

HDL Management: Recent Advances And Perspectives Beyond LDL Reduction

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Atherosclerotic diseases are a major cause of morbidity and mortality worldwide¹. Among the classic risk factors known, elevated levels of LDL-cholesterol (LDL-C), and reduced levels of HDL-cholesterol (HDL-C) are associated with a significant increase in the incidence of atherosclerotic cardiovascular disease. With the objective of reducing this risk, the main focus of lipid-lowering therapy has been the reduction of LDL-C levels using statins. However, although a major benefit has been obtained, and although there has been significant reductions in LDL-C levels with intensive lipid-lowering treatment, a significant number of events still cannot be prevented^{2,3}.

Therefore, there is a great interest in identifying therapies that can reduce the risk of cardiovascular events even further. A therapeutic target that has aroused great interest is the increase in HDL-C levels, since reduced levels of this type of cholesterol constitute the lipid abnormality most widely found in patients with established coronary artery disease (CAD). Some studies have demonstrated that an increase in HDL-C serum levels in the region of 1mg/dl reduces the incidence of CAD by 2-3%^{4,5}. It has also been demonstrated that elevated levels of HDL-C may prevent the progression of atherosclerotic plaque and even promote its regression⁶ (chart 1).

The objective of this study is to review HDL metabolism, to determine its role in the development of atherosclerotic disease, and to study the current treatment of low levels of HDL-C and the perspectives for new therapies.

HDL metabolism

The endogenous metabolism of lipids comprises two major systems. One of them is responsible for the transport and formation of cholesterol-carrying particles bound to Apolipoprotein (Apo) B100 (VLDL, IDL and LDL) and the other is associated to Apo AI and to HDL metabolism.

High-density lipoproteins (HDL) are a family of heterogeneous particles that vary in size, density and chemical composition as a result of their rates of synthesis and catabolism and of continuous intravascular remodeling by the action of enzymes and transport proteins. The main function of HDL seems to be the removal of excess free cholesterol from the periphery, the conduction of cholesterol to the liver and the promotion of its metabolism and secretion into the bile, which is known as

reverse cholesterol transport⁷.

HDL particles originate from a phospholipid-apolipoprotein complex, called nascent-HDL. Apo AI accounts for 70-80% of its structure. These particles capture free cholesterol by binding to a receptor of peripheral cells which is known as ABC A-1 (*ATP Binding Cassette A-1*). The LCAT enzyme (lecithin-cholesterol acyltransferase) acts on the transformation, into HDL3, of nascent-HDL, which are small particles, poor in cholesterol. This enzyme, in addition to facilitating the transport of free cholesterol from the peripheral cells to HDL particles, also converts free cholesterol into cholesterol esters, thus facilitating greater acceptance by HDL3 which progressively increase in size to become HDL2⁷.

From this point on, cholesterol esters can be transferred to other lipoproteins that contain Apo B by the action of CETP - *Cholesteryl Ester Transfer Protein*. This cholesterol is exchanged for triglycerides (TG) contained in TG-rich lipoproteins (chylomicrons, VLDL and remnants), thus reducing the cholesterol content of HDL. The reverse cycle of cholesterol is completed when HDL particles are captured by SR-B1 (*Scavenger Receptor*) hepatic receptors that remove their cholesterol content, initiating the process of excretion of cholesterol into the bile.

It has also been suggested that HDL may have pleiotropic effects beyond the reverse cholesterol transport. These effects include anti-inflammatory, antioxidizing, antiaggregating, anticoagulant and profibrinolytic properties, which have been demonstrated in *in vitro* studies. Some of these properties are also present with infusion of HDL-cholesterol *in vivo*^{8,9}. Environmental factors such as diet, obesity and exercises, in addition to genetic and gender-related factors also influence HDL-C serum levels¹⁰.

Metabolic disorders that cause low HDL levels may occur at any stage, including alterations in receptors, enzymes and transporters. It is possible that new medication may control these disorders, increasing reverse cholesterol transport and activating the potential pleiotropic effects obtained with the increase of HDL-C serum levels.

Role in ischemic heart disease

There is growing evidence of an inverse relationship between HDL-C levels and the risk of CAD¹¹. In Framingham's study, each 4mg/dl decrease in HDL-C levels increases the

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Study	Design	Intervention	Outcomes	Results
HHS, 1987 (Helsinki Heart Study)	Randomized Double-blind Placebo-controlled Primary Prevention Non-HDL Cholesterol >200mg/dl	N:4081 Gemfibrozil 1200mg/ day (n:2051) Placebo (n:2030)	Lipid levels. C u m u l a t i v e incidence of CAD in 5 years.	34% reduction in the incidence of CAD in the Gemfibrozil group.
BIP, 2000 (Bezafibrate Infarction Prevention Study)	Multicentric Randomized Double-blind Placebo-controlled Secondary prevention Low HDL-C, median LDL-C and TG levels	N:3090 Bezafibrate 400mg/ day (n:1048) Placebo (n:1042)	Primary: fatal or non-fatal AMI or sudden death. Lipid levels.	18% increase in HDL-C and 21% reduction in TG. There was no significant reduction in primary outcomes. Subgroup with TG>200mg/ dl had a 39.5% reduction in outcomes in the gemfibrozil group.
HATS, 2001 (HDL-Atherosclerosis Treatment Study)	Multicentric Randomized Double-blind Placebo-controlled Secondary prevention Low HDL-C, normal LDL-C and high TG	N:160 Four treatment regimens: 1) Simvastatin + niacin 2) Antioxidizing 3) Simvastatin + niacin + antioxidantizing 4) Placebo.	Arteriographic evidence of change in coronary stenosis. O c c u r r e n c e of the first CV outcome: death, AMI, CVA and revascularization.	Mean increase of 31mg/dl in HDL-C. Mean regression of coronary stenosis of 0.4% in the group simvastatin + niacin. 90% reduction in combined outcome in the group simvastatin + niacin.
VA-HIT, 2001 (Veterans Affairs High- Density Lipoprotein Cholesterol Intervention Trial)	Multicentric Randomized Double-blind Placebo-controlled Secondary prevention Low HDL-C and LDL- C	N: 2531 Gemfibrozil, 1200 mg/d (n = 1264) or Placebo (n = 1267)	Baseline lipid levels and mean in the first 18 months. C o m b i n e d outcome: non- fatal AMI and CV death.	Reduction by 11% in combined outcomes with Gemfibrozil for each 5mg/dl increment in HDL-C, irrespective of LDL-C and TG levels.

Chart 1 - Major clinical studies with HDL management

incidence of CAD by 10%¹². The last report issued by the *National Cholesterol Education Program* (NCEP-ATPIII) defined that an HDL-C serum level below 40mg/dl is an independent risk factor for CAD¹.

More recently, the results of the *MIRACL (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering)* study suggest that HDL-C levels, as presented by patients with acute coronary syndrome, have a greater influence on the short-term prognostic than LDL-C levels¹³. Data from the Helsinki study on primary prevention with gemfibrozil suggest that for each 1% increase in HDL-C there was a 2-3% reduction in the incidence of coronary events⁵.

Some years ago, the *Air Force/Texas Coronary Atherosclerosis Prevention Study* (AFCAPS/TexCAPS) analyzed the use of lovastatin for the primary prevention of CAD in a population with average LDL-C levels and low HDL-C levels. Lovastatin, in comparison with the placebo, increased HDL-C levels by 6% and reduced LDL-C levels by 25%, with a 37% reduction in cardiac events^{14,15}.

The VA-HIT (*Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial*) investigated the benefits of

secondary prevention with gemfibrozil in patients with CAD and low HDL-C levels and LDL-C levels below 140mg/dl. The results showed a 22% reduction in the incidence of coronary events in the group treated with gemfibrozil¹⁶.

The HATS (*HDL-Atherosclerosis Treatment Study*) analyzed the use of simvastatin combined with niacin in patients with CAD, normal LDL-C levels and low HDL-C levels during 3 years (mean). On average, this combination promoted a 42% reduction in LDL-C levels and a 26% increase in HDL-C levels. When compared with the placebo, there was improvement in the lesions on angiography and a 90% reduction in major clinical events. An analysis carried out after the study demonstrated the safety and tolerability of this combination in patients with and without diabetes. However, this was a small study, designed to show the effects on the plaques rather than the improvement of clinical outcomes, which indicates that we should analyze its results with caution⁴.

Therapy of low HDL levels

Change in lifestyle - Although individual responses vary greatly, changing one's lifestyle plays a key role in the primary

and secondary prevention of major cardiovascular events. The last NCEP-ATP III consensus states that weight reduction increases HDL-C by 5-20%; smoking cessation increases [HDL-C] by approximately 5% and regular physical activity may increase HDL-C by up to 30%.¹

Alcohol consumption - Moderate alcohol consumption (30-60 g/day) increases HDL-C and Apo A-I levels by 5-10%, and this effect may account for up to half the probable benefit attributed to alcohol as regards the reduction of CAD. However, due to its high addictive potential and to other diseases secondary to its consumption, alcohol cannot be recommended as a therapeutic method for the population at large¹.

Omega-3 fatty acids - Omega-3 fatty acids are polyunsaturated fats derived primarily from fish oil. They have antithrombotic properties and improve the lipid profile, and may reduce triglyceride levels by up to 30%. They have little effect, however, on HDL-C levels, and increase HDL-C serum levels by less than 3%¹⁷.

Estrogen - Epidemiological and experimental studies have demonstrated the benefits of estrogen on serum lipid levels. Estrogen replacement, in addition to reducing LDL-C levels, increases HDL-C by 10-20%, especially because of the activation of Apo A-I production, and it also reduces LDL-C levels¹⁸. This effect is mitigated in part and in a variable manner by the concurrent use of progestogen.

However, clinical studies have not proven the clinical benefits of hormone replacement therapy, and therefore, it is not recommended to treat low HDL-C levels or to prevent CAD¹⁹⁻²⁰.

Niacin (nicotinic acid) - Nicotinic acid is the drug used in clinical practice which has the greatest ability to increase HDL-C (15-40%). It also reduces LDL-C (5-25%) and triglyceride (20-50%) levels. Likewise it increases the diameter of LDL particles, reducing the concentration of small and dense LDL particles, thus making the profile of LDL subclasses less atherogenic.

Nicotinic acid acts on many stages of lipid metabolism, inhibiting the mobilization of fatty acids in the adipose tissue and decreasing the influx of these fatty acids into the liver, therefore decreasing the production of VLDL and the formation of LDL. Niacin also inhibits the degradation of HDL particles by mechanisms that are not yet fully known. For all these reasons it can be used to treat all types of dyslipidemia⁴.

Well conducted studies have demonstrated that niacin is able to reduce the size of atherosclerotic plaques and major cardiovascular events²¹. It is a good choice for patients with a high risk of developing coronary disease, especially those with metabolic syndrome, diabetes and obesity who typically have an atherogenic lipid triad (high TG, low HDL and small and dense LDL particles).

In most cases, it should not be used in isolation, but rather in combination with statins or fibrates, in order to improve the overall lipid profile which in turn translates into increased HDL-C, reduced LDL-C and TG and shift to a less atherogenic profile of LDL particles. The combination with statin is well tolerated and there seems to be no intensification of its side effects²². When the extended release formulation is used, the doses vary from 1-2 g/day, starting with 250 to 500 mg of nicotinic acid per day after dinner and increasing the dose by

250 to 500 mg every two weeks. The combination with fibrate has also been studied with favorable results, but more in-depth studies are required to demonstrate clinical benefits²³.

The frequent side effects of nicotinic acid greatly limit its use, as these effects become more intense with the increase in dose. The most common adverse effects are skin reactions (flushing and itching), irritation of mucosae and gastrointestinal disorders such as diarrhea and nausea. The most severe are hepatotoxicity, hyperuricemia and hyperglycemia. One way to reduce side effects is using a single dose of extended-release niacin before bedtime. In the case of flushing, the incidence can be reduced with the concurrent use of ASA. Glycemia is altered with higher doses (>3g) and recent studies with diabetic patients did not show significant alteration with lower doses of the drug²⁴⁻²⁵.

Statins - These drugs act by inhibiting the main enzyme involved in the synthesis of cholesterol, the HMG-CoA reductase, thus reducing LDL-C serum levels by 18-60% and triglyceride levels by 7-30%. Their action on HDL metabolism is not well defined, but it is known that they increase HDL-C serum levels by 5-15%²⁶.

Statins have a well defined benefit in the reduction of major cardiovascular events due primarily to their action on LDL metabolism^{27,28}. Some studies have demonstrated that the combination of statin and extended-release niacin significantly improves the lipid profile of patients with good safety and efficacy²⁹. The combination with niacin is good due to its coverage in the treatment of dyslipidemias, because the drugs are not antagonist, but rather coadjutants in the treatment of mixed dyslipidemias. Although there is little proof of the benefit of this combination, a study has demonstrated an important reduction in major cardiovascular events⁴.

Fibrates - These medicines derive from fibric acid, used mainly in the treatment of hypertriglyceridemia. Their metabolism is complex and causes a reduction in TG serum levels of up to 60%, and in LDL-C serum levels of 5-20%. They also cause an increase in HDL-C serum levels of 10-35%. One of the actions of fibrates is due to the agonist effect of receptors activated by peroxysome proliferators, known as PPARs, which will be discussed in detail ahead.

Because fibrates, in addition to increasing HDL-C also reduce atherogenic triglyceride-rich lipoprotein which cannot be measured only through fasting triglyceride levels, it is difficult to attribute any kind of clinical benefit obtained with this group of medicines to the isolated increase of HDL-C.

Data from the *Helsinki Heart Study* on primary prevention with the use of gemfibrozil demonstrated a 37% reduction in fatal and non-fatal infarctions, but with no alterations in total mortality⁶.

The VA-HIT study, with the use of gemfibrozil for secondary prevention, analyzed patients with slightly elevated LDL-C and TG and with HDL-C below 40mg/dl showed a significant reduction in major cardiovascular events which are partly attributed to HDL increase. The combination with niacin has been considered - and may significantly reduce - cardiovascular events in patients with known CAD³⁰. However, the *Bezafibrate Infarction Prevention Study*, which evaluated the use of bezafibrate in the incidence of coronary events in patients

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with CAD, with CT levels between 180-250mg/dl, TG below 300mg/dl and HDL-C below 45mg/dl, demonstrated no clinical benefit despite the 12% increase in HDL-C levels; the exception was a subgroup of patients with TG above 200mg/dl, that presented a 40% reduction in the primary outcome with the use of bezafibrate in a *post hoc* analysis³¹. Additionally, a large prevention study with diabetic subjects with the use of fenofibrate did not show benefits in the reduction of non-fatal infarction and death due to CAD³². This is the reason why more clinical trials are required to prove the clinical benefits.

Resins - Colestipol and cholestyramine are examples of exchange resins that decrease the intestinal absorption of bile salts and cholesterol. Their major action is to lower LDL-C, especially when used in combination with statins³³. Secondly they promote an increase in the synthesis of Apoprotein A1 with little elevation of 3-5% in HDL-C levels. These are drugs with little systemic toxicity, but with many side effects in the gastrointestinal tract. They tend to increase TG serum levels and are therefore contraindicated for people with dysbetalipoproteinemia and with hypertriglyceridemia above 400mg/dl³⁴. They can be used in patients with diabetes and have a better effect when combined with nicotinic acid³⁵⁻³⁶.

Ezetimibe - This is an intestinal inhibitor of the absorption of cholesterol with a small effect on HDL-C, with an increase of less than 5% in serum level. It has been used mostly in combination with statins to heighten the effect of these drugs, also increasing HDL-C levels³⁷.

Advances and perspectives (chart 2)

Synthetic peptides – HDL - mimetic - Apo A-1 is the major constituting particle of nascent HDL, with an important function in the capture of free cholesterol. Individuals with a natural and uncommon variant of this protein, known as Apo

A-1 Milano, have been discovered in Italia. Although they present low HDL-C levels, they had less atherosclerosis than the expected vis a vis their HDL-C levels.

Based on this discovery, mimetic peptides of this apoprotein were synthesized which are a promising form of therapy for low HDL-C levels. ETC-216 is a synthetic variant of HDL, formed by a phospholipid complex and recombinant Apo A-1 Milano with the purpose of mimicking Apo A-1 Milano.

Experimental studies with rats have shown that the infusion of high doses of recombinant Apo A-1 mobilizes tissue cholesterol reducing the lipid content and the macrophages in the plaques³⁸. Promising results have also been demonstrated in phase 2 studies through the analysis of atherosclerotic plaques by intravascular ultrasound (IVUS) reducing the volume of plaques by approximately 4% and preventing their progression¹⁰.

Recombinant HDL is not yet available for clinical usage. One of the major limitations, in addition to the high cost, would be the need for intravenous administration in high doses. This is why other products have been developed to try oral administration and increase the possibilities of use.

PPAR Agonists – peroxisome proliferators - activated receptors - PPA receptors play an important role in cell function, including lipid metabolism, cell proliferation, differentiation, adipogenesis and inflammatory signaling, in addition to interacting with some medications used in the treatment of metabolic diseases. There are three subtypes of PPARs, defined as alpha, gamma and delta.

The activation of alpha receptors produces an increase in HDL-C serum levels and a decrease in TG serum levels, whereas the activation of gamma receptors produces a decrease in peripheral insulin resistance and a slight HDL elevation, and the activation of delta receptors produces the three effects³⁹.

Category	Name /number	Administration route	Stage of development	Effects
Apo A1 Milano mimetic drugs	ETC-216	IV	Phase 3	Reduction of lipid content and of inflammation in atherosclerotic lesions
	D4-F	PO	Phase 1	
PPAR Inhibitors	Fibrates	PO	Phase 4	Alpha action: increase in HDL-Cholesterol and reduction in triglycerides.
	Glitazones (Tesaglitazar)	PO	Phase 3	Alpha/gamma action: Reduction of insulin resistance and reduction of triglycerides
	Torcetrapib	PO	Phase 3	CETP inhibition with an increase of up to 100% in HDL-Cholesterol levels
CETP Inhibitors	JTT-05	PO	Phase 2	35-40% increase of HDL-Cholesterol
	CETi-1 Vaccine	-	Phase 2	Induction of autoantibodies that actively inhibit CETP, increasing HDL-Cholesterol levels by up to 8%

Chart 2 - New therapeutic options to elevate HDL-cholesterol

Fibrates have an alpha agonist action, glitazones have a gamma action^{40,41}. The ideal solution would be to have drugs that have the broadest possible effect on these receptors. Some PPAR agonists are currently being developed, and one of the most promising ones is tesaglitazar, a drug with alpha and gamma actions presently at a very advanced stage of research⁴².

One of the concerns relative to the development of these new drugs has to do with their side effects, since studies with animals have demonstrated that there was a significant increase in the development of tumors.

CETP inhibitors - CETP is a serum glycoprotein with a key role in the exchange of cholesterol esters of the HDLs for TGs of TG-rich lipoproteins. People with defects in the CETP-modulating gene and the consequent deficiency in the gene's operation have very high levels of HDL-C and Apo A-1 and low levels of LDL-C. Phase 2 and 3 studies with CETP-inhibitors have shown a great increase in HDL serum concentration⁴³.

Torcetrapib acts by inhibiting the action of CETP on HDL, decreasing its degradation and causing an increase of up to 100% in HDL-C levels. The effect has been observed with the use of CETP in isolation or in combination with atorvastatin. The clinical effect resulting from the action of torcetrapib is currently being assessed and the results of the related studies are to be published in the coming years. JTT-705 also inhibits the action of CETP and phase 2 studies have demonstrated a 35-40% increase in HDL-C serum levels⁴⁴.

A vaccine against CETP has been studied that promotes the induction of autoantibodies that bind specifically to this protein, promoting the inhibition of its activity, but preliminary studies show slight increases, in the region of 8% in HDL-C levels, only in selected subjects with low HDL-C and normal LDL-C levels. The results are controversial, the experiment is limited, and further studies are required⁴⁵⁻⁴⁶.

The doubt about these drugs is whether HDLs formed through the inhibition of CETP have the same effect as the natural ones. It is expected that clinical studies may reveal more consistent information on the effect of these medications, especially in the prevention of coronary events and death.

SR-BI hepatic receptor - SR-BI is an HDL hepatic receptor which, when stimulated, promotes a reduction in serum HDL-C, mediating the transport of cholesterol from the blood to the bile. Studies with animals have shown a reduction in atherosclerosis with SR-BI stimulation while the absence of

this receptor increased HDL-C serum levels, but produced a worsening of the atherosclerotic process⁴⁷.

Conclusion

Cardiovascular diseases are currently the leading causes of death and, according to forecasts of the WHO for the coming years, this leading position will be consolidated further. Many therapeutic and preventive advances have contributed to reduce these rates. However, in order to substantially reduce deaths from heart conditions more advances are required in the control of risk factors.

Obesity and smoking are public health problems worldwide, and mobilize efforts towards their reduction, but with unsatisfactory results. Among diabetic patients, the adequate control of glycemia produces benefits. However, as regards mortality, the gains are modest. There is a more defined therapeutic arsenal with established control goals for arterial hypertension, for which treatment benefits have also been compellingly proven.

In addition to these interventions, the hope of decreasing the number of deaths from cardiovascular diseases lies on actions on lipid metabolism. In recent years, the efforts of the scientific community have focused on LDL-C reduction, with major achievements as regards mortality reduction. However, even with substantial reductions in LDL-C levels, a large number of CAD cases have not yet been prevented.

One perspective to be considered is the intervention on HDL metabolism with a view to increase reverse cholesterol transport. The current therapy, directed at the management of low HDL-C levels still provides unsatisfactory benefits, since well tolerated medications promote a slight increase, while more potent drugs have more adverse effects, which prevents their use in up to 30% of the patients. For these reasons, new drugs are needed that have different mechanisms of action able to alter HDL metabolism and promote more sustained alterations, adding benefits to those of existing drugs.

There is no doubt that low HDL-C levels predispose patients to atherosclerosis. There is strong epidemiological evidence and data from experimental and angiographic studies showing that the increase of HDL-C levels or the infusion of Apo AI reduces atheroma. However, clinical evidence that the therapy designed to isolatedly increase HDL-C levels reduces the risk of coronary disease and cardiovascular mortality is still hypothetical.

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