients with diabetes continued to mount. In addition, patients in the treatment arm showed a significant improvement in proteinuria. This ACCORD study also showed that the statin/fenofibrate combination was safe, with no observed increase in myositis.

The ACCORD EYE study investigated the effect of glucose lowering, blood-pressure lowering and fenofibrate on retinopathy progression. Perhaps surprisingly, the numerically largest benefit was seen with fenofibrate. While glucose lowering also showed a benefit, blood-pressure lowering did not. Some animal studies and human data support the idea that fibrates may reduce microvascular complications, but the literature is mixed in this regard.

Figure 5: **Nicotinic Acid and Atherosclerosis: Effect on Clinical Outcomes – Randomized Controlled Clinical Trials of Nicotinic Acid and Effect on HDL-C and Clinical Outcomes**

Source Clinical Outcome Studies	Special Agent(s)	Patient Receiving Treatment n/ Total (%)	Increase in HDL-C Levels %	Follow-up Duration y	Outcomes‡
CDP	Niacin	1119/8341 (13.4)	NR	6	Decreased (27%) nonfatal MI
CDP follow-up	Niacin	1119/8341 (13.4)	NR	15	Decreased (11%) death
Stockholm	Niacin + clofibrate	279/555 (50.3)	NR	5	Decreased (26%) death; decreased (36% CAD death
HATS	Niacin + simvastatin	38/160 (23.8)	26	3	Decreased (90%) first death, MI, stroke, or revascularization
AFREGS	Niacin + gemfibrozil + cholestyramine	71/143 (49.7)	36	2.5	Decreased (13%) composite clinical outcome of angina, MI, TIA, stroke, death, and cardiovascular procedures; decreased focal coronary stenosis (secondary outcome)

HDl-C=high-density lipoprotein cholesterol; CDP=Coronary Drug Project; Stocholm=Stockholm Ischemic Heart Disease Secondary Prevention Study; HATS=HDL Atherosclerosis Treatment Study; AFREGS=Armed Forces Regression Study; NR=not reported; MI=myocardial infarction; CAD=coronary artery disease; TIA=transient ischemic attack
‡ Death indicates all-cause mortality
Adapted with permission from Singh IM et al. *JAMA* 2007;298:786-798.

Niacin trials

Niacin was used as a lipid-lowering agent as early as 1955. In addition to significantly lowering LDL, the drug is still the best among available agents for raising HDL and lowering TG. As we all know, the challenge has been to get patients to persist with the drug at sufficiently high doses.

As illustrated in Figure 5, randomized controlled trials of niacin show a consistent benefit on atherosclerosis; however, as many of these studies used a mix of drugs, it is difficult to draw definitive conclusions from them. (*Figure 5*).

Angiographic studies, such as the earlier FATS and SCRIP and the more recent HATS and AFREGS, showed improvements in atherosclerosis associated with niacin usage. In the ARBITER 6 study, statin-treated patients with optimized LDL levels received either ezetimibe or niacin. Carotid intimal medial thickness (IMT) improved in the niacin group, but not in the ezetimibe group. The study's lead author concluded that raising HDL may have more significant cardiovascular benefits than lowering LDL, but most experts do not support this conclusion. Given the fact that the study's subjects had very low LDL at baseline, it is not surprising that they did not stand to derive much extra benefit from ezetimibe's additional LDL-lowering effect.

Niacin also shows a benefit in outcome studies. In the Coronary Drug Project, niacin was associated with a significant reduction in events by the end of the 6-year study period and a significant reduction in mortality at 15-year follow-up. The Stockholm study had similar results. It has been argued that the ASA patients took to prevent flushing, rather than the niacin itself, could have led to the benefit in these trials, and the argument has some plausibility. Flushing does remain a problem even with newer forms of niacin, such as the extended release Niaspan, and market data suggest that fewer than 10% of Niaspan prescriptions are written at the recommended 2g dose, even though the drug's effect on lipids is much less marked at the 1g dose.

Niacin's potential glucose-raising effect has raised concerns among researchers, though the current consensus is that this effect may have been overemphasized. In the ADVENT study, in which patients with diabetes received Niaspan 1,000 or 1,500 mg/day, treatment yielded minimal if any increase in A1C at 16 weeks. It is true that investigators were permitted to adjust patients' antihyperglycemic medication regimens. Still, the provisional conclusion is that niacin does not generally worsen blood glucose if antihyperglycemic mediations are adjusted as needed. In fact, follow-up results from the Coronary Drug Project linked niacin to a reduction in cardiovascular events even in those patients who developed diabetes over the course of the trial. Other research suggests that niacin's adverse effects on glucose may diminish with long-term use.

In summary, data to date suggest that niacin has a cardiovascular benefit in various patient subgroups. Although one large niacin outcomes trial, entitled AIM-HIGH was stopped due to futility, another niacin trial HPS2 THRIVE is still ongoing. At the end however, it may be difficult to ascertain whether any benefit from this agent derives uniquely from its HDL-raising effect.

Dr. Jacques Genest

HDL protects the vascular system through several mechanisms:

- Mediating reverse cholesterol transport
- Potent antioxidant effects
- Potent anti-inflammatory effects
- Improving vascular endothelial function
- Promoting vascular endothelial progenitor cells
- Anti-apoptosis
- Anti-thrombotic effects
- Anti-trypasonomial activity

To what extent do these effects translate into reduced cardiovascular outcomes? Post-hoc analysis from several clinical trials (PROVE-IT, TNT and JUPITER) suggest that when statin therapy optimizes LDL levels, HDL no longer predicts cardiovascular events. However, such studies have limited predictive power. Had we relied on the epidemiological links between LDL and cardiovascular event risk to guide preventive cardiology, statins would not be used today. Hence, clinical trials are the best (and only) way to determine whether a therapeutic approach is effective, and the future utilization of HDL-raising drugs will depend on outcome studies.

CETP inhibition: the new frontier?

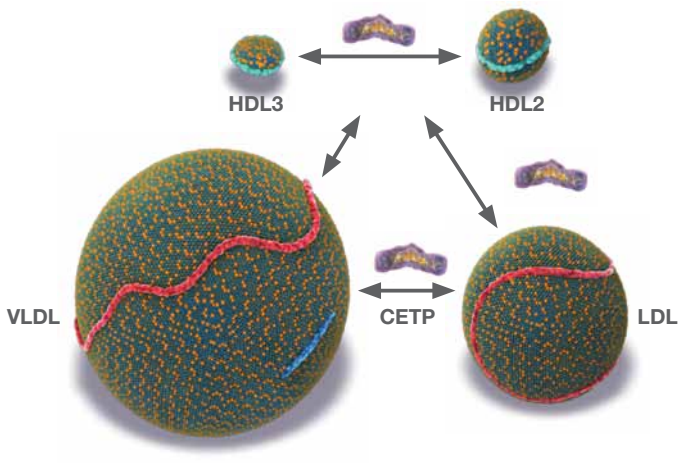
CETP inhibitors target just one of the complex metabolic pathways of HDL. Inhibition of CETP has a degree of biological plausibility as a therapeutic target. CETP mediates the equimolar exchange of cholesterol esters for triglycerides between lipoproteins (mostly HDL- and Apo-B-containing lipoproteins). However, it appears that CETP can also facilitate the net transport of cholesterol esters to Apo-B-rich lipoproteins, thus modulating the metabolism of HDL to lipid-poor particles. CETP inhibition can counteract this process (see *Figure 6, next page*).

Clinical evidence

Torcetrapib

The debate about CETP inhibition has been well addressed in the literature. Clinincal research on the CETP inhibitor torcetrapib was stopped in 2007 in the interest of patient safety. In the ILLUMINATE trial that led to this decision, patients on torcetrapib had a 72% increase in HDL and a 25%

Figure 6: **CETP Activity: Transfer of Neutral Lipids Among All Lipoproteins**



Adapted from Niesor EJ, Magg, C, Ogawa N et al. JLR 2010; 51: 3443-54

decrease in LDL relative to those on placebo. Despite these encouraging results, treatment was associated with a twofold increase in mortality – probably due to off-target effects of the drug. We also know that blood pressure increased in patients in the torcetrapib group. Although the increase in mortality was not statistically significant, it raised enough concerns that the Food and Drug Administration (FDA) mandated ending the trial.

Dalcetrapib

The CETP modulator dalcetrapib differs from torcetrapib in that it contains an active sulfhydryl group, which forms a covalent bond with CETP. By thus inducing a conformational change in the CETP molecule, dalcetrapib inhibits CETP's interactions with lipoproteins. Dalcetrapib can be safely prescribed with other drugs, though plasma exposure to dalcetrapib may be reduced when it is co-administered with most statins (pravastatin being the exception).

Dalcetrapib is effective at modulating CETP activity and raising HDL at doses of 300, 600 and 900 mg. While it shows a good dose-response curve through these doses, "diminishing returns" start taking effect at the 600-mg dose.

In a Phase IIb trial of the drug, the 600-mg dose yielded significant improvements in several key parameters relative to placebo. In addition to being effective at raising HDL, the drug was well tolerated and caused no significant changes in blood pressure or adverse cardiovascular events (*Figure 7*).

Research has linked dalcetrapib to an increase in the amount of prebeta HDL-1, which we believe is active in promoting cellular cholesterol efflux. However, the drug does not appear to affect the exchange of lipids between HDL3 and HDL2. Because it does not act equally on all CETP pathways, dalcetrapib will most likely be promoted as a CETP modulator rather than inhibitor.

These data supported the move toward phase III trials. The phase III program for dalcetrapib, called dal-HEART, will test the hypothesis that raising HDL through CETP modulation attenuates cardiovascular risk. The principal trial in the Phase III program, dal-OUTCOMES, involves over 15,000 patients with stable CHD, three months after a recent acute coronary syndrome (ACS). After optimizing standard medical therapy, patients were randomized to dalcetrapib or placebo.

Figure 7

Parameter	Dalcetrapib 600 mg (n=67)
HDL-C	+29.1%
CETP activity	-22.4%
CETP mass	+77.5%
Apo A-I	+12.6%
Apo A-II	+7.4%

Stein et al. *Am J Cardiol* 2009;104:82-91

The primary outcomes are CHD death, major coronary events, and fatal or nonfatal stroke. Launched in 2008, the trial will continue until 1,600 events have occurred and is expected to yield results in 2013.

Other components of the phase III program include:

- dal-VESSEL: To assess the effect of dalcetrapib on endothelial function and blood pressure, which has recently reported at the ESC 2011 meeting indicating that treatment with dalcetrapib is not associated with an adverse effect on endothelial function or blood pressure.
- dal-PLAQUE: To assess the effect of dalcetrapib on inflammation, plaque size and burden, also recently reported at the ESC 2011 meeting providing evidence that treatment with dalcetrapib has a beneficial effect on plaque progression and plaque inflammation.
- dal-PLAQUE 2: To assess the effect of dalcetrapib on atherosclerotic disease progression using IVUS and CIMT
- dal-ACUTE: To assess the effect of dalcetrapib on HDL when treatment is initiated within 1 week of ACS

The dal-ACUTE study is of particular interest because, if HDL has acute effects on vascular endothelial cells, endothelial progenitor cells, and nitric oxide production, the best time for an HDL-raising intervention would be during or immediately after ACS.

Dalcetrapib singularities within the cetrapib class:

- **Bonds covalently with CETP**
- **Raises prebeta HDL-1**
- **Increases fecal sterol excretion**

Anacetrapib

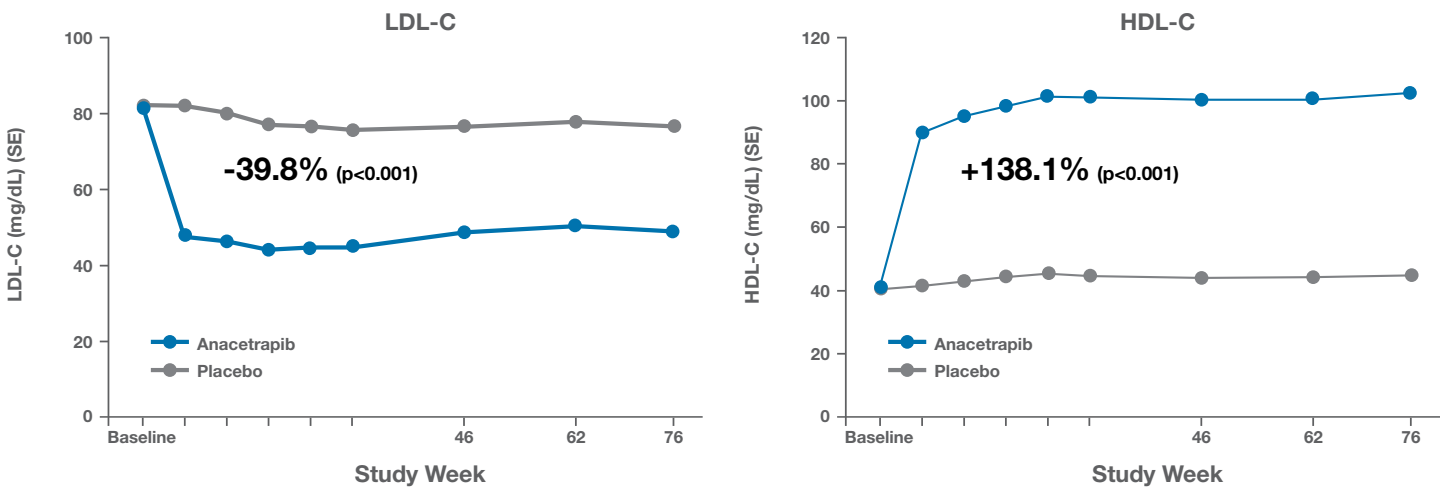
Anacetrapib is structurally closer to torcetrapib than to dalcetrapib. Some data from cell culture studies suggest that anacetrapib promotes cellular cholesterol efflux. Similarly, anacetrapib-treated HDL appears more effective than wild-type HDL in attenuating the inflammatory process (as measured by the secretion of macrophage inflammatory protein (MIP) alpha and interleukin-6). Unlike dalcetrapib, anacetrapib is associated with a decrease in prebeta HDL-1 in human plasma studies.

The trial that put the spotlight on anacetrapib, DEFINE, assessed the effect of anacetrapib on lipid parameters in patients with CHD or CHD risk equivalents. Statin-treated patients were treated with either anacetrapib 100 mg or placebo for 76 weeks, followed by a 3-month post-study follow-up. Primary endpoints were change in LDL and tolerability. Not only did LDL decrease by 40% by the end of the study, but HDL went up by a dramatic 138%. Lipoprotein (a) also went down significantly. The drug appears to be safe and well tolerated, with no effect on blood pressure or the renin-angiotensin-aldosterone system (RAAS) (*Figure 8*).

Anacetrapib's phase III program revolves around the 4-year REVEAL trial, which will recruit about 30,000 patients worldwide, including 3,500 in Canada. All patients will take atorvastatin and will be randomized to anacetrapib 100 mg or placebo. The primary outcome is coronary death, myocardial infarction or coronary revascularization. When the trial is complete, we will hopefully have the data to differentiate anacetrapib – a potent HDL-raising drug – from dalcetrapib, a drug that raises HDL less dramatically but promotes the formation of prebeta HDL-1.

HDL-modulating agents may well be the next frontier in cardiovascular risk management, and the manner by which we raise HDL may prove to be relevant.

Figure 8: **Effects of anacetrapib on LDL-C and HDL-C**



Cannon CP et al. *N Engl J Med* 2010 Dec 16;363(25):2406-15

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