The failure of LDL cholesterol reduction and the importance of reverse cholesterol transport. The role of nicotinic acid

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Abstract

Low-density lipoprotein cholesterol (LDL-C) reduction alone has consistently achieved a statistically significant 25–30% reduction in clinical events in multiple clinical trials. This degree of clinical benefit is inadequate, however, to stem the tide of coronary artery disease. A focus on low-density lipoprotein (LDL) reduction alone reduces the rate of coronary atherosclerosis progression but leaves a large number of patients experiencing clinical events despite adequate LDL-C control. One major contributor to coronary atherosclerosis that is not improved with LDL reduction is high-density lipoprotein (HDL) and reverse cholesterol transport. Clinical trials funded by the US National Institutes of Health (NIH) have demonstrated that a combination of LDL reduction and HDL increase can achieve better clinical and arteriographic outcomes compared to LDL reduction alone. HDL heterogeneity helps to explain differences in the efficiency of reverse cholesterol transport. This process can be enhanced through appropriate diet, loss of excess body fat and physical activity. Nicotinic acid and fibric acid derivatives can enhance reverse cholesterol transport and have been used in multiple clinical trials. The combination of nicotinic acid and a statin drug are particularly beneficial in NIH-sponsored clinical trials. The HDL increase induced by nicotinic acid is primarily HDL2. By combining a two-staged LDL-C reduction and HDL-C raising strategy, improved clinical outcomes can be achieved for patients with coronary artery disease.

Key words: coronary artery disease, atherosclerosis, low-density lipoprotein, high-density lipoprotein, HDL2, nicotinic acid, niacin, statin, HMGCoA reductase.

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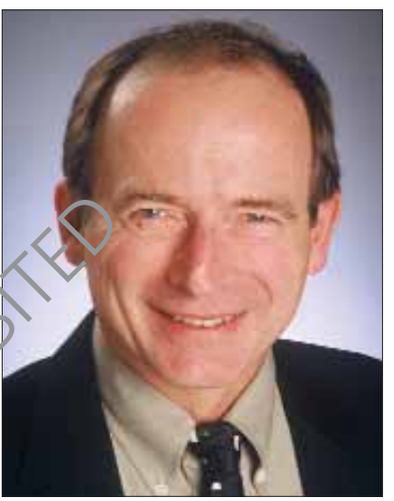

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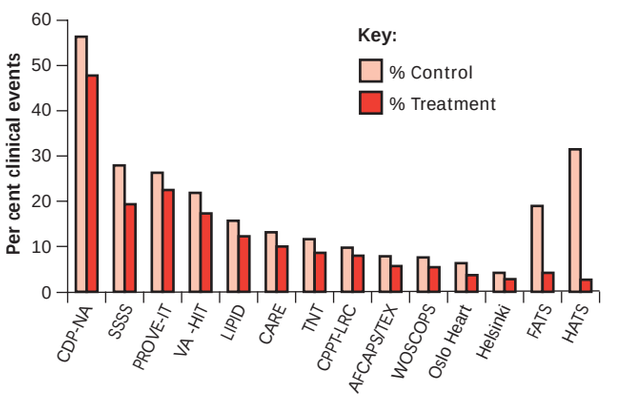
Introduction

Coronary atherosclerosis is the result of a complex interaction of genetic, metabolic and environmental factors. Some of these issues have received considerable attention and are the focus of national health campaigns such as hypertension, dyslipidaemia, obesity and the metabolic syndrome.[1-4] One major focus has been professional and public campaigns designed to reduce levels of low-density lipoprotein cholesterol (LDL-C). Despite these successful efforts, coronary atherosclerosis continues to be the leading cause of death for both men and women.[5] Reduction of LDL-C in clinical trials has resulted in an approximately 25% reduction in clinical events, which has been used as the foundation for the argument that the lower the LDL-C level, the better the patient care.[6] However, close examination of these trials indicates that the average 25% reduction in events, while laudable, ignores the large number of patients that continue to have cardiovascular events despite LDL-C reduction (figure 1).[7] PROVE-IT (The PRavastatin Or atorVastatin Evaluation and Infection Therapy study) examined the effect of treatment with either 40 mg/d pravastatin or 80 mg/d atorvastatin and documented significantly greater LDL-C reduction in the 80 mg/d atorvastatin group associated with a statistically significant 16% reduction in cardiac risk.[8] However, this 16% reduction in risk actually represents the difference between a 26.3% event rate in two years in the

Figure 1. Cholesterol-lowering studies representing the per cent of subjects in the control group and the treatment group experiencing a cardiovascular event. This illustrates that despite a statistically significant difference, a large number of patients in the treatment group continue to have cardiovascular events. The difference in clinical events when aggressive combination therapy is used is illustrated by the two studies on the right, FATS and HATS



pravastatin group compared to a statistically significant, but not clinically profound, 22.4% event rate in the atorvastatin group. The recent report from the TNT (Treating to New Targets) study comparing 10 mg/d atorvastatin with 80 mg/d atorvastatin indicated a significant 26% reduction in events but this represented 584 events in the 10 mg/d group compared to 434 events in the 80 mg/d group.[9] While this indicates progress, it was of little comfort to the 434 individuals with coronary events while taking 80 mg atorvastatin each day for a mean of 4.9 years.

This statistically significant but clinically inadequate control of coronary artery disease (CAD) risk is, in part, due to a lipid treatment focus on LDL-C alone with a resultant neglect of other important aspects of lipoprotein metabolism. One established metabolic lipoprotein pathway that is intimately involved with cardiovascular health and disease is reverse cholesterol transport (RCT). Recent clinical trials highlight the clinical importance of this aspect of atherosclerosis management. A recent European consensus panel on high-density lipoprotein cholesterol (HDL-C) has stated that raising HDL-C is an appropriate therapeutic intervention for patients with low HDL-C or elevated CAD risk, and that nicotinic acid is the most potent agent for raising HDL-C.[10]

RCT history

The observation that different 'types' of high-density lipoproteins (HDL) exist was first observed by John Gofman in 1951 with the use of analytic ultracentrifugation.[11] The possible role of different HDL subtypes in the atherogenic process was discussed using the results of the Lawrence Livermore study in 1966.[12] Almost 40 years ago the heterogeneity of HDL and the concept of RCT as a dynamic process was proposed by John Glomset and colleagues – in its current version it involves the role of genetics, apoproteins, enzymes, transfer proteins, membrane modulators and HDL subclasses.[13]

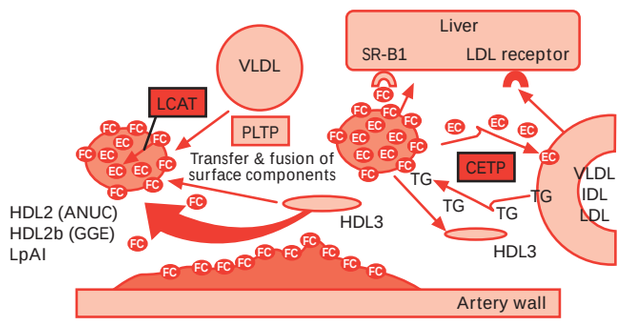
The results of the historically important Coronary Primary Prevention Trial generated the now famous 1% to 2% rule, which stated that for every 1% reduction in LDL-C, a 2% reduction in clinical events could be expected. At the same time, a less widely quoted report from the same study and data-set indicated in 1986 that, for each 1 mg/dL (0.026 mmol/L) increment in HDL-C, a 5.5% reduction in risk was observed.[14,15] In this investigation of LDL-C reduction, the incidence and mortality rates from coronary heart disease were twice as high in men with baseline lower HDL-C levels (< 1.03 mmol/L) compared to those with higher HDL-C levels (> 1.29 mmol/L). Other studies have reported higher mortality in patients with low HDL-C including the Coronary Drug Project and the Israeli Ischemic Heart Disease Study.[16,17] A constant difficulty in attributing independent clinical benefit to increasing HDL-C and improved RCT is the inverse relationship with other atherogenic lipoproteins such as intermediate-density lipoprotein (IDL), small, dense LDL, and triglycerides.[18] HDL subfractions, and in particular low HDL2, has also been shown to help predict CAD severity and arteriographic progression.[19,20]

Evidence that HDL-C raising is of cardiovascular benefit was initially presented with the results of VA-HIT (Veterans Affairs High-density lipoprotein cholesterol Intervention Trial).[21] Demonstration of a statistically independent role for increasing HDL-C is of minor importance to clinicians. This is because clinical trials using multi-drug therapy that can lower LDL-C, small LDL and IDL, and can increase HDL-C and lipoprotein AI (LpAI or HDL2b), have demonstrated both clinical event and arteriographic benefit when changes in multiple lipoprotein subclasses are induced.[22] An increase in HDL-C in response to nicotinic acid and statin treatment has been associated with an improvement in arteriographic evidence of CAD progression.[23] Increases in HDL-C, in particular HDL2 (LpAI), have been shown to be associated with significant arteriographic benefit and a dramatic reduction in cardiovascular events.[24] The complexity of drug-specific HDL subclass change during a clinical trial is illustrated by LOCAT (the Lopid Coronary Angiography Trial).[25] Analysis of HDL subclass change revealed a 9% increase in HDL-C with a 5% increase in HDL2-C and a 9% increase in HDL3-C. This trial indicated that during the trial, HDL3-C but not HDL2-C was associated with arteriographic benefit when the fibric acid derivative, gemfibrozil, was used to modify lipoprotein concentrations and distribution.

RCT pathway

Understanding the RCT process is a clinically important topic since current lifestyle and pharmacological treatments can have a beneficial or harmful effect on this process. New pharmacological and molecular treatments are currently in clinical trials. There are five components of RCT that are useful for the clinician to understand: enzyme activity, transfer proteins, membrane modulators, apoproteins, and HDL subclasses.[26] HDL particles

Figure 2. Reverse cholesterol transport pathway



Key: VLDL = very low-density lipoprotein; SR-B1 = scavenger receptor B1; LDL = low-density lipoprotein; LCAT = lecithin cholesterol acyltransferase; PLTP = phospholipase transfer protein; CETP = cholesteryl ester transfer protein; IDL = intermediate-density lipoprotein; TG = triglycerides; HDL = high-density lipoprotein; LpAI = lipoprotein AI; FC = free cholesterol; EC = esterified cholesterol

that are low in lipid content are produced in four basic ways. First, as nascent HDL by hepatocytes; second, by intestinal mucosa cells; third, by disassociation from triglyceride-rich chylomicrons and very-low-density lipoprotein (VLDL) following the action of lipoprotein lipase (LPL); and fourth, by inter conversion of HDL2 and HDL3 by cholesteryl ester transfer protein (CETP), phospholipase transfer protein (PLTP) and hepatic lipase (HL). Lipid-free apolipoproteins acquire phospholipids and unesterified cholesterol from cells assisted by the adenosine-5 triphosphate (ATP) binding cassette transporter 1 (ABC1) which plays a role in lipid efflux from peripheral cells.

In general, small, lipid-poor nascent HDL particles are created when lipids combine with apoliprotein AI (apoA-I) that is derived from both a hepatic and intestinal source. This immature form of HDL (preB-HDL) is enriched with esterified cholesterol through the action of lecithin cholesterol acyltransferase (LCAT) and PLTP to produce cholesterol-rich HDL2 particles (figure 2). HDL particles can be removed from the circulation by either the scavenger receptor B1 (SR-B1) or by the apoE or apoA-I receptors. Lipids stored within HDL particles can be removed through the action of CETP, HL, and endothelial lipase (EL). Lipids in HDL2 can be removed by SR-BI, CETP and HL which results in the conversion of HDL2 into HDL3 which can then be reconverted into HDL2.

HDL subclass distribution can be a reflection of the efficiency of RCT and a guide to therapy. There are four basic well-established methods to determine HDL subclass distribution: density, size, cholesterol content following double precipitation, and apolipoprotein content. Based on the relative density obtained in the analytic ultracentrifuge (ANUC), the more dense, relatively cholesterol-poor form of HDL is termed HDL3 (1.125 to 1.21 g per ml) and the less dense, relatively cholesterol-rich form is termed HDL2 (1.062 to 1.125 g per ml).[27-29] Sequential immunoaffinity chromatography can isolate two HDL subclasses defined by their apo A-I and A-II content as those with A-I only (LpAI) and those with AI and A-II (LpAI:AII).[30]

The RCT pathway involves interaction of these subparticles with specific lipoproteins and neutral exchange factors which results in cholesterol esters being transferred to modified VLDL particles which are further metabolised and finally identified as LDL-C and eventually taken up by the LDL receptor. While low total HDL-C is an established CAD risk factor in epidemiological investigations, differences in HDL subclasses exist within the 'normal' HDL-C range and may contribute to CAD risk in individuals with 'normal' HDL-C values. The prevalence of disorders of HDL subclass distribution may differ by ethnic group. Individuals of Asian Indian descent have been found to have abnormally low HDL2b compared to matched Caucasian subjects despite 'normal' HDL-C levels.[31] Cardioprotection in high HDL-C patients appears to be related to differences in HDL subclass distribution. Hyperalphalipoproteinaemia, that is primarily HDL2 (or LpAI), is also associated with decreased HL activity and cardioprotection while those with high HDL-C values but primarily composed of LpA-I:A-II exhibit less protection.[32] Finally, the inheritance of HDL subclasses has revealed correlations among family members for specific HDL subclasses, which are independent of HDL cholesterol and apo A-I.[33]

Treatment

Standard therapeutic manoeuvres can have a differential effect on HDL subclass distribution and RCT. Such treatments may increase specific HDL subfractions to a greater or lesser extent than revealed by HDL-C measurements alone. These manoeuvres include diet, exercise and body fat reduction, and medications.

Diet and lifestyle

Low-fat diets have been recommended as the foundation for treating lipid disorders that involve elevations in LDL-C.[2] However, when diets are reduced in fat content, replaced calories are often derived from simple carbohydrates. Prospective, randomised studies at the University of California (Berkeley) have revealed that shifting diet calories from fat comprising 20% of total calories to comprising 10% of calories, while maintaining total calories unchanged, results in a 15% reduction in HDL-C but a 56% reduction in HDL2.[34] These HDL subclass changes are often but not always accompanied by increases in triglyceride-rich lipoproteins. Alcohol may increase HDL-C level but it appears to be primarily HDL3.[35] Loss of excess body fat (4–6 kg) either through exercise or reduced dietary calories can increase HDL-C by 10% but increase HDL2 by 40%.[36] Thus, lifestyle manoeuvres can have a significantly greater effect on HDL subclass distribution than reflected by standard HDL-C measurements.

Nicotinic acid

Nicotinic acid has been used to treat dyslipidaemia since the mid-

Table 1. Mean baseline values (mmol/L) and per cent change in values after 16 weeks of treatment with 40 mg atorvastatin/day, 40 mg simvastatin/day, or the combination of 40 mg lovastatin plus 2,000 mg prolonged release nicotinic acid per day[42]

	Baseline	Atorvastatin 40 mg	Simvastatin 40 mg	Nicotinic acid 2,000 mg/ lovastatin 40 mg
N		82	76	79
LDL-C	4.94	-49%	-39%	-42%
HDL-C	0.98	+6%	+7%	+32%
TG	1.99	-29%	-10%	-38%
HDL2b (%)	11	+3%	+13%	+34%

Key: LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein; TG = triglycerides

1950s and has been shown to be effective in decreasing arteriographic rates of CAD progression and reducing clinical events.[37] It is the most effective agent available today for increasing HDL-C and HDL2, and has the broadest effect on all atherogenic lipoprotein particles. Only recently has its mechanism of action been elucidated. Nicotinic acid produces these beneficial HDL effects by three major mechanisms: first, by decreasing fatty acid mobilisation from adipose tissue; second, by inhibiting hepatic diacylglycerol acyltransferase 2; and third, by inhibiting the removal of HDL-apo AI by hepatocytes.[38] These mechanisms help to explain the reduction in atherogenic apo B-containing lipoprotein particles and increase in HDL, LpAI, and HDL2 that is not apparent from other available lipid medications. Fenofibrate and gemfibrozil can reduce triglycerides and increase HDL-C but by a different mechanism. Nicotinic acid (but not gemfibrozil) has been reported to decrease the uptake of (125)I-labelled LpAI and increase plasma LpAI levels.[39] Nicotinic acid (2,000 mg/d) was reported to increase LpAI by 24% while gemfibrozil had no consistent effect on LpAI levels. Fenofibrate may be superior to gemfibrozil in regard to increasing plasma apoA-I.[40] This helps to explain the difference between the fibric acid derivatives fenofibrate and gemfibrozil, and nicotinic acid, on HDL-C and HDL subclass distribution. The HMGCoA reductase inhibitor group of medications has no differential effect on HDL subclass distribution.

We have previously reported that treatment with nicotinic acid results in a significant reduction in small, dense LDL, often accompanied by an increase in HDL2.[41] A recent investigation reported the effect of three lipid treatments on standard lipoprotein measurements as well as LDL subclass distribution, atorvastatin, simvastatin, and a combination of lovastatin plus nicotinic acid.[42] At the dose levels of 40 mg/d atorvastatin, 40 mg/d simvastatin, and 40 mg/d lovastatin plus 2,000 mg/d nicotinic acid, the LDL-C reduction was similar in all groups at 49%, 39% and 42%, respectively (table 1). But HDL-C was increased considerably more in the nicotinic acid/lovastatin group and HDL2b was increased 34%, well in excess of either of the statin only groups.

The clinical relevance of this differential effect of nicotinic acid on HDL subclass distribution is derived from clinical trials that incorporated nicotinic acid as part of the treatment modality. In FATS (Familial Atherosclerosis Treatment Study), multivariate analysis indicated that a reduction in the level of apolipoprotein B (LDL-C), a reduction in systolic blood pressure, and an increase in HDL-C correlated independently with regression of coronary lesions. Clinical events were reduced as well: 19.2% of the conventionally treated patients had an event compared to 4.2% in the nicotinic acid plus colestipol group.[23] In HATS (HDL-Atherosclerosis Treatment Study), the combination of nicotinic acid and simvastatin increased HDL-C and HDL2 significantly more than the control group: 31.6% of the control group experienced a clinical event compared to 2.6% of the nicotinic acid plus simvastatin group (table 2).[24] Thus, combination therapy produces greater reductions in clinical events and arteriographic improvement compared to monotherapy studies.

Table 2. Plasma lipid changes (mmol/L) in the treatment arms of arteriographic trials using statin monotherapy (REGRESS and MAAS) compared to arteriographic trials using combination therapy that included nicotinic acid[43-46]

Trial	REGRESS[43]	MAAS[44]	CLAS[45]	SCOR[46]	FATS[23]	HATS[24]
Baseline TG	1.77	1.92	1.71	1.49	2.23	2.28
% difference TG	-17.5%	-12.5	-27.2	-21.5	-33.2	-37.6
Baseline LDL-C	4.30	4.38	4.42	7.32	4.93	3.41
% difference LDL-C	-24.7%	-31.1	-43.3%	-39.2%	-31.4	-43.2
Baseline HDL-C	0.93	1.10	1.15	47.2	1.06	0.80
% difference HDL-C	+8.6%	+7.3	+36.3%	+25.4%	+41.5%	+29.0
HDL2-C	NA	NA	NA	NA	0.12	0.10
% difference HDL2-C					+200%	+60.5%
Treatment	Pravastatin	Simvastatin	Nicotinic acid Colestipol	Nicotinic acid Colestipol Lovastatin	Nicotinic acid Lovastatin	Nicotinic acid Simvastatin

Key: TG = triglycerides; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; NA = data not available

Key messages

- Low-density lipoprotein cholesterol (LDL-C) reduction alone is inadequate to control coronary heart disease
- Enhancing reverse cholesterol transport along with LDL reduction can improve clinical outcomes and regress coronary atherosclerosis
- High-density lipoprotein 2 (HDL2) is associated with cardiovascular risk when low, and cardiovascular benefit when raised
- Nicotinic acid is the most powerful drug for increasing HDL and HDL2
- Fibric acid derivatives can increase HDL
- Combination LDL reduction and HDL increase have been used in multiple clinical trials funded by the US National Institutes of Health

The future

A focus on enhancing reverse cholesterol transport has been embraced by the pharmaceutical industry. Active research projects are investigating the possible role of agents that modify cholesteryl ester transfer protein (CETP), lecithin cholesterol acyltransferase (LCAT), ATP binding cassette transporter 1 (ABCA1), hepatic lipase (HL), and membrane modulators. In the relatively near future, compounds that affect CETP will become available as well as methods of infusing recombinant HDL particles, gene transfection and peptide infusion, all in an attempt to supercharge the reverse cholesterol transport system. The CETP inhibitor torcetrapib has been reported to raise HDL-C by 16–91% depending on the dose used, and the combination of the CETP inhibitor JTT-705 and pravastatin is reported to increase HDL-C by 28% and reduce LDL-C by 5%.[47,48] Use of recombinant HDL in mice has been shown to significantly reduce plaque lipid load in a matter of hours and improve intravascular ultrasound (IVUS) defined coronary artery disease in humans.[49,50]

Significant LDL-C reduction can be achieved through the use of statin medications and can result in an approximate 25–30% reduction in clinical events. By addressing both LDL-C reduction and improving reverse cholesterol transport, the clinician can reduce clinical events by 80–90% and can achieve arteriographic regression. Thus, a combined approach to LDL-C and HDL-C modification is in the best interest of patients and ultimately the entire health care system.

Conflict of interest

The Fuqua Heart Centre has received research funds from Roche Molecular, Agilent Technologies, Abbott Laboratories, and Pfizer. Medical education activities have been supported by Kos Pharmaceuticals, Abbott Laboratories and Pfizer.

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