Emerging Importance of HDL-C

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This *Heartbeat* will summarize some information to explain why, how and when raising low high-density lipoprotein cholesterol (HDL-C) is beneficial. The decision to treat depends on the individual's overall risk of coronary heart disease (CHD). Strategies to raise HDL-C can include various lifestyle changes in conjunction with drug therapy, which are tailored to each individual patient. No current therapy is optimal, but many can result in modest increases of HDL-C, which translate into reduced risk of cardiovascular events and improved outcomes.

Cardiovascular disease (CVD)—CHD and stroke—is the principal cause of death in the industrialized world today. Low-density lipoprotein cholesterol (LDL-C) lowering by statins has a significant impact on the treatment and prevention of CVD. Different clinical trials with statins have shown a decrease in LDL-C by 35% and a reduction of coronary events by as much as 30%. Despite this significant clinical impact, 60-70% of events still occur. Obviously more needs to be done.

HDL-C is considered an independent risk factor and has an inverse relation with coronary events (Fig. 1).

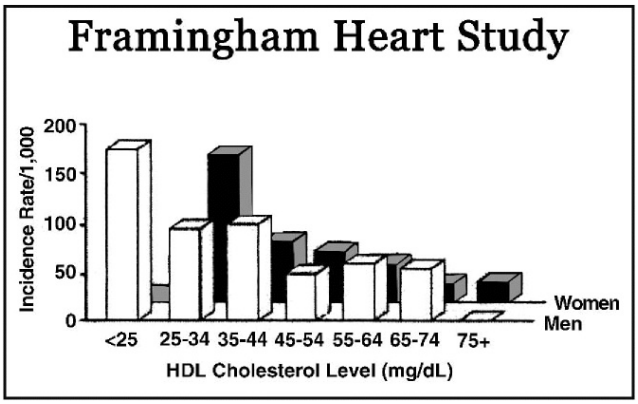

Figure 1. Framingham Heart Study An increase in high-density lipoprotein (HDL) cholesterol concentration is associated with an independent relative risk reduction on the incidence of coronary events in both women and men. *From:* Viles-Gonzalez: Curr Opin Cardiol, Volume 18(4).July 2003.286-294.

This highlights the critical role of HDL-C for protection from atherothrombosis (atherosclerosis combined with and extended by thrombus) and its progression. Recent National Cholesterol Education Program (NCEP) guidelines have highlighted the importance of HDL-C in the prevention and treatment of CVD.[1] Low HDL-C (<40mg/dL) is the most common lipoprotein abnormality in patients with CHD and is predictive of subsequent CHD events, even when total cholesterol is within the desirable range. Despite these findings, physicians still underestimate the clinical significance HDL-C levels, especially the risk of low HDL-C.

Anti-atherothrombotic Effects:

HDL-C appears to exert its anti-atherothrombotic protective effect through multiple mechanisms, including reverse cholesterol transport; antioxidant effects; inhibition of homing of monocytes, apoptosis, platelet activation, and factor X activation; decreased inflammation and improvement of or normalization of endothelial function (Fig. 2).

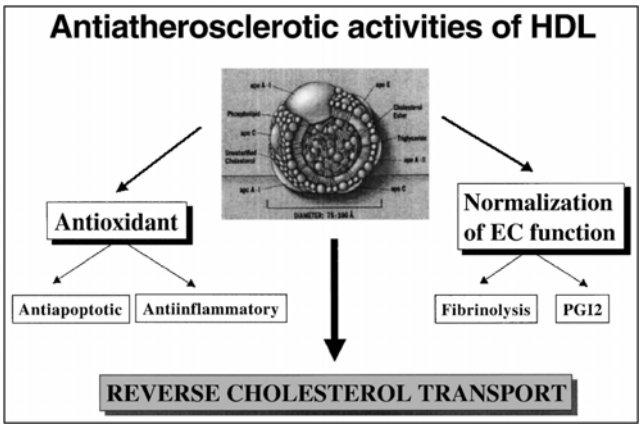

Figure 2. Antiatherosclerotic activities of high-density lipoprotein High-density lipoprotein has multiple mechanisms of action to exert its antiatherogenic effect. Reverse cholesterol transport is the most widely accepted. apo, apolipoprotein; EC, endothelial cell; PG, prostaglandin. *From:* Viles-Gonzalez: Curr Opin Cardiol, Volume 18(4).July 2003.286-294.

Cholesterol transport

Cholesterol deposition is the consequence of the imbalance between the mechanisms responsible for the influx and efflux of cholesterol to the extra-hepatic tissues. LDL-C and HDL-C play different roles within lipid metabolism. LDL-C is responsible for the transport toward the tissues (progression of atherothrombosis) whereas HDL-C is responsible for reverse cholesterol transport (RCT), which transfers cholesterol from peripheral cell membranes, including vascular macrophages, to the liver for biliary excretion (regression of atherothrombosis). HDL cholesterol is associated independently and inversely with cardiovascular disease, largely because of its pivotal role in cholesterol transport.

Endothelial Dysfunction/inflammation

Cholesterol is caustic to the arteries primarily through formation of oxidized LDL-C. Oxidized LDL-C induces expression of adhesion molecules, cytokines, and chemokines, as well as other inflammatory mediators. While LDL-C and other lipoproteins undergo oxidation and contribute to the inflammatory cascade, HDL-C exerts an anti-inflammatory effect in the vasculature, in part by inhibiting oxidized LDL-induced increase of adhesion molecules.

Neutralization of tumor necrosis factor, decrease in complement activation and cytokine-induced vascular cell adhesion molecule induction may all contribute to the ability of HDL-C to inhibit the initiation and progression of vascular plaque formation. Additionally, HDL-C increases prostacyclin (prostaglandin I_2), which inhibits platelet activation and vascular smooth muscle cell growth and migration. HDL also decreases complement activation and has anti-inflammatory properties with direct effects on the vasculature—resulting in inhibition of macrophage-induced oxidization of LDL. Thus, by its anti-inflammatory and antioxidant properties, which improve endothelial dysfunction (ED), HDL may function not only by ameliorating the initial steps of plaque formation, but also by limiting plaque growth and thrombotic potential.[2]

Lipoproteins have direct effects on the vascular endothelium. High levels of LDL cholesterol correlate with a decreased capacity of the endothelium to vasodilate, and oxidized LDL has been shown to decrease endothelial nitric oxide synthase. HDL-C levels are directly and indirectly related to endothelium-dependent vasomotion. Low HDL-C contributes to ED and the increased risk of atherothrombosis and CHD.[3] Interestingly, two intervention studies showed a restoration of endothelial function (assessed by forearm venous occlusion plethysmography) after increasing HDL levels in dyslipidemic subjects. [4] [5] The therapeutic implications of these observations are very important, because ED is the hallmark of early atherogenesis. Hence, increasing plasma levels of HDL may allow us to stop the progression of atherosclerosis at an early stage of the disease.

TLC to increase HDL

There are a number of therapeutic lifestyle changes (TLC), which are important in helping raise HDL-C, but often not enough. Initially HDL-C levels vacillate with *diet and weight loss*. The good news is that weight loss ultimately improves the lipoprotein profile after some possible transient reductions in HDL-C levels during the beginning of active dieting. There are no magic dietary bullets that selectively raise HDL-C levels. Overall, while diet and weight-loss are important components of treatment for low HDL-C, they are often insufficient for optimizing these levels.

Exercise on the other hand is the most important non-pharmocologic method for raising low HDL-C levels. Average increases are in the range of 10-20%, and are usually related to duration of exercise rather than intensity.[6] However aerobic conditioning is less likely to raise HDL-C levels in those with low baseline level (< 40mg/dL) than in those with higher levels. This shouldn't stop us from encouraging exercise, in view of its other well established cardiac benefits.[7] [8] In addition, *hs*-CRP, an inflammatory marker associated with high-risk CHD, is decreased by regular exercise.

Moderate *alcohol consumption* can raise HDL-C levels by 5-10%, and this is associated with enhanced HDL-mediated anti-oxidant effects and RCT—accounting for about 50% of alcohol benefit.[9] Other potential CV benefits of moderate alcohol consumption are reduced platelet aggregation, enhanced fibrinolysis, and improved endothelial function—probably accounting for the other 50%. Moderate consumption is defined as 1-2 oz/day and these effects occur whether the alcohol is in the form

of wine (two 4oz glasses), beer (two 12oz bottles) or spirits (2 shots).

There are modest effects of *omega-3 fatty acids* on HDL-C and a recent policy statement from the American Heart Association endorses it for CHD risk prevention.[10] Capsules are available, but increased fish intake (especially salmon)—1-2x per week—is preferred.

Drug therapy to raise HDL

Niacin: The most potent agent currently available for raising HDL-C levels is niacin or nicotinic acid, producing increases that often approach or exceed 30%. Niacin blocks fatty acid flux from adipose tissue and suppresses the release of very low density lipoproteins from the liver. This decreases the number of small, dense LDL particles and increases the HDL half-life by reducing its degradation. It also decreases cholesterol, LDL-C and triglycerides.

The limitation of niacin is its side effects, primarily flushing (>90 % in the immediate-release form). Other side effects are pruritis (~15%) and rash (~10%). The most serious side effect, hepatotoxicty, is related to higher than recommended dosages of sustained release formulations.

Fortunately, niacin raises HDL-C levels at relatively low doses (~1000mg/day). This supports the pneumonic for niacin treatment of lipoproteins, "Low (dose) to (increase) high and high (dose) to (decrease) low." There is also a "creeping effect" of treatment over time (continued increase of HDL-C), sometimes for as long as a year. Sustained-release formulation (Slo-Niacin—over the counter) or extended-release formulation (Niaspan) are preferred to minimize side effects.

Fibrates: The fibrates, gemfibrozil (Lopid) and fenofibrate (Tricor), raise HDL-C levels significantly (as much as 10-15%). They activate peroxisome proliferator-activated receptor alpha (PPARα), which in turn enhances expression of HDL regulating genes, which produce several related metabolic actions that stimulate RCT. The fibrate effect on HDL-C is greater with higher triglycerides.

Statins: The HMG-CoA reductase inhibitors (statins) raise HDL-C levels by 5-10%, but clinical trials have shown that they have a larger impact on CHD risk than these relatively modest gains would imply.

Clinical trials:

The relation between changes in HDL-C and CAD in the statin trials is difficult to ascertain as a result of the major reduction of LDL-C seen in these trials. There are only a few limited clinical trials focusing on the effects of raising HDL cholesterol on cardiovascular outcomes. Although statins may not commonly be thought of as HDL-raising agents, they do produce modest increases in HDL levels (5-10%). The AFCAPS/TexCAPS trial was a study of healthy subjects with average LDL cholesterol and low HDL cholesterol.[11] Treatment with lovastatin resulted in a 36% reduction in coronary events, and the greatest risk reduction was in the group with the lowest HDL. Thus, the ability of statin therapy to raise HDL levels likely plays a role in their beneficial effects.

Analysis of the lipid changes in the Helsinki Heart Study, the first primary prevention trial with gemfibrozil, indicated a predominant role for the HDL-raising effect of the drug in preventing coronary events: *Every 1% increase in HDL-C was associated with a 3% reduction in coronary events*, independent of changes in LDL-C and triglycerides.[12] The Veterans Affairs HDL Intervention Trial (VA-HIT) trial was the first to demonstrate that raising HDL-C levels in secondary prevention is at least partly responsible for a significant reduction in CAD risk. This study showed a 22% reduction in events, without significant changes in total cholesterol, but an increase of >7% in HDL-C—again supporting that 3:1 rule. Moreover, the benefit was independent of the concentration of LDL-C and triglycerides.[13] It is important to note that fibrates also reduce concentrations of atherogenic particles, normalize LDL composition, and reduce fibrinogen, which could have also contributed to the benefits of VA-HIT.

The protective effect of HDL-C is well known, while decreasing LDL-C gets most of the press. Two studies discussed at the ACC' 03 meeting support the concept that aggressively targeting low HDL-C and increasing it can slow the progression of atherothrombosis and reduce mortality. Treatment included fibrates, and/or niacin along with a CV workout program and a heart-healthy diet. Don't under estimate the beneficial cardiac effects of non-pharmocologic therapy. *Prevention of CHD does not always come in pill form.*

Conclusion:

The protective effects of high levels of HDL have been clearly established by epidemiologic, experimental, and clinical evidence. As such, the *recent NCEP Guidelines have incorporated a low HDL plasma level as a target for pharmacologic treatment and high levels of HDL as a protective factor*.

There is now evidence that raising HDL-C as well as lowering LDL-C has beneficial effects on inflammation (lowering of *hs*-CRP) and endothelial function that might contribute to the reduction in clinical CV events with currently available lipid altering therapies. RCT has a pivotal role in HDL benefits.

Recommendations for Treatment

A modest 5-10% increase in HDL-C can significantly reduce CHD event rates.[14] Therapies to raise low HDL-C levels should be individually tailored based on the patient's overall CHD risk. TLC should always be recommended. Medical therapy will depend on other factors. Statins are still the agents of choice for all with known vascular disease of any kind because of their proven outcomes benefits in clinical end-point trials. They are also the drug of first choice for patients with CHD equivalent disease (DM or those with > 20% 10yr risk of CHD). Fibrates and/or niacin should be used as adjunctive agents with TLC and statins if the HDL-C remains below 40mg/dL. (Patients should be warned of the increased risk of myopathy and rhabdomyolysis with the combination of statins and fibrates or niacin—greater with fibrates compared to niacin. However, the benefit outweighs the risk.)

The decision to treat isolated HDL-C in the absence of known vascular disease or CHD risk equivalents depends on other factors. Those with metabolic syndrome, tobacco dependence disorder, hypertension, strong family history of premature CHD (before age 50 in a first-degree relative) or 10-20% 10yr risk of CHD with a high-risk *hs*-CRP (>3) should be strongly considered for treatment.

Increasing low HDL-C should be part of our global risk reduction strategy to improve CVD outcomes.

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