High-Density Lipoprotein as a Therapeutic Target: Treatment Strategies.

MAU Chowdhury[1], SY Ali[1], MM Rahman[1], AEMM Islam[1], AKMM Islam[2]

[1]Department of Cardiology, Faridpur Medical College, Faridpur; [2]Department of Cardiology, National Institute of Cardiovascular Diseases, Dhaka.

Key words:
High density lipoprotein; Coronary artery disease

Abstract:

Coronary artery disease (CAD) is one of the most important causes of morbidity and mortality worldwide despite considerable therapeutic advances that control the risk factors. Numerous clinical trials have shown an inverse association between high density lipoprotein cholesterol levels and the risk of coronary artery disease. So, high density lipoprotein has become a new therapeutic target after low density lipoprotein in the management of risk factors of coronary artery disease. In this review, we explore existing and future treatment strategies along with their benefits and failures which will guide our management strategy. HDL raising therapies showed very promising results in many clinical trials but larger clinical trials are ongoing.

(Cardiovasc. j. 2012; 5(1): 73-80)

Introduction:

Lipids have a central role in the pathogenesis of CAD. So far the therapy for lipid modification of atherosclerotic coronary artery disease focused on mainly lowering low density lipoprotein cholesterol (LDL-C). Introduction of 3-hydroxy 3-methyl glutaryl coenzyme A reductase inhibitors has resulted in relative risk reduction of one third in major vascular events as compared with placebo.[1] To further improve the outcome, other risk factors have also been evaluated beyond lowering LDL. High density lipoprotein cholesterol (HDL-C) is traditionally considered as good cholesterol. HDL-C particles are able to remove cholesterol from within artery and transport it back to the liver for excretion or reutilization. This is why the cholesterol carried within HDL particles is sometimes called "good cholesterol". HDL-c is one of the five major lipoprotein, which, in order of sizes, largest to smallest, are chylomicrons, VLDL, IDL, LDL and HDL-C, which enable lipids like cholesterol and triglycerides to be transported within the water-based blood stream.

Framingham heart study in 1980s demonstrated that the risk of CAD was significantly lower in persons with higher levels of HDL-C. CAD risk increases sharply as HDL-C levels fall progressively below 40 mg/dl.[2] In one study, low HDL-C occurred in approximately 63% of patients with coronary artery disease.[3] In the Quebec cardiovascular study, for every 10% reduction in HDL-C, risk for CAD increased 13%.[4] Many clinicians believe that low HDL is associated with increased CAD risk because it is a marker for hypertriglyceridemia and elevated remnant particle concentrations. The Prospective Cardiovascular Münster Study, however, demonstrated that the increased risk associated with low HDL is independent of serum triglyceride levels.[5] Aggressive LDL lowering with statin therapy does not eliminate all risk for CAD, as low HDL-C still remains a significant risk factor. Currently HDL-C raising therapy has become a new target to reduce the CAD risk.

Prevalence

Men tend to have lower HDL-C levels, with smaller size and lower cholesterol content, than women. Low levels of HDL-C are most prevalent in South Asians compared with other Asians.[6] It is also very high in Latin America, where the prevalence is as high as 46% in men.[7] In the United States, low HDL-C is present in 35% of men and 15% of women.[8] Epidemiological studies have shown that high concentration of HDL-C (over 60 mg/dl) has a protective value against stroke and myocardial infarction.[9]

Address of Correspondance: Md. Ashraf Uddin Chowdhury, Department of Cardiology, Faridpur Medical College, Faridpur, Bangladesh. E mail: ashraf_k45@yahoo.com

Biological role of HDL-C

HDL-C is a heterogeneous class of lipoprotein with diverse functions and anti-atherogenic effects. The most important anti-atherogenic function of HDL-C is believed to be its ability to drive cholesterol transport by which HDL-C transports excess cholesterol from arterial wall's foam macrophages to the liver, bile and faeces.[10]

HDL-C's anti oxidative activity further protects against atherosclerosis.[11] Apo lipoprotein A-1 is a major factor in this process.

There are other roles of HDL-C in atherosclerosis like inhibition of adhesion molecules for monocytes in the arterial wall thereby inhibiting their migration into subendothelial space. HDL-C reverses endothelial dysfunction, stimulates prostacyclin production, inhibits endothelial apoptosis and inhibits LDL oxidation also.[12] HDL-C enhances nitric oxide synthase and increases NO production, inhibits coagulation cascade and platelet activation.[13]

HDL raising therapies

Considering the ability of HDL-C's protective role in coronary and cerebrovascular diseases, various methods have been tried to raise blood HDL-C levels.

A. Non pharmacological interventions

Aerobic exercise

Physical exercise can increase HDL-C significantly. Anti-inflammatory benefits of HDL-C are also seen after short period of exercise.

Diet

Diet has a crucial role in lipid metabolism. Purely low fat diet decreases HDL-C and LDL-C both. Diets high in monounsaturated fats including olive oil and canola oil have been shown to reduce LDL-C without adversely affecting HDL-C. Some polyunsaturated fats, including omega 3 poly unsaturated fatty acids, largely found in fish oil, can elevate HDL-C, especially among persons with high triglycerides. Furthermore foods with low glycaemic index can increase HDL-C level.

Weight loss

Obesity is associated with low HDL-C and high triglyceride levels. Losing weight by aerobic exercise and proper diet can result in increase HDL-C level.

Tobacco cessation

Smoking is associated with a drop in HDL-C by 4mg/dl in men and 6 mg/dl in women. Smokers have significantly lower levels of HDL-C than nonsmokers. It was observed in some meta-analysis that smoking cessation can raise HDL-C by 4mg/dl.[14]

Alcohol

Moderate alcohol intake appears to have protective effect in coronary artery disease. Part of this protection may be mediated by an associated increase in HDL-C. But heavy alcohol intake is associated with increase in cardiovascular and all cause mortality.

B. Pharmacological intervention

Various drugs are used for pharmacological modification of HDL-C with variable success. As with LDL-C and triglyceride lowering, HDL-C raising therapy is currently under much interest.

Statins

The decrease in LDL-C level with statin therapy is associated with a decrease in progression of atherosclerosis, as well as, in reduction in occurrence of cardiovascular events.[15-19] Statin therapy causes 5-15% increase in HDL-C level but this effect is relatively small compared with the LDL-C effects. Statins promote formation of a favourable HDL-C particle, thereby promoting regression in atherosclerotic plaque.[20]

Niacin

Niacin is one of the most effective pharmacological agent to raise HDL-C in current practice. Niacin lowers total cholesterol and LDL-C and raises HDL-C levels by 15 to 35%.[21,22] The coronary drug project (CDP) evaluated the role of niacin over 5-year periods in 8341 men with a history of MI during 1966 to 1975. Incidence of nonfatal re-infarction was reduced by 27% and all cause mortality reduction was 9%.[23]

When combined with colestipol, a bile acid sequestrant, in the FATS (Familial atherosclerosis treatment study), HDL-C increased by 43% with angiographic atherosclerosis regression in 39% and a 73% reduction in CAD rates over a 2.5-year follow up period.[24] The CLAS (Cholesterol Lowering Atherosclerosis Study) also showed beneficial role of niacin with colestipol in regression of atherosclerosis.[25]

The major problem with niacin is its side effects. The beneficial effects of niacin occur at doses of 1 to 1.5 gm per day.[21,22] But at this dose common side effect is facial pruritus and flushing caused by prostaglandin mediated vasodilatation. These flushing symptoms can be ameliorated with once daily extended release formulations which are also effective. However, higher doses of niacin can slightly worsen glycaemic control in diabetic patients.[26]

Niacin is evaluated when combined with simvastatin in the HATS ((HDL-C Atherosclerosis Treatment Study). In this study, patients with CAD, HDL-C <35mg/dl and LDL-C < 145mg/dl treated with both simvastatin and extended release niacin had an increase in HDL-C levels by 26%, slight regression in proximal coronary artery stenosis by angiography and a 90% reduction in CAD events.[27]

In the ARBITER 2 (ARterial Biology for the Investigation of Treatment Effects of Reducing cholesterol 2) trial, extended release niacin was given to patients with CHD, HDL-C < 45mg/dl and LDL-C <120mg/dl who were already receiving statin therapy. This treatment resulted in a 21% increase in HDL-C and a trend toward a decrease in the progression of carotid intima media thickness over a 1 yr follow up.[28] The follow up ARBITER 6 study was also very promising in which niacin was combined with statin.[29]

The AIM-HIGH (Atherosclerosis Intervention in Metabolic Syndrome with low HDL-C/High triglyceride and Impact of Global Health Outcomes) study was done in patients with CAD with evidence of the metabolic syndrome with HDL-C < 40mg/dl and triglyceride> 150mg/dl , not already given statin therapy. In this study, patients allocated to statin therapy with simvastatin alone or simvastatin and extended release niacin are evaluated over a 5 yr period to better define the additive effects of HDL-c raising therapies.[30] Participants were selected for AIM-HIGH because they were at risk for cardiovascular events despite well-controlled LDL. Their increased risk was due to a history of cardiovascular disease and a combination of low HDL and high triglycerides. The AIM-HIGH trial enrolled 3,414 participants in the United States and Canada. Researchers began recruiting participants in early 2006. The study was scheduled to finish in 2012. The average age of the participants was 64 years. Pre-existing medical conditions included coronary artery disease (92 percent); metabolic syndrome, which is a cluster of risk factors for heart disease (81 percent); high blood pressure (71 percent); and diabetes (34 percent).[30]But the result of this AIM-HIGH study was disappointing. The National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH) stopped this clinical trial 18 months earlier than planned termination. The trial found that adding high dose, extended-release niacin to statin treatment in people with heart and vascular disease did not reduce the risk of cardiovascular events, including heart attacks and stroke. During the study's 32 months of follow-up, participants who took high dose, extended-release niacin and statin treatment had increased HDL cholesterol and lowered triglyceride levels compared to participants who took a statin alone. However, the combination treatment did not reduce fatal or non-fatal heart attacks, strokes, hospitalizations for acute coronary syndrome, or revascularization procedures to improve blood flow in the arteries of the heart and brain. The study's data and safety monitoring board (DSMB) concluded that high dose, extended-release niacin offered no benefits beyond statin therapy alone in reducing cardiovascular-related complications in this trial.The DSMB also noted a small and unexplained increase in ischemic stroke rates in the high dose, extended-release niacin group. This contributed to the NHLBI acting director's decision to stop the trial before its planned conclusion. During the 32-month follow-up period, there were 28 strokes (1.6 percent) among participants taking high dose, extended-release niacin versus 12 strokes (0.7 percent) reported in the control group. Nine of the 28 strokes in the niacin group occurred in participants who had discontinued the drug at least two months and up to four years before their stroke. Previous studies do not suggest that stroke is a potential complication of niacin, and it remains unclear whether this trend in AIM-HIGH arose by chance, was related to niacin administration or some other issue.[30]

Fibrates

Fibrates lower LDL-C by 10 to 20%, lower triglyceride by 25 to 45% and increase HDL-C modestly by 10 to 15%.[31] The VA-HIT (Veteran

Affairs High density lipoprotein cholesterol Intervention Trial) evaluated patients with CAD, LDL-C <140 mg/dl, triglyceride < 300 mg/dl and HDL-C <40 mg/dl while on gemfibrozil.[32] LDL-C level did not differ significantly between the study groups over the 5 yr study period, so the 22 % reduction in CAD events was attributed to the 6% increase in HDL-C in a subsequent multivariate analysis.[32] It was the first trial that demonstrated a relationship between HDL-C increase and CAD event reduction in patient with moderate LDL-C levels.

In the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study, the effect of fenofibrate was evaluated in patients with type 2 DM not receiving statins. Fenofibrate did not significantly alter HDL-C levels. The FIELD trial failed to demonstrate a significant benefit of an agent that predominantly reduces triglyceride in a high risk population.[33]

Thiazolidinediones

Thiazolidinediones are insulin sensitizing agents that were approved for the treatment of type 2 DM. Pioglitazone and rosiglitazone are currently used members of this group. But the initial agent troglitazone was withdrawn because of idiosyncratic liver injury. Insulin resistance contributes to the metabolic syndrome, which includes hyperglycemia, elevation in triglyceride and reductions in HDL-C levels. Insulin sensitizers like thiazolidinediones were prepared to not only correct hyperglycemia but also to potentially correct lipid abnormalities.[34]

A meta-analysis of 23 randomized trials demonstrated that pioglitazone increased HDL-C level by 4.6 mg/dl and rosiglitazone increased HDL-C levels by 2.7 mg/dl.[35] But rosiglitazone also increased LDL-c and total cholesterol and did not decrease triglyceride. Pioglitazone was evaluated in the PROACTIVE (Progressive Pioglitazone Clinical Trial in Macrovascular Events) trial in patient with type 2 DM.[36] Pioglitazone increased HDL-C by 8.9% and decreased triglyceride by 9.6% with a 16% reduction in combined secondary end point of mortality and non fatal myocardial infarction and stroke.[36] There was only 0.6% decrease in HbA1c level so it was speculated that part of the clinical benefits of pioglitazone could be related to the HDL-C raising benefits of these agents.

These favourable effects of Pioglitazone are not seen in other thiazolidinediones. Rosiglitazone does not have same favourable lipid profile.[35] On the contrary, a recent meta analysis suggested that rosiglitazone treatment results in a significant risk of MI.[37] Currently, thiazolidinediones are not used solely for HDL-C raising therapy. But in patients with type 2 DM with low HDL-C, these agents may be useful.

Glitazars

Glitazars are a new class of agents being evaluated for raising HDL-C along with treating metabolic syndrome. Ragaglitazars increases HDL-C by 31%, decreases triglyceride by 62% and HbA1c by 1.3%, but the adverse effects of edema, anaemia and leucopenia have limited its use. [38] Muraglitazar increases HDL-C by 16% but adverse effects like weight gain and edema are very common.[39] Moreover, an increased risk of death, cardiovascular events and congestive heart failure are associated with muraglitazar.[40] Aleglitazar increased HDL-C by 20% and also decreased HbA1c in phase 2 trial. Aleglitazar can cause edema but not congestive heart failure or MI. So it is now under further evaluation.[41]

CETP inhibitors

These are the most promising new class of drugs for raising HDL-C. Currently many trials are ongoing on these agents. Humans with cholesteryl ester transfer protein (CETP) deficiency due to molecular defects in the CETP gene have markedly elevated plasma levels of HDL-C and apolipoprotein A-1.[42] People with CETP deficiency and higher HDL-C levels tend to have lower rates of atherosclerotic disease.[43] These people have large cholesterol rich HDL-C particles formed through CETP inhibitors, promote cholesterol efflux and reverse cholesterol transport.[44] Such observation is the basis of this concept that pharmacological CETP inhibitors might favourably increase HDL-C levels.

Several CETP inhibitors are evaluated in various trials. In ILLUMINATE (Investigation of Lipid Level Management to Understand Impact in Atherosclerotic Events) trial, torcetrapib was evaluated in 15,067 patients with a history of cardiovascular disease or type 2 DM. Patients receiving torcetrapib had a 72% increase in HDL-C,

24.9% decrease in LDL-C and 9% decrease in triglyceride over 1 year.[45] But this trial was prematurely terminated due to increase in cardiovascular events and all cause mortality in torcetrapib group.

The ILLUSTRATE (Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL-C Elevation) study showed that some regression of coronary atherosclerosis occurred only in patients with highest levels of HDL-C increase.[46] In patients with familial hypercholesterolemia RADIANCE 1 (Rating Atherosclerotic Disease Change by Imaging with a New CETP inhibitors 1) study also did not show a change in carotid intima media thickness despite a 55.5% increase in HDL-C with torcetrapib.[47] In the RADIANCE 2 trial, patient with mixed dyslipidaemia also had a similar increase in HDL-C, without an effect on carotid intima media thickness.[48] Torcetrapib was associated with a small increase in blood pressure in all these trials.

Dalcetrapib is another CETP inhibitor that demonstrated a 28% to 34% increase in HDL-C without an increase in blood pressure and cardiovascular events.[49] The phase 3 Dal-OUTCOME trial is ongoing in 15,600 patients with recent acute coronary syndrome to evaluate this dalcetrapib.

Anacetrapib is a potent CETP inhibitor that can raise HDL-c up to 129% without an effect on blood pressure in a phase 1 trial in healthy subjects.[50] Anacetrapib seems to exhibit HDL-C increasing effect greater than that seen with other investigational drugs in this class and LDL-C lowering effect similar to statins.[50] The DEFINE (Efficacy and Tolerability of CETP inhibitors with Anacetrapib) trial is currently ongoing to evaluate this agent.

ACAT inhibitors

Acyl coenzyme A cholesterol acyl-transferase (ACAT) esterifies cholesterol in many tissues. Theoretically ACAT inhibition would slow progression of foam macrophage. Subsequently, free cholesterol would be available for reverse cholesterol transport. But in phase 2 A-Plus (Avasimibe and Progression of Lesions on Ultrasound) study avasimibe, a nonselective ACAT inhibitor did not alter HDL-C levels and had no effect on coronary atherosclerosis.[51] Pactimibe in ACTIVATE (ACAT Intravascular Atherosclerosis Treatment Evaluation) trial raised HDL-C in only 5.4% and unfortunately limited atherosclerosis regression.[52] In CAPTIVATE (Carotid Atherosclerosis Progression Trial Investigating Vascular ACAT Inhibition Treatment Effects) study, pactimibe had no effect on HDL-C. Rather there was an increase in mean carotid intima thickness and significant increase in rate of cardiovascular death, MI and stroke with pactimibe.[53] Therefore ACAT inhibitors are of less interest now.

Reconstituted HDL infusion

Short term infusion of reconstituted HDL has been evaluated for reverse cholesterol transport. In ERASE (Effect of rHDL on Atherosclerosis Safety and Efficacy) study, reconstituted HDL-C infusion was given in patients with acute coronary syndrome within 2 weeks of symptoms. There was a nonsignificant trend toward an improvement in coronary atheroma but the study was postponed due to a high incidence of liver function abnormalities.[54]

Apo lipoprotein A-1 Milano infusion

Apo lipoprotein A-1 is currently the most effective proven HDL agent. Apo lipoprotein A-1 Milano is a variant of Apo lipoprotein A-1 that has an arginine to cysteine mutation. This Apo lipoprotein A-1 Milano was first traced in Italy in 1980, where some people despite having very low HDL-C levels (10-30 mg%) had a low incidence of atherosclerosis.[55] In one study recombinant Apo lipoprotein A-1 Milano infusion (ETC 216) was randomly infused in 57 patients within 2 weeks of acute coronary syndrome. There was significant reduction in intravascular ultrasound measured coronary atheroma.[56] Although promising, these results require confirmation in larger clinical trials with morbidity and mortality end points.

Apo lipoprotein A-1 mimetics

These are also experimental agents that have been formulated to promote reverse cholesterol transport and to regress coronary atheroma. After multiple modifications an orally active agent 4F peptide made with D-amino acid was experimented in mice and it could decrease atherosclerotic lesion and promote reverse cholesterol transport.[57]

Phase 1 data showed that this D 4F may be safe for human with CHD and it may improve the HDL-C anti inflammatory index, but for the clinical use more studies are needed.[58] There are several other Apo lipoprotein A-1 mimetics in very early experimental stage. May be this strategy of using peptide mimetics to treat atherosclerosis in its infancy but carries the potential to become one of the most important therapies in future.

Apo lipoprotein A-1 up regulation

RVX-208 is a novel peptide, that increases transcription of Apo lipoprotein A-1 thereby promoting reverse cholesterol transport. Phase 1 data showed a dose dependent increase in Apo lipoprotein A-1 and thereby HDL functionality.[59] Further evaluation is needed to fully examine its ability to treat coronary atherosclerosis.

HDL targets

The National Cholesterol Education Program (NCEP) defines an HDL-C level <40 mg/dl as a categorical risk for coronary artery disease.[60] Virtually all cardiologists can point to patients in their practice whose only risk factor for CAD is low HDL-c. Despite this, only few physicians target it for therapeutic elevation. Because raising HDL-C is challenging and frequently requires lifestyle modification and drugs. But currently no pharmacological intervention available that effectively raise HDL-C and leave other lipid levels unchanged. And it is also unclear that whether raising HDL-C reduces risk for cardiovascular morbidity and mortality.

There are clearly articulated goal by the NCEP for LDL and non HDL cholesterol based on global cardiovascular risk evaluation, similar targets for HDL are yet undefined. An expert group on HDL cholesterol has recommended that HDL be raised to >40 mg/dl in patients with CVD, metabolic syndrome or CAD risk equivalents.[61]

Conclusion:

Despite much advances, treatment and prevention of cardiovascular diseases are far from reaching the target. Reduction of cardiovascular risks by raising HDL-C is of much interest in this regard. Non-pharmacological measures, including lifestyle modification are effective, but often inadequate. A number of established drugs raise HDL-C to some extent along with controlling other parameters of dyslipidaemia. More potent and specific molecules are in different stages of development. At present, CETP inhibitors, especially anacetrapib appear to be the most promising agent with acceptable safely profile. In near future, more effective reduction of cardiovascular risk factors by reaching HDL-C target will hopefully be possible.

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