High-Density Lipoprotein Cholesterol and the Role of Statins

Pang H. Chong, PharmD; Robert Kezele, RPh*; Cory Franklin, MD**

Low levels of high-density lipoprotein cholesterol (HDL-C) are currently considered to be a major risk factor for the development of coronary artery disease (CAD). Deficiencies in the HDL metabolic pathway promote atherosclerosis and contribute to CAD. Low HDL-C levels are included in the Framingham 10-year risk assessment for CAD although they are not yet targeted for therapy. Recent clinical trials have shown benefits from raising HDL-C, particularly in patients with lower baseline levels. The statin class of drugs, used primarily to lower the level of low-density lipoprotein-cholesterol, may be able to raise the HDL-C level as well. Statins could potentially affect HDL-C by different modes of action, most importantly by altering reverse cholesterol transport. Among the currently available statins, simvastatin has demonstrated the most consistent ability to raise HDL-C level, but further large-scale studies at an early stage will be needed to prove the antiatherogenic effects of this class of drugs. (Circ J 2002; 66: 1037 – 1044)

Key Words: Cardiovascular risk factor; High-density lipoprotein-cholesterol; Reverse cholesterol transport; Statins

Reducing the level of low-density lipoprotein cholesterol (LDL-C) is highly effective in the primary and secondary prevention of coronary artery disease (CAD) by reducing coronary events. Although the focus of drug therapy has been toward lowering LDL-C levels, those of high-density lipoprotein cholesterol (HDL-C) have recently been cited as a target of intervention. It is estimated that 40% of patients with CAD have normal levels of LDL-C (<100 mg/dl or at most 130 mg/dl) and will not necessarily benefit from further reduction. At the same time, more than half of these patients also have isolated subnormal levels of HDL-C (≤35 mg/dl), drawing attention to its role in the development of CAD!

A number of mutations affecting HDL structure and/or function have been described in human and animal populations, with the suggestion of an effect on cardiovascular risk. Patients with Tangier Disease, a rare genetic disorder characterized by extremely low levels of HDL and a biochemical defect in the cellular efflux of cholesterol to HDLs (ie, defects in ABCA1, discussed later in the review), have a 5- to 6-fold increased risk of CAD compared with matched controls. Homozygous mice without the cholesterol transporter of HDL do not have circulating HDL and have a marked increase in the development of atherosclerosis compared with heterozygous mice, which have half of the normal HDL level and a marked decrease in atherosclerosis. Of note, human heterozygous ABCA1 deficiency is pro-atherogenic.

Epidemiological studies have indicated an inverse and independent association between HDL-C level and CAD. Studies have also demonstrated an increased risk for coronary artery disease (CAD) in patients with premature CAD who have lower levels of serum HDL-C than those without CAD. The Framingham Heart Study reported that men with a HDL-C level less than 35 mg/dl had 4 times the rate of death from CAD compared with those with a concentration greater than 55 mg/dl, regardless of the level of total cholesterol or LDL-C. The study suggests that for each 1 mg/dl increase in HDL-C, a 2% and 3% decrease in the incidence of CAD occurs in men and women, respectively. Additionally, the Prospective Cardiovascular Munster (PROCAM) study, a 6-year follow-up of asymptomatic men aged 40–65 years, determined that HDL-C <35 mg/dl was a significant risk factor for the development of myocardial infarction (MI) [p<0.001] in every LDL-C category. Overall, PROCAM showed the coronary risks increased by 2–3% for every 1% reduction in HDL-C level and suggested that a high concentration of HDL-C is more protective than a low level of LDL-C. Studies have also demonstrated an increased risk for coronary restenosis in the presence of low HDL-C levels.

In one study, subjects with normal cholesterol levels, angiographic evidence of CAD and HDL-C <35 mg/dl had decreased survival compared with those with HDL-C >35 mg/dl, possibly as a result of more rapid disease progression. Thus, the pathogenesis of a low or functionally deficient level of HDL is an area of active research and HDL-C has become an important component of the algorithms that assess the global cardiovascular risk of patients. It is also a target for therapeutic intervention and for the definition of treatment goals.

Here we focus on the effects of statin therapy on the risks inherent in patients with low levels of HDL-C, reviewing...
the current guidelines and implications for treatment, with special attention devoted to the potential effects of statins on the metabolic pathways of HDL. Relevant differences between the statins in raising HDL-C levels, the findings in large randomized clinical trials, and the use of statins in clinical practice are discussed.

**Low HDL-C Levels: An Independent Risk Factor for CAD**

The National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) provides clinical guidelines for cholesterol management. The initial risk assessment for CAD includes 5 major risk factors, including low HDL-C, that modify the goal of LDL-C-lowering therapy. In general, the HDL class protects against the development of CAD, but there is not yet consistent evidence that any one HDL subtraction (HDL2; HDL3) is superior to another. Low HDL-C levels, together with total cholesterol, systolic blood pressure and smoking, in men and women are used to identify patients for more aggressive therapy according to the Framingham absolute 10-year risk assessment for CAD. The current NCEP increased the cut-off point of low HDL-C as a risk factor from <35 to <40 mg/dl, to better reflect a depressed level of HDL-C based on untreated rather than pharmacologically altered levels. The Framingham scoring model allocates points for HDL-C levels <40 mg/dl and subtracts them for HDL-C levels >60 mg/dl. Patients should be identified as having either a primary or a secondary cause of low HDL-C that can be then addressed accordingly.

Elevated triglycerides are almost always associated with low levels of HDL-C in conjunction with alcohol intake and estrogen therapy because of the close link between the metabolic pathways shared by both HDL and triglycerides. The presence of elevated LDL-C and triglycerides in patients with low HDL-C is known as mixed hyperlipidemia. Low HDL-C is frequently found as a component of metabolic syndrome, coexisting with elevated triglycerides, small dense LDL, glucose intolerance or overt diabetes mellitus, hypertension, obesity, and hyperinsulinemia. The common root of all these cardiovascular risk factors appears to be insulin resistance. Isolated low HDL-C level without elevated triglycerides affects approximately 10% of Americans. In clinical practice, individuals with low levels of HDL-C also require profiling for both LDL-C and triglyceride levels. For patients with these risk factors, particularly the elderly (>70 yrs) and those with type 2 diabetes, aggressive lifestyle modifications should be initiated and continued during drug therapy. Drug therapy is reserved for patients with low HDL-C levels that are resistant to lifestyle modification. If the triglyceride level is <200 mg/dl, drug therapy that raises HDL-C (ie, fibrates or niacin) should be used as an adjunct to weight loss. For individuals with triglyceride levels between 200 and 499 mg/dl, in the presence of low HDL-C, the primary target of therapy is lowering LDL-C with the secondary target of raising HDL-C. There are several drug classes available that increase HDL-C levels, including niacin (15–35%), fibrates (10–20%), bile acid sequestrants (3–5% in the setting of non-hypertriglyceridemia), hormone replacement therapy (ie, estrogens, 5–15%), and statins.

**Potential Effects on HDL-C**

Currently, the race is on to uncover the effects of statins on the HDL metabolism (the reverse cholesterol transport [RCT]) system, and the associated clinical benefits of raising HDL-C levels. Statins have been shown to increase HDL-C and apo A-I levels during treatment of both healthy subjects and those with CAD. In humans, HDL-C and apo A-I promote the removal and transfer of cholesterol from artery walls back to the liver. The increase in HDL in humans may result from a decrease in the fractional catabolic rate (FCR) of apo A-I and/or increased production of apo A-I under the inhibition of HMG-CoA reductase. The fractional synthetic rate (FSR) equals FCR in the steady state. In support of this, one study showed statin-induced increases in apo A-I levels through the activation of its promoter, the peroxisome proliferator activator receptor-α (PPAR-α). Statins activate PPAR-α by inhibiting the Rho A signal transduction pathway. These results provide a molecular basis for the increase in HDL-C levels in response to statins and establish a potential synergy between the statins and another common PPAR-α activating class of drugs, the fibrates.

In addition, a recent study showed that statins might abolish associations between certain cholesteryl ester transport protein (CETP) gene loci with high CETP concentrations and low levels of HDL-C, thus resulting in delayed progression of atherosclerosis in those with CAD. This suggests the statin-induced increase in HDL-C levels may be caused by delayed HDL catabolism, which is often observed in CETP deficiency. Under normal circumstance, CETP mainly catalyzes the transfer of cholesterol esters from HDL for triglycerides from apo-B100-containing lipoproteins such as VLDL and LDL. Thus, CETP participates in RCT by facilitating the transfer of cholesteryl esters to lipoproteins that can be subsequently removed from circulation by the liver via LDL receptors or LDL receptor-related proteins. Alternatively, these cholesterol esters-enriched apo-B-containing lipoproteins can also be taken up by peripheral cells and are thus proatherogenic. CETP deficiency and the associated increase in HDL-C levels (≥60 mg/dl) may or may not be associated with an antiatherogenic effect. This apparent paradox is explained.
by observations that CETP deficiency may impair the RCT system by producing large, cholesterol ester-enriched HDLs that are unable to extract cholesterol from macrophages. On the other hand, impaired RCT caused by CETP deficiency may be compensated for by the anti-inflammatory and antioxidant effects of HDL.

In summary, the data suggest that promotion of the RCT system has a potential role in an antiatherosclerotic effect, yet to be elucidated, and that it is not the increase or decrease of HDL-C concentrations per se but rather the kinetics of HDL metabolism and the cellular mobilization and transport of lipids that determines the efficacy of RCT. These findings suggest several new approaches to raising HDL-C levels, including upregulation of transcription of ABCA1, a cellular protein that mediates cholesterol efflux in RCT, through nuclear receptors such as LXR and RXR, and raising HDL-C and apo A-I levels by inhibiting CETP.

In any given patient, the antiatherogenic effect of HDL probably depends on which type is being elevated and the associated relative capacity for RCT.

Non-Lipid-Lowering Effects

A brief mention of the non-lipid-lowering effects of statins in the role of antiatherogenesis is in order. These mechanisms include decreases in smooth muscle cell proliferation and endothelial activation, reductions in C-reactive protein (CRP), and positive antithrombotic effects. The pharmacology of statins is complex and poorly understood and which combination of their pleiotropic effects will prove to be of primary importance in their ability to reduce coronary events is unknown.

HDL-C-Elevating Effects of Statins

The effects of the 5 statins currently in use on HDL-C levels are summarized elsewhere. Statins raise HDL-C levels in neither a non-linear nor a dose-dependent fashion such that low-dose or high-dose statin effects the same moderate increase.

Currently, atorvastatin, simvastatin, pravastatin, and fluvastatin are approved as drugs to elevate HDL-C levels, but there are few comparative data of their effects on HDL-C levels. However, simvastatin, at higher doses, has been shown to be considerably more effective at raising HDL-C levels with similar LDL-C reductions than atorvastatin, considered the most potent. In an open-label trial, Crouse et al. reported that simvastatin at doses of 40 mg/day increased HDL-C by 6.7% (p<0.001) compared with 4% with atorvastatin at doses of 20 mg/day, and both drugs had similar LDL-C reductions. In the simvastatin-treated group, there was also a greater increase in HDL-C (p=0.008) in those with lower baseline HDL-C levels (<35 mg/dl).

A similar conclusion was drawn in another open-label comparison of simvastatin 40 mg/day and atorvastatin 20 mg/day: the change in HDL-C level with simvastatin compared with atorvastatin was +9.6% vs +5.1% (p<0.005). The same study also showed a change in HDL-C of -0.1% at higher doses of atorvastatin (80 mg/day), suggesting that its HDL-C increasing effect declines as the dose increases and which may be related to decreased apo A-I expression by atorvastatin as opposed to increased production with simvastatin. This result is consistent with reports from Wierzbicki who noticed slightly decreased HDL-C levels, and from Brown and Ma, who noticed lesser elevation of HDL-C levels with increasing doses of atorvastatin.

In another study, pravastatin increased HDL-C levels by 13% through increased expression of apo A-I. In a double-blind study, simvastatin at 80 mg/day increased HDL-C by 9% compared with 6.7% with atorvastatin at 40 mg/day (p<0.05). Additional elevations in HDL-C may come from the ability of simvastatin and atorvastatin to decrease circulating levels of CETP.

These data indicate the possibility of differences in the metabolic effects of statins, although this remains to be fully established and there is currently no evidence of independent differences in HDL metabolism between statins, leading to different effects on clinical outcome.

Landmark Clinical Statin Trials: Effects on HDL-C Levels

Several prospective studies in humans have shown that the pharmacologic increase of post-treatment HDL-C levels with lipid-lowering drugs (eg, niacin and gemfibrozil) either reduces the risk for CAD or improves outcomes in patients with relatively high HDL-C levels. The relative benefits of niacin and gemfibrozil are discussed elsewhere. No reports are available of trials designed specifically to determine whether raising the level of HDL-C with statins translates into a reduced risk for CAD. Some large randomized clinical trials, which addressed other questions, have shown through subgroup analysis the effectiveness of raising serum HDL-C with statins (eg, simvastatin, pravastatin, lovastatin, fluvastatin and the concomitant improvement in CAD-related outcomes. Post-hoc analysis has shown that patients with low baseline levels of HDL-C who were treated with statins had a reduced coronary risk that was similar to that of patients with a higher baseline HDL-C.
who were given placebo (Fig 1). Those patients also had a lesser progression of existing coronary lesions. In those studies, a low HDL-C level was <35 mg/dl and subjects with a baseline level of triglycerides ≥450 mg/dl were excluded from analyses.

Secondary Prevention

The Scandinavian Simvastatin Survival Study (4S) randomized 4,444 patients with CAD and total cholesterol levels of 212–309 mg/dl to a regimen of simvastatin 20–40 mg/day or placebo for a mean of 5.4 years. When comparing the lowest quartile HDL-C patients on simvastatin (<39 mg/dl) with placebo patients with the highest quartile HDL-C levels (≥52 mg/dl), the relative reduction in the risk of coronary events (nonfatal myocardial infarction [MI], CAD death) was reduced by 22.5% vs 24%, respectively. In post hoc analysis, each 1% increase in HDL-C in the simvastatin group was associated with a 0.8% decrease in the relative reduction in the risk of coronary events (p=0.039). In another post hoc analysis of the 4S study, CHD patients with the lipid triad (ie, high LDL-C and lowest HDL-C and highest triglyceride quartile) received greater benefit from simvastatin therapy than those with isolated LDL-C elevation. That analysis supports the use of statin therapy in patients with the characteristics of metabolic syndrome and a similar lipid profile.

The Cholesterol and Recurrent Events (CARE) trial evaluated 4,159 patients with average cholesterol levels (LDL-C, 115–174 mg/dl) treated with pravastatin 40 mg/day for 5 years. Pravastatin raised HDL-C levels by 5% and reduced the incidence of CAD death or nonfatal MI by 24%. Patients with HDL-C levels ≤37 mg/dl had fewer coronary events compared with those with higher levels of HDL-C receiving placebo (23% vs 25%). In the post-hoc analysis of the CARE trial, using criteria identical to those of the 4S trial, there was an inverse relationship between baseline values for HDL-C and coronary event rates in the combined treatment arms. For each 10 mg/dl decrement in baseline HDL-C, there was an 11% greater likelihood of experiencing coronary death or nonfatal MI (p=0.049). This influence was similar in placebo and pravastatin-treated patients. The lowest quartile HDL-C patients on pravastatin had an 11.1% risk of coronary event rate compared with 11% in the highest quartile HDL-C patients on placebo.

The Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) trial showed a 6% increase in HDL-C among 9,014 patients treated with pravastatin at 40 mg/day over a 6-year period. These were patients with cholesterol levels of 155–271 mg/dl who had either had an acute MI or been hospitalized for unstable angina. Total mortality in the pravastatin group was reduced by 23% (p=0.00002) compared with placebo. Also in the pravastatin group, patients with lower baseline HDL-C levels (<39 mg/dl) had a 13% risk of coronary events (CHD death or nonfatal MI) compared with 14% in those with higher levels (≥39 mg/dl) in the placebo group.

The Lipoprotein and Coronary Atherosclerosis Study (LCAS) study enrolled 420 patients with LDL-C levels between 115 and 190 mg/dl, and showed an increase in HDL-C of 8.7% associated with fluvastatin 20 mg twice-daily monotherapy. After 2.5 years, there was significant less coronary lesion progression and fewer new lesions in the treated group (p=0.001). A post-hoc analysis of LCAS evaluated 68 patients who had low HDL-C levels (mean = 32 mg/dl) with equivalent baseline LDL-C levels.

the levels of HDL-C increased by 15.9% in the group with lower HDL-C levels compared with 7.4% in the group with elevated baseline HDL-C levels. Fluvastatin was also associated with a significant decreased in coronary lesion progression (p=0.0004) in patients with initially low HDL-C levels when compared with the placebo group. In patients with higher HDL-C levels, lesion progression was reduced, but the reduction was not statistically significant (p=0.09) compared with placebo. The change in minimum lumen diameter reductions of qualifying lesions was significant in the comparison of low HDL-C vs high HDL-C patients (p=0.01). These data raise the possibility that statins may confer greater benefit to those with mild to moderate elevations of LDL-C who also have low levels of HDL-C. There is the further suggestion that those with low HDL-C levels have improved event-free survival (time to first clinical event of MI, presentation with unstable angina, total mortality, percutaneous transluminal coronary angioplasty, coronary artery bypass graft) when compared with placebo (4.6% vs 32%, respectively; p=0.002) although there was no difference among those with higher HDL-C levels (15% vs 9.8%, respectively).

Primary Prevention

Clinical data from the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), which evaluated lovastatin 20–40 mg/day for 5.2 years in 6,505 subjects with mean levels of HDL-C of 36 mg/dl in men and 40 mg/dl in women and LDL-C of 156 mg/dl, showed a reduction in the first major acute coronary event (composite end-points of nonfatal and fatal MI, unstable angina, sudden cardiac death) by 37% (p<0.001). Treatment resulted in a mean increase in HDL-C at 1 year of 6% to an average level of 39.3 mg/dl. Lovastatin reduced the risk for first major coronary event in lower HDL-C patients to approximately that of placebo patients with higher HDL-C (3.8% vs 4.1%). The relationship between baseline and on-treatment of HDL-C levels and the occurrence of first major acute coronary events in AFCAPS/TexCAPS was examined using a logistic regression analysis. HDL-C levels at baseline were significantly predictive for a reduction of risk for first major coronary events (p=0.019). At 1 year, however, the predictability became non-significant, as was the percent change from baseline. However, the LDL-C level was predictive only if baseline HDL-C was also included in the logistic regression model and was adjusted for variable confounder. Thus, HDL-C levels were a key component of risk assessment in those subjects and there were strong data and impetus for its inclusion in the Framingham risk assessment. Also, as serum levels of apo A-I increased, the risk for coronary events decreased.

The West of Scotland Coronary Prevention Study (WOSCOPS) involved 6,595 men with mean LDL-C levels of 190 mg/dl and CAD who were treated with pravastatin 20–40 mg/day for 5 years. Overall, the pravastatin-treated group showed a 29% reduction in the risk for developing coronary events (CAD death or nonfatal MI). There was a reduction in risk of coronary events (6.7%) in those with below–median HDL-C levels taking pravastatin compared with those with median levels (6.2%) in the placebo arm.

Conclusions From Trials

In each of the landmark clinical trials (4S, CARE, LIPID, AFCAPS/TexCAPS, WOSCOPS), statins exerted only moderate effects on HDL-C levels, and none was
specific for HDL. The subgroup of patients with low levels of HDL-C (and normal or high cholesterol levels) receiving placebo had the highest rates of CAD events. Patients with low HDL-C levels had recognizable clinical and angiographic benefits from statin therapy, including a reduced coronary risk approximately equal to that of patients with higher HDL-C levels on placebo (Fig 1). The trials also suggested that inclusion of HDL-C levels with the LDL-C and triglyceride levels in coronary risk analysis yielded a better prediction of CAD events than simply looking at HDL-C levels alone. This may be explained by the fact that the atherogenic effects of LDL-C and triglyceride-enriched lipoproteins can be more pronounced in patients with lower baseline HDL-C levels. Statins may also have exerted antiatherogenic effects through non-lipid-lowering effects (e.g., hemostatic, inflammatory) and these ancillary changes may contribute to beneficial effects unrelated to changes in HDL-C, although their potential contribution is hard to quantify. It has yet to be demonstrated that the ability of statins to elevate HDL-C levels accounts for the positive benefits.

Because increased expression of human apo A-I is associated with a marked increase in HDL-C levels and regression of established plaque, the trials also raise the question of whether the statin effects on HDL-C are in part explainable by statin-mediated changes in the apo fractions of HDLs (e.g., apo A-I). This is compatible with the finding of AFCAPS/TexCAPS that showed greater predictability in apo ratios (apo A/ apo A-I) with statin therapy.

Similar conclusions were drawn by Sacks et al. who reviewed the HDL-C and non-LDL-C effects of statins. Their study demonstrated that for patients (n=2,600) in the CARE and LIPID trials who had a baseline LDL-C <125 mg/dl (lowest quintile), there was little evidence of any risk reduction and they suggested that these patients may have required a non-LDL-C-related treatment before or after statin (pravastatin) treatment if coronary events were to be further reduced. In contrast to LDL-C, HDL-C was a strong inverse risk factor in the placebo group, as in the pravastatin group. The results were similar in the 4S and WOSCOPS insofar as the lower incidence of major event rates associated with increasingly low baseline HDL-C was similar in the placebo-treated patients, demonstrating that statin therapy did not remove the HDL-C-associated risk. Similarly, although there was a trend to less reduction of coronary events in those with high baseline HDL-C, the AFCAPS/TexCAPS trial showed that there was no significant difference in event reduction according to baseline level of HDL-C, a similar pattern as other statin trials. The conclusion drawn was that the increase in HDL-C observed with statin therapy is associated with mild reduction in coronary events, indicating that HDL-C is an important factor. However, the risk of low HDL-C is not altered by statin therapy.

Additionally, some of these trials (CARE, LIPID, 4S, AFCAPS/TexCAPS, WOSCOPS) included many patients with type 2 diabetes, which showed relative size reduction of coronary events and suggests that HDL-C may be a very important lipid target in this rapidly increasing group of patients who were treated with statins. It also indicates a possible treatment threshold for HDL-C in people with diabetes.

Clinical Use of Statins In Patients With Low HDL-C Levels

In patients with low HDL-C levels, although raising those levels may be beneficial, the main objective is achieving LDL-C treatment goals with lipid-lowering drugs including statins. Lifestyle and behavioral modifications precede and work in conjunction with drug therapy. Although the association in large, randomized clinical trials of statin-mediated changes in HDL-C is encouraging, maximizing the HDL-C target goals is not a high priority because the pathophysiology of triglycerides/HDL-C metabolism and the pleiotropic (i.e., non-lipid) effects of the statins are still not well understood.

Based on the results of AFCAPS/TexCAPS, patients with isolated low HDL-C levels, and normal triglyceride levels may benefit from receiving statins in order to lower LDL-C levels. It may be appropriate to add a statin after lifestyle modifications have been effected in those patients with low HDL-C levels and multiple risk factors for CAD. In those with CAD or those at very high risk for CAD (e.g., diabetes, strong family history of premature CAD) with moderate-to-high elevations in LDL-C and low levels of HDL-C, statin therapy should be used in an attempt to lower LDL-C levels. For patients with elevated triglyceride levels and low HDL-C levels, the reduction of triglycerides is generally associated with an increase in HDL-C levels.

The selection of drug therapy is based on the degree of triglyceride lowering required. Statins moderately reduce triglycerides by 7–30% but fibrate or niacin therapy is more effective (both reduce triglycerides by 20–30%). Consideration should be given to both niacin and fibrate therapy because they are more effective in raising HDL-C when given to patients with concomitant hypertriglyceridemia. Although statins are not considered the first-line drug in this setting, when LDL-C reduction is indicated, they should be considered. Recent short-term studies suggest that some statins may be very effective in raising HDL-C levels (16–21%) in patients with elevated total cholesterol and triglycerides >300 mg/dl. Even in those situations, non-HDL-C is probably the culprit, meaning that triglycerides and LDL-C should be the primary targets of therapy. Future addition of newer, more potent statins may lead to indications to raise HDL-C levels.

This review raises the question “To what extent should we specifically attempt to raise HDL-C levels in preference to lowering the LDL-C?” In the presence of a low baseline HDL-C, should we simply lower LDL-C more vigorously or should there be additional therapy to raise the HDL-C further if satisfactory levels are not achieved? Recently, Brown et al. demonstrated that a statin plus niacin produced clinical and angiographic benefit in patients with CAD and low baseline HDL-C levels. In addition, extended-release niacin/lovastatin showed favorable dose-dependent effects on all lipid parameters and was well tolerated. Their study lends further support for recognition and treatment of patients with low HDL-C levels.

Summary

Low levels of HDL-C are considered to be a major risk factor for CAD, independent of other lipoprotein concentrations and comorbid diseases. The current cholesterol guidelines include low HDL-C in the global risk assessment of an individual patient. Some studies have suggested statins...
modulate HDL metabolism and the RCT system. The ability of statins to raise HDL-C levels varies within the drug class and in the large randomized clinical trials this effect may have played a role in the unexpected changes in clinical outcomes. The data should be interpreted cautiously in view of the diverse functionality of HDL and the non-lipid effects of these drugs. Thus, early stage functional, and controlled interventional clinical outcome studies are needed to demonstrate the antiatherogenic effects of HDL-C-elevating drugs, including the statins. Whether or not this proves to be a promising avenue of treatment, any intervention that promotes the benefits of elevation of HDL-C must be regarded as speculative at present.

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