18 *Strategies to Improve HDL Cholesterol—A New Target*

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Abstract: The plasma concentration of HDL cholesterol (HDL-C) is a significant independent predictor of risk for Coronary Heart Disease (CHD). Long term observational studies such as Framingham heart study and the Prospective Cardiovascular Munster study (PROCAM) have conclusively shown that low HDL-C levels are associated with increased CHD risk.[1,2] And this risk is independent of levels of serum LDL-C [3] or triglyceride.[4] Low HDL-C is frequently encountered lipid abnormality specially in patients who are obese or have metabolic syndrome, and often occurs in the absence of raised LDL-C levels. Prospective epidemiological studies also indicate that every 1mg/dl increase in HDL is associated with 2-3% decrease in risk of CHD. The primary mechanism for this protective effect is believed to be Reverse cholesterol transport (RCT). However several other functions of HDL like anti-inflammatory, antioxidant, antithrombotic, antiproliferative and antiischemic agents have also been identified. In recognition of these beneficial antiatherogenic effects, recent guidelines from NCEP ATP III have increased the threshold for defining low levels of HDL for men and women.

The first step in achieving the targets of HDL-C is therapeutic lifestyle changes. Exercise, smoking cessation, weight control, alcohol intake in moderation, and diet modification have all shown beneficial effects on raising HDL-C and when these measures are not adequate to reach targets, pharmacotherapy specific to lipid profile of patient should be instituted.

Niacin therapy, currently the most effective drug for raising HDL-C, should be initiated in cases with isolated low HDL-C. Cases who have both low HDL-C and elevated LDL-C should receive a statin or statin-niacin combination and cases with Low HDL-C and elevated triglyceride should receive Fibrate initially with a Statin and Niacin or Ezitimibe may be added thereafter as required to attain NCEP targets.

Large number of newer molecules to raise HDL-C are in advanced stage of development.[5,6] Among these are (a) Apo A-I mimetic peptides ("artificial HDL") either as long term oral therapy or by infusion for subacute treatment. (b) CETP inhibitors (Torcetrapib, JTT-705);[7] (c) Vaccines against CETP antigens;[8] (d) drugs to inhibit HDL-Apo AI catabolism (Endothelial lipase inhibitors) A/2; (e) Inhibitors of Acyl coenzyme A- cholesterol acyl transferase (ACAT inhibitors); (f) Type 1 Endocannabinoid receptor antagonists (Rimonabant) (g) Dual PPAR alpha and PPAR – gamma agonists;[9] (h) Nuclear receptor (e.g. Liver x receptor–alpha) agonists.[10] Out of these, rimonabant, Apo AI mimetics like Apo AI milano and CETP inhibitors e.g. Torcetrapib have been studied in recent clinical trials and have been found to be promising.

INTRODUCTION

The serum level of HDL cholesterol has been consistently shown to be inversely related to CAD risk. In the Framingham Heart Study, patients initially free of clinically apparent cardiovascular disease (CVD) and who had the highest HDL cholesterol values at study enrollment had the lowest risk of developing CAD during the next 35 years.[4] This inverse relation between HDL cholesterol and CAD risk was noted at all levels of total cholesterol, including levels below the current desirable level of 200 mg/dl.[11] In the Israeli Ischemic Heart Disease Study, patients with low serum total cholesterol and high HDL cholesterol experienced the lowest rates of CAD-related morbidity and mortality.[12]

Among men enrolled in the Physicians' Health Study (PHS), low serum levels of HDL cholesterol were associated with increased risk for CAD even when total cholesterol levels were low.[13] Among postmenopausal women in the Nurses' Health Study (NHS), it is estimated that a 17-mg/dl elevation in HDL cholesterol reduces risk for developing CAD by approximately 40%.[14]

Low serum levels of HDL cholesterol are associated with increased risk for myocardial infarction (MI), restenosis after angioplasty, sudden death, and stroke.[15-17] Low HDL cholesterol is frequently found in patients with established CVD. In a study of men with angiographically documented premature CAD, the most frequent lipid abnormality noted was isolated low HDL cholesterol.[18] In a study of 8,500 men with CAD, 64% had HDL cholesterol $\leq$ 40% mg/dl.[19] Among patients with CAD and a normal total cholesterol, 73% had very low HDL cholesterol (< 35 mg/dl).[20]

Diabetes mellitus and the metabolic syndrome are often associated with an atherogenic dyslipidemia characterized by a lipid triad of low HDLc, high TG levels, and a preponderance of small, dense LDLc particles, secondary to metabolic changes induced by insulin resistance.[11,21]

Among patients with diabetes, in the United Kingdom Prospective Diabetes Study (UKPDS), CAD risk factors, in order of strength, included high LDL, low HDLc, hyperglycemia, systolic hypertension, and smoking.[22]

Atheroprotective Mechanisms of High-Density Lipoprotein Cholesterol

Reverse Cholesterol Transport

The primary mechanism by which HDL exerts its atheroprotective efficacy is reverse cholesterol transport (RCT), a process by which cholesterol is extracted from macrophages, Foam cells, and atherosclerotic plaque, and delivered back to the liver for elimination as bile salts or biliary cholesterol. HDL also delivers cholesterol to steroidogenic organs, where it is converted into steroid hormones.

Other Proposed Antiatherogenic Mechanisms

In andition to RCT, several other antiatherothrombotic mechanisms have been proposed for HDL particles. These include the inhibition of LDL oxidation via paraoxonase[23] and redox active centers inhibition of thromb induced platelet aggregation and platelet fibrinogen binding by HDL3,[24] inhibation of cytokine-induced expression of such adhesion molecules as vascular –1 by endothelial cells,[25] stimulation of endothelial nitric oxide production[26] and myocardial perfusion *in vivo*,[27] the induction of prostacyclin (prostaglandin I2) production and release in blood vessel walls,[28] and inhibition of endothelial cell apoptosis,[29] among other effects. Patients with the metabolic syndrome experience a marked elevation in the expression of inflammatory mediators and also develop a pro-oxidative and prothrombotic milieu within the vasculature. These changes are highly atherogenic. HDLs appear to be able to buffer at least a part of the toxicity associated with these pathophysiologic transitions.

Clinical Evidence for Raising High-Density Lipoprotein Cholesterol

Several lines of research point to the advantage of raising HDL cholesterol to reduce CAD risk. In a meta-analysis of 4 long-term population studies, every 1 mg/dl increase in HDL cholesterol was associated with a 2% decrease in CAD risk in men and a 3% decrease in women, independent of other CAD factors including LDL.[30] Furthermore, mupltiple placebo-controlled treatment trials also have shown significant associations between raising HDL cholesterol and reductions in CAD risk. In the Helsinki Heart Study (HHS), a primary prevention trial, treatment with gemfibrozil increased HDL cholesterol levels by 11% and decreased TG and LDL levels by 35% and 11% respectively.[31] These changes were associated with a 34% reduction in the incidence of MI and CAD deaths compared with placebo. In the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT), a secondary prevention trial of gemfibrozil, a 6% increase in HDL cholesterol and a 30% reduction in TG levels reduced cardiovascular risk by 22%, independent of LDL levels that remained stable throughout the study.[32] A subsequent analysis showed that most of this reduction correlated with the increase in HDL cholesterol, and estimated an 11% reduction in CAD events for every 5-mg/dl increase in HDL cholesterol.[33] In VA-HIT, neither TG levels nor LDL predicated CAD risk in multivariate analysis. In a post hoc evaluation of the Bezafibrate Infarction Prevention Trial (BIP), a significant risk reduction (41%, $p < 0.01$) was seen only in patents with TG levels > 200 mg/dl and HDL cholesterol < 42 mg/dl. at baseline, a lipid profile frequently encountered with the metabolic syndrome.[34]

In the coronary drug project, niacin monotherapy reduced the risk of MI by 26%, stroke by 24%, and the need for coronary revascularization by 67% compared with placebo in men with CAD.[35] A long-term mortality follow-up, 9 years after treatment discontinuation, showed an 11% relative reduction in mortality.[36] Although the Coronary Drug Project (CDP) did not measure the effect of niacin on serum HDL cholesterol levels, the study clearly demonstrated the ability of niacin to reduce risk for cardiovascular morbidity and mortality in the secondary prevention setting. In the smaller HDL Atherosclerosis Treatment Study (HATS), patients with CAD (mean baseline HDL and LDL cholesterol of 31 and 125 mg/dl, respectively) treated with simvastatin-niacin combination therapy experienced a 24% elevation in HDL cholesterol and a 42% reduction in LDL. These changes were associated with a small degree of angiographic regression of stenosis (-0.4%) and a 90% relative reduction in the risk of major cardiovascular events.[37]

ARBITER-2 study (Arterial biology for the investigation of the treatment effects of reducing cholesterol)[38] was a 12 months study conducted in patients with CHD who were already at goal for LDL-C (85-90 mg%). The addition of 1 gm of extended release niacin to Simvastatin increased HDL by 21% (without further changing LDL levels) and reduced progression of carotid wall thickening by 68% compared with simvastatin treatment alone. In a preliminary evaluation of patients with CAD and recent acute coronary syndromes, the weekly intravenous infusion of an HDL mimetic consisting of ApoA-I Milano/phospholipid complexes was associated with a 4.2% absolute reduction in atheroma volume over a 5-week period.[39] These data strongly indicate that HDL can in fact induce relatively rapid plaque regression and resorption, thus potentially rendering atherosclerosis a reversible disease.

High-Density Lipoprotein Cholesterol Goals

Based on accumulating epidemiologic and clinical data, expert groups have begun recognizing HDL cholesterol as a critical CAD risk factor, and new, more stringent goals are being recommended to reduce the overall risk of CAD. The NCEP ATP III report continued to focus on treating elevated LDL in patients at risk for CAD, but it also emphasized the importance of evaluation and treating low HDL cholesterol. Although it did not define a strict goal for HDL cholesterol, it did increase the definition of low HDL cholesterol from < 35 mg/dl to < 40

mg/dL.[11] The NCEP recommends therapeutic lifestyle changes (TLCs) and pharmacotherapy to increase HDL cholesterol and reduce CAD or CAD risk equivalents.[11] In 2002, the Expert Group on HDL cholesterol specifically recommended an HDL cholesterol goal of > 40 mg/dl for patients with CAD or CAD risk equivalents.[40] In 2004, the American Heart Association (AHA) increased the definition of low HDL cholesterol for women to < 50 mg/dl,[41] and, consistent with these recommendations, the American Diabetes Association (ADA) now advocates an HDL cholesterol goal of > 40 mg/dl for men and > 50 mg/dl for women with diabetes.[42]

TREATMENT STRATEGIES

Lifestyle Modifications

Exercise

Regular aerobic exercise increases the HDL cholesterol level by 3 to 9 percent in healthy, sedentary persons. This increase is related to the frequency and intensity of physical activity, with greater increases in HDL cholesterol occurring with frequent, low-intensity exercise (e.g., five 30-minute sessions per week vs three 60-minute sessions). However, there is little evidence that walking significantly increases HDL cholesterol levels. HDL cholesterol levels may increase with as little as eight weeks of regular exercise, although changes may not be evident for two years. Exercise may increase HDL cholesterol levels by stimulating the production of pre-beta HDL-C and reverse cholesterol transport.

Regular exercise yields greater increases in HDL-C in men with low HDL cholesterol levels, elevated triglyceride levels, and abdominal obesity than in those with isolated low HDL-C levels. Weight loss may be crucial for an increase in HDL-C to occur. In one randomized, controlled trial, persons who walked or jogged 10 miles per week but did not lose weight, did not have different HDL-C levels from those of controls. *Nevertheless, it is reasonable to recommend a program of regular, brisk aerobic exercise for 30 minutes on most days of the week.*

Smoking Cessation

Cigarette smoking is associated with reduced HDL cholesterol, lecithin-cholesterol acyltransferase (LCAT) activity, and cholestery-ester-transfer protein (CETP activity). After smoking cessation, HDL-C increases (by a mean of 4 mg/dl, more so in women than in men and in persons with elevated baseline HDL cholesterol levels (> 47 mg/dl). *A comprehensive approach to smoking cessation (involving pharmacotherapy, nicotine replacement, and counseling) should be recommended.*

Weight Control

Obesity is associated with reduced HDL-C levels and elevated serum Triglyceride levels. A negative correlation exists between HDL-C and body-mass index. A meta-analysis examining the effect of weight loss on HDL-C levels demonstrated that the levels increased by 0.35 mg/dl per kg of weight reduction in subjects who achieved a stabilized reduced weight ($P < 0.01$) but decreased by 0.27 mg/dl in subjects during active weight loss ($P < 0.05$). In subjects who maintained a stable weight for six weeks after weight loss, HDL-C levels, lipoprotein lipase levels, and LCAT activity increased; these increases may contribute to enhanced cholesterol esterification and reverse cholesterol transport. *A reasonable weight-loss goal for overweight or obese patients is 1 pound (0.45 kg) per week, with a target body-mass index of less than 25.*

Alcohol Intake

Moderate alcohol consumption raises HDL cholesterol levels. A meta-analysis indicated that the consumption of 30 gm (1 fluid oz) of alcohol per day increases HDL cholesterol levels by a mean of 4 mg/dl, irrespective of the kind of alcohol consumed. *The potential risks associated with alcohol intake outweigh the benefits in persons with hepatic dysfunction or the potential for addiction.* Also the

controversy exists to the fact that what alcohol raises is primarily subclass HDL3 which does not help much in reverse cholesterol transport mechanism (NEJM 1984,310-805). Alcohol consumption may elevate HDL levels by increasing cellular cholesterol efflux and plasma cholesterol esterification

Dietary Modification

A number of dietary items have been claimed to increase HDL, like orange juice, beans, oat bran, onions, soya products, soluble fibers like in grapes, apples and citrus fruits. Low fat diets have been recommended as the foundation for treating lipid disorders that involve elevation in LDL. However when diets are reduced in fat content, replaced calories are often derived from simple carbohydrates which actually reduce HDL levels. The lowered levels of HDL may increase again with sustained weight loss as insulin resistance becomes progressively better. The concominant decrease in LDL cholesterol that occurs with a diet low in saturated fat may override the effects associated with the decline in HDL cholesterol. Native Alaskan populations that eat a diet rich in n-3 polyunsaturated fatty acids have high HDL-C levels. Although a diet high in monounsaturated fats does not elicit a significant change in HDL levels, the dietary glycemic load (which represents the equivalent elevating effect on blood-glucose levels of 1 g of pure glucose or white bread) is negatively correlated with HDL levels. *Thus, a diet rich in n-3 polyunsaturated fatty acids – sources include oils (olive, canola, soya, flaxseed), nuts (almonds, peanuts, walnuts, pecans), cold-water fish (salmon, mackerel), and shellfish – with limited carbohydrates that contribute a high glycemic load (such as those found in ready-to-eat cereals, potatoes, white bread, and snack foods) can be recommended to increase serum HDL-C values.*[43,44]

Herbal and Natural Supplements

Various products which have been found to raise HDL-C in clinical trials are Guggul (the gum resin from mukul myrrh tree), policosanol, inositol hexanicotinate or no flush niacin, curcumin, chromium, calcium citrate, etc.

Lifestyle and Modifying Factors

Improvement in HDL cholesterol levels associated with exercise, alcohol consumption, and weight loss is greatest in persons with the highest baseline HDL-C levels (> 60 mg/dl); those with low baseline levels have less improvement. Interactions between genes and the environment may influence the magnitude of improvement in HDL-C levels associated with lifestyle modifications. Specifically, improvement with exercise may depend on individual CETP and endothelial lipase genotypes. However, genetic tests for these factors are not currently used in routine practice, and lifestyle changes as described above should be recommended routinely, both to raise HDL-C levels and to lower LDL-C levels and improve other cardiovascular risk factors.

Drug Therapy

Pharmacological therapy should be instituted when lifestyle changes are not adequate to achieve HDL cholesterol goals. The currently available drugs include statins, fibrates and niacin alone or in combinations. Number of newer agents are being developed to raise HDL which are at advanced stage of research.

Statins

Statins are preferred first line therapy for patients with dyslipidemia with elevated LDL.
Statins also reduce CAD riskand checks atheromatous progression to a greater extent in patients with high LDL and Low HDL than those with high LDL and normal HDL possibly as a result of their pleiotropic effects and capacity to increase HDL modestly (3-10%).[45] Mechanism of increase in HDL by Statins may be an indirect effect of lowering triglycerides. Reducing the number of TG

rich (Apo B containing) acceptor particles results in decreased CETP mediated transfer of cholesterol out of HDL, thereby increasing plasma HDL-C. Various statins did not differ much in this regard, however, simvastatin 40 mg produced greater elevation in HDL cholesterol than atorvatatin 40mg (9.6% vs 4.8% P< 0.05). In a similar study[46] rosuvastatin produced slightly more increase in HDL as compared to other statins.

Patients with hypertriglyceridemia can experience elevations in HDL of upto 18% and 22% by taking simvastatin[47] and rosuvastatin[48] respectively. Statins are extremely safe drugs. Incidence of significant myopathy is less than 0.1% and is more common in older patients, frail patients, small frame patients, patients with multisystem disease or in perioperative period, patients on multiple medications including those on cytochrome P-450 inhibitors, cyclosporines, macrolide antibiotics and azole antifungals.[11,49,50]

Statins are also occasionally associated with slight elevations in liver enzymes, with increase > 3 times the upper limit of normal occurring in 0.5-2% of treated patients.[50] More serious hepatotoxicity is very rare. Active and chronic liver disease is a contraindication to statin therapy.[11]

Niacin

Niacin (nicotinic acid vitamin B_3) is the most effective agent currently available for increasing HDL cholesterol causing increase of 20-35% and is recommended for the treatment of isolated low HDL cholesterol. Coronary drugs project demonstrated a significant reduction in the incidence of death and myocardial infarction after 5 years of niacin treatment among men with a history MI.

Niacin blocks a hepatic receptor that mediates the holoparticle uptake and catabolism of HDL. It preferentially increases HDL2 and LPA-1 particles.[2,51] It inhibits lipolysis in adipose tissues and decreases TG by 20-50%, increases LDL particle size and produces more modest reductions in LDL (by 5-25%). Niacin therapy is associated with improved endothelial function and no synthase activity.

Niacin is available in 3 formulations, immediate release, sustained release and extended release. Out of these, only immediate release and extended release formulations are approved for treatment of dyslipidemia. In a 1 year study, extended release niacin /lovastatin 2000 mg/40 mg per day increased HDL-C by 41%, reduced LDL by 45% and reduced TG by 42%.[52]

Adverse effects with niacin includes flushing, gastrointestinal distress, hyperglycemia, hyperuricemia and hepatotoxicity. Contraindications include chronic liver disease, gout (niacin can increase serum uric acid levels by stimulating proximal tubular reuptake), and the peptic ulcer. Although niacin has been considered relatively contraindicated in diabetics, recent studies[53,54] show that it can be given safely to most patients with appropriate monitoring of diabetic status. Flushing which is largely mediated by prostaglandins, may be minimized with the use of an extended release formulation of niacin (not the same as sustained release niacin), with the concurrent consumption of a low fat snack at bed time, 30 minutes after ingestion of an aspirin and with a regimen that begins with a low dose (e.g. 500 mg each night) and increases gradually. Unlike fibrates, statin-niacin combinations do not appear to produce any significant drug – drug interaction.

Fibrates

Fibrates such as gemfibrozil and fenofibrate raise HDL-C by 10-15% and are best known for their TG lowering effects. They are recommended for patients whose primary abnormality is elevated triglycerides and low HDL cholesterol. Fibrates belong to class of PPAR (peroxisome proliferator-activated receptor) agonists[2,8,5,56] which are a family of nuclear hormone receptors that are widespread throughout the body. Fibrates stimulate PPAR alpha in the liver, leading to expression of multiple genes involved in lipoprotein metabolism resulting in stimulation of

lipoprotien lipase activity. They stimulate Apo A-I and A-II synthesis, decrease synthesis of TG, and enhance catabolism of TG rich particles.

In two large trials of fibrate therapy, gemfibrozil (1200 mg/day) increased HDL cholesterol by 6%[32] whereas bezafibrate (400 mg/day) produced a 14% increase compared with placebo.[34]

In patients with combined dyslipidemia, Fibrate-Statin combination therapy can be very effective to decrease LDL and TG and simultaneous increase in HDL-C.[57]

Atorvastatin (20 mg/day) and micronized fenofibrate (200 mg /day) administered for 6 months in Type-2 Diabetic population increased HDL cholesterol by 22%, decreased LDL by 46% and decreased TG levels by 50%.[58]

No clinical event data are currently available for therapies using statin-fibrate combinations. ACCORD trial (Action to Control Cardiovascular Risk in Diabetes) is evaluating the effects of intensive glycemic control, intensive BP control and intensive lipid management with simvastatin + fenofibrate on CV risk in adults with type-2 DM.[59]

Fibrates are contraindicated in severe renal or hepatic disease. The risk of side effects of combination therapy although marginally higher than that of individual drugs, actually depends on which fibrate has been used with statin. Gemfibrozil can block the glucuronidation and elimination of statin, leading to increased serum concentration of statin and increased risk for toxicit. Fenofibrate does not appear to block the glucuronidation of statins. For this reason, fenofibrate may be the fibrate of choice when considering combination therapy with statins.[60]

Drugs of the Future

Two different approaches are currently under development for raising HDL-C.

The first approach is the development of HDL mimetics. In a direct test of the athero-protective effects of HDL, patients with established cardiovascular disease were given five weekly infusions of a complex consisting of Apo AI milano and phospholipids and were compared with controls by means of intravascular ultrasound to quantitate coronary atheroma. The total volume of atheroma decreased by 4.2% within 6 weeks.[61] Additional approaches to short term HDL therapy include the infusion of synthetic peptides based on the amphipathic structure of Apo AI and the reinfusion of autologous delipidated HDL. Detailed data from clinical trials will now be required in order to establish whether short term therapy consisting of HDL infusions will provide protection against cardiovascular events.

A second approach to HDL therapy is the development of agents that would increase the HDL-C levels effectively for a long or indefinite period. The most advanced clinically tested such agents are CETP inhibitors. CETP mediates the exchange of cholesteryl ester for triglycerides between HDL and VLDL-LDL and may be proatherogenic if the CETP mediated VLDL-LDL cholesteryl ester is taken up by arterial macrophages, or may be antiatherogenic if this cholesteryl ester is returned to the liver through the LDL receptor by means of the pathway of reverse cholesterol transport that is initiated by HDL.[62] The administration of a chemical CETP inhibitor, JTT 705 to cholesterol fed rabbits resulted in a doubling of the HDL-C levels, a 50% decrease in the levels of non-HDL cholesterol, and a 70% decrease in atherosclerosis. In contrast, patients in whom CETP activity is completely absent have large cholesterol enriched, dysfunctional HDL particles with decreased capacity to remove cellular cholesterol and have been reported to be at risk for cardiovascular disease. These findings indicate that partial inhibition of CETP may be atheroprotective but the complete absence of CETP activity can create a proatherogenic lipid profile.

Brousseau, et al reported in 2004[63] a single blind study of torcetrapib, a CETP inhibitor, used alone or in combination with 20 mg of Atorvastatin, on the lipoprotein phenotype in 19 patients with a low HDL levels. Subjects received torcetrapib for 4 weeks at a dose of 120 mg, either alone or in combination with atorvastatin, and a subgroup of subjects in the torcetrapib alone group then received 120 mg of torcetrapib twice daily for an additional 4 weeks. The HDL-C levels increased by 46% in the group that received torcetrapib alone for 4 weeks, by 61% in the group

that received torcetrapib plus atorvastatin for 4 weeks, and by 106% in the subgroup that received the additional 4 weeks of torcetrapib treatment, the LDL decreased by 17%, 8% and 17% in the three group respectively. Torcetrapib therapy was well tolerated, and there was no major adverse events. Despite the small number of patients, the results suggest that torcetrapib can effectively increase the HDL-C levels in subjects with low levels; moreover, the addition of statin to torcetrapib therapy is associated with a further reduction in the LDL-C levels. Future trials on these drugs will decide the optimum doses and will look for data to prove CV protection.

Other modalities being explored to improve HDL-C are Inhibitors of acyl coenzyme A cholesterol acyl transferase (ACAT), vaccines against CETP antigens A/8S), drugs that inhibit HDL-ApoAI catabolism or the remodeling of HDL particles (e.g., endothelial lipase inhibitors) A/2, type 1 endocannabinoid receptor antagonists (Rimonabant), dual PPAR alpha and gamma agonists and nuclear receptos (e.g., liver X receptor alpha) agonists.[7,9,10]

SUMMARY AND CONCLUSION

Results of statin trials over last two decades have provided irrefutable evidence that lowering LDL-C levels reduces CV risk by 20-30%. Nevertheless, the residual risk even for those at LDL-C targets, remains unacceptably high, hence the focus on lipid therapy currently includes managing other lipid abnormalities.

Low level of HDL-C is an important and independent risk factor for future cardiovascular events. A comprehensive approach to achieve optimal HDL-C levels (40 mg/dl or more in males and 50 mg/dl or more in females) should include lifestyle changes, followed by drug therapy in high risk patients. Of the several drugs available to increase HDL-C, niacin and fibrates have the greatest effects. Although data are currently lacking to prove that elevating HDL-C with drugs reduces the incidence of CV events, medication to raise the levels should be considered, once the target LDL-C has been achieved, in persons who have established atherosclerotic disease or have major risk factors such as diabetes and in whom HDL-C levels remain low despite lifestyle modifications. Drugs of the future will take advantage of evolving knowledge about HDL metabolism and may have a role in the short term management of acute coronary syndromes in addition to long term preventive effect on CHD.

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