Patients with low levels of high-density lipoprotein cholesterol: to treat or not to treat?

S Tavintharan, S C Lim, C F Sum

ABSTRACT

Clinical evidence indicates that a low level of high-density lipoprotein cholesterol (HDL-C) is a major risk of atherosclerosis. Raising HDL-C reduces this risk significantly, making HDL-C levels an important target of treatment for dyslipidaemia, especially in pre-existent atherosclerosis. HDL-C is protective against atherosclerosis, largely due to its function of reverse cholesterol transport. Additionally, some important roles include fibrinolysis, antioxidant functions, and reduction of platelet aggregability.

A number of agents potentially modify HDL favourably. Niacin is the most potent HDL-C raising agent currently available in clinical practice, followed by fibrates. CETP inhibitors show greater HDL-C rising, but are still used in trial settings only. HDL mimetic agents are another group of agents that offer much promise. Clinical outcome data are awaited for these newer therapeutic agents.

Keywords: apolipoprotein A-I, atherosclerosis, high-density lipoprotein, hypoalphalipoproteinaemia

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INTRODUCTION

Over the past two decades, modifying low-density lipoprotein cholesterol (LDL-C) has been the major target for preventing atherosclerotic cardiovascular disease (ASCVD). However, an increasing number of trials, both observational and interventional, have shown the association of low levels of high-density lipoprotein cholesterol (HDL-C) and ASCVD, and the benefits of raising low levels of HDL-C in reducing the risk of ASCVD[1-3]. This has led to the recognition of low levels of HDL-C as an important major cardiovascular risk factor[4], and led to HDL-C levels being included as a target of treatment of dyslipidaemia, especially in high-risk patients, such as those with diabetes mellitus (DM)[5].

Approximately one-quarter to one-third of patients with pre-existing coronary disease and "desirable" total cholesterol (TC) [less than 5.2 mmol/L] have low levels of HDL-C (less than 1.0 mmol/L) as the primary abnormality[6]. Regardless of LDL-C levels, it has been estimated that each 1 mg/dl (0.03 mmol/L) increase in HDL-C reduces the risk of cardiac events by 2% in men and by 3% in women[1]. While the relationship between TC and LDL-C and ASCVD risk is a curvilinear one, where the slope is shallow up to approximately 5.2 mmol/L for TC (approximately 3.4 mmol/L for LDL-C) and significantly rises above this level[9], the relationship for HDL-C is virtually a mirror image of this with the risk rising sharply when the levels are below 1.0 mmol/L[1]. It is this group of patients, with "desirable" TC and LDL-C levels, but low levels of HDL-C that we wish to discuss in this paper.

This review aims to address the following:

- Clinical trial evidence of the role of HDL-C in ASCVD.
- Biochemical and physiological considerations.
- Therapeutic considerations and practical recommendations in the management of patients with isolated low HDL-C levels.
- Agents that raise HDL-C levels.

CLINICAL TRIAL EVIDENCE

Over the last two decades, several large trials have proven the "lipid hypothesis" that lowering cholesterol levels does indeed lower the risk of ASCVD. However, studies specifically focusing on patients with isolated low HDL-C levels have been few and these trials are now summarised in this section.

Primary prevention trials

Of the primary prevention studies, two studies include details on patients with low HDL-C levels. Table I highlights the features of these studies, which suggest that in patients without pre-existing ASCVD, regardless of LDL-C levels, those with lower HDL-C

Department of Medicine
Alexandra Hospital
378 Alexandra Road
Singapore 159964

S Tavintharan, FRCP, FAMS
Consultant

S C Lim, FRCP, FAMS
Consultant and Director, Clinical Research

C F Sum, FRCP, FAMS
Senior Consultant and Director, Diabetes Centre

Correspondence to:
Dr S Tavintharan
Tel: (65) 6379 3461
Fax: (65) 6379 3936
Email: tavintharan_subramaniam@alexhosp.com.sg

Table I. Summary of primary prevention studies involving patients with low HDL-C.

Study	Medication used	Study population with baseline characteristics	Key results
Helsinki Heart Study[8] (5 year follow-up)	Gemfibrozil vs placebo	4,081 men Age 40 to 55 years Mean baseline TC 7.40mM, HDL-C 1.20 mM	34.0% reduction in new CHD (p<0.02). Subjects with HDL-C <1.1mM had greater benefit
AFCAPS/TexCAPS[9] (5.2 year follow-up)	Lovastatin vs placebo	5,608 men, 997 women, Mean baseline TC 5.71 mM, LDL-C 3.89 mM, HDL 0.94, Triglyceride (Tg) 1.78mM	37% reduction n first major coronary event (p<0.001) Subjects with HDL <1.0mM had greater benefit

Table II. Secondary prevention angiographical studies involving patients with low HDL-C.

Study	Medication used	Study population with baseline characteristics	Key results
Harvard Artherosclerosis Reversibility Project (HARP)[10] (2.5 year follow-up)	Pravastatin Nicotinic acid Cholestyramine Gemfibrozil (added stepwise to achieve TC <4.1mM, LDL/HDL <2.0	79 patients Mean age 58 years Mean TC 5.50mM, HDL-C 1.07 mM	No measurable benefit on coronary arteries noted
Familial Atherosclerosis Treatment Study (FATS)[11] (2.5 year follow-up)	Niacin/colestipol or ovastatin/colestipol vs conventional therapy	146 men <62 yrs with elevated apo B (≥125 mg/dL) Angiogram at baseline and 2.5 years Mean LDL-C 4.8mM HDL-C 0.8 mM	Slowing of progression, promotion of regression in groups on intensive treatment compared to conventional therapy (p<0.005) Lowering of clinical cardiovascular events by 73% (p=0.01)
Lopid Coronary Angiography Trial (LOCAT)[12] (2.5 year follow-up)	Gemfibrozil vs placebo	395 men who had undergone coronary bypass surgery Mean age 59 years Mean TC 5.48mM LDL 3.84mM Tg 1.69mM HDL 0.88mM	Less progression in the gemfibrozil group compared with placebo (p=0.09)
HDL Atherosclerosis Treatment Study (HATS)[13] (3-year follow-up)	- Simvastatin + Niacin - Simvastatin + Niacin plus antioxidants - Antioxidants alone - Placebo alone.	160 patients Average age 53 years Mean TC 5.1mM LDL-C 3.2 mM HDL 0.8mM Tg 2.3mM	Slowing of progression of stenosis and regression in the group with simvastatin +niacin.

Reduction of 90% in the composite primary endpoint of coronary death or cardiovascular events (p=0.03)

levels are likely to have greater benefit in terms of coronary heart disease (CHD) prevention.

Secondary prevention regression studies

At least four recent studies looking at regression of coronary narrowing[10-13] included patients of interest in this paper. The results of these are summarised in Table II. The negative result seen in the Harvard Artherosclerosis Reversibility Project (HARP) could be because follow-up was too short to detect changes in normocholesterolemic patients. Authors of this study reiterate that luminal diameter may not correlate with plaque stability, fissuring and endothelial function, all of which can abruptly trigger coronary events.

The Familial Atherosclerosis Treatment Study (FATS) showed an improvement in coronary stenosis after intensive treatment of dyslipidaemia, even in the normal LDL-C subgroup. However, compared to the group in the HARP study, this subgroup of FATS patients had high initial triglycerides (3.4 mmol/L vs. 1.9 mmol/L) and lower HDL-C (0.8 mmol/L vs. 1.0 mmol/L), suggesting that the greater rise in HDL-C may have contributed to stenosis retardation. The Lopid Coronary Angiography Trial (LOCAT) demonstrated that only

Table III. Secondary prevention clinical outcome studies involving patients with low HDL-C.

Study	Medication used	Study population with baseline characteristics	Key results
Veterans Administration HDL Intervention Trial (VA-HIT)[15] (5.1 year follow-up)	Gemfibrozil vs Placebo	2,531 men Mean age 64 years Mean LDL-C 2.87mM HDL-C 0.82mM Tg 1.80mM	A 6% increase in HDL-C and a decrease in Tg of 24.5% resulted in a 22% reduction in the primary endpoint of nonfatal myocardial infarcts (MI) and coronary deaths (p=0.006).
Bezafibrate Infarction Prevention (BIP) Study[17] (6.2 year follow-up)	Bezafibrate vs placebo	3,090 patients Mean age 60 years Mean TC 5.4mM LDL-C 3.8mM HDL-C 0.89mM Tg 1.62mM	In overall population, no significant reduction in fatal or non-fatal MI or sudden death (primary endpoint).

Only subgroup with baseline Tg > 2.2mM had significant reduction in primary endpoint.

HDL-C was a strong protective factor against progression, especially that of focal CHD, findings similar to that seen in the Bezafibrate Coronary Atherosclerosis Intervention Trial (BECAIT)[14].

The HDL Atherosclerosis Treatment Study (HATS) provides convincing evidence that in addition to lowering LDL-C with hydroxy methyl glutaryl coenzyme A reductase inhibitors (statins), adding an agent like niacin to raise HDL-C provides profound additional benefits. HATS looked at men and women with CHD, angiographical evidence of stenosis, desirable LDL-C levels, and HDL-C levels of below 0.9 mmol/L[13]. Patients were randomised to four regimens, namely: simvastatin plus niacin, simvastatin-niacin plus antioxidants, antioxidants alone, or placebo alone. The group receiving simvastatin plus niacin, without antioxidants, fared best with an LDL-C reduction of 42% and elevation of HDL-C by 26%. This translated to regression of plaque, and compared to the placebo group, a 90% reduction in the composite primary endpoint of coronary death or cardiovascular events.

Secondary prevention: clinical outcome studies

Table III highlights two secondary prevention clinical outcome studies that tested the benefits of raising low HDL-C levels in patients with pre-existent ASCVD. In the Veterans Administration HDL Intervention Trial (VA-HIT)[15], the robust benefits were achieved without any change in LDL-C, suggesting that the benefits were essentially a result of changes in the HDL-C. By multivariate analysis, the investigators proved that only the assignment of gemfibrozil and the baseline HDL-C level independently predicted the clinical outcome of this study[16].

The negative results of the Bezafibrate Infarction Prevention (BIP) Study[17] were seen despite a mean 18% increase in HDL-C, a 21% decrease in triglycerides, and a 6.5% decrease in LDL-C. A post hoc analysis did however show a 39.5% reduction (p=0.02) in the cumulative probability of the primary end point in the subgroup with triglycerides ≥2.2 mmol/L. The magnitude of event reduction by bezafibrate in these patients with triglycerides ≥2.2 mmol/L was similar, regardless of whether their HDL-C was <0.9 mmol/L or ≥0.9 mmol/L.

The unexpectedly low reduction in primary end-point overall in this study could have at least four possible reasons:

- The study population had a mean baseline LDL-C of 3.8 mmol/L (compared to 2.8 mmol/L in VA-HIT) and a 6.5% reduction in LDL-C in the bezafibrate treated group, would mean that a large proportion of patients did not achieve LDL-C ≤3.3 mmol/L, let alone 2.6 mmol/L, the target set by NCEP for secondary prevention.
- The mean baseline HDL-C was higher than in the VA-HIT study (0.9 mmol/L versus 0.8 mmol/L) and this may explain why the patients in the VA-HIT study showed greater benefits of raising HDL-C.
- 373 patients, two-thirds of whom were from the placebo treated group, received open-labeled lipid modifying therapy for better LDL-C control, thus possibly lowering their event rate.
- Patients with DM were under-represented in this study. Patients with DM have a characteristic dyslipidaemia of raised triglycerides and small dense LDL levels, together with a low HDL-C, a triad that responds well to fibric acid derivatives, and perhaps including these patients may have shown greater benefit with bezafibrate.

The Heart Protection Study (HPS) included patients requiring both primary and secondary prevention for CHD and will be briefly discussed in this section. This study investigated the risk reduction

potential of simvastatin in a population of 20,000 subjects with high-risk (75% CHD, 25% DM or multiple risk factors) and normal lipid levels (51% of subjects had an LDL below 3.4 mmol/L[18]. Patients with low HDL at start experienced the most impressive benefit in this trial. The effect of treatment in subjects with a starting HDL lower than 0.9 mmol/L was a 7.3% absolute risk reduction in first major vascular event for a number needed to treat (NNT) of 14, compared with a 3.9% absolute risk reduction and an NNT of 26 in the subjects with baseline HDL-C ≥1.1mM.

In summary, the available data indicates that both in terms of clinical events and angiographical progression/regression, patients who benefit most from aggressive pharmacological interventions are those with significantly elevated LDL-C levels and those with significantly depressed HDL-C levels. While benefiting from combination therapy to raise HDL-C and lower LDL-C in a patient with desirable LDL-C but low HDL-C is proven[13], whether raising the subnormal HDL would confer greater clinical benefit than further lowering an already normal or desirable LDL-C, remains to be determined.

BIOCHEMICAL AND PHYSIOLOGICAL CONSIDERATIONS OF HDL

HDL is the smallest of the five lipoprotein classes. HDL is rich in protein, containing approximately 50% of lipid and 50% of protein by weight. It contains a hydrophobic lipid core of cholesteryl esters and triglycerides (Tg) surrounded by phospholipids, unesterified cholesterol and apolipoproteins. Apoproteins (Apo)A-I and ApoA-II are the main structural proteins in HDL, accounting for approximately 70% and 20%, respectively, of total HDL protein mass. ApoA-I can exist on its own, and is present in all HDL subclasses, but ApoA-II is present only with ApoA-I. The two main HDL fractions, according to the ultracentrifugation density, are HDL2 and HDL3. HDL2 particles are less dense, having a higher relative amount of cholesterol and phospholipids than HDL3 particles.

HDL can also be classified on the basis of their apolipoprotein composition into A-I containing lipoproteins without A-II, lipoprotein A-I (LpA-I), and A-I containing lipoproteins with A-II (Lp AI+AII). LpA-I particles are denser and have higher cholesterol content than Lp AI+AII particles. Overall, subclasses based on apolipoprotein content do not exactly correspond to those separated by ultracentrifugation, and they widely overlap. LpA-I predominates in HDL2 density range, while LpAI+AII predominates in HDL3 density range. Recent studies have shown that HDL particles containing only ApoA-I (Lp A-I) are more potent in effluxing cholesterol from certain tissues (e.g. adipocytes) than particles than contain both ApoA-I and A-II (Lp AI+AII)[19]. Lp A-I is also a better donor of cholesterol to the liver indicating that this HDL subfraction is more efficient in reverse cholesterol transport than Lp AI+AII .

Plasma HDL concentrations is determined by synthesis (from liver and intestines) of ApoA-I and other apoproteins (A-II, C and E) and by the catabolism of its components. ApoA-I is a lipophilic apoprotein that can efflux tissue (e.g. arterial) cholesterol, which is then esterified and eliminated by the liver by a process known as reverse cholesterol transport. Thus, agents that stimulate the production rate of ApoA-I in theory may be more efficient, than agents that increase HDL-C by reduction in the fractional catabolic rate of ApoA-I, in mediating reverse cholesterol transport because of increased transport of tissue cholesterol in reverse transport to the liver for final elimination. For example, patients with Tangier disease have very low HDL-C levels (often less than 0.3 mmol/L), yet they do not suffer ASCVD as severe as would be expected from such low levels. The reason for this is that the ApoA-I production rate is normal and the underlying defect, a mutation in the adenosine triphosphate binding cassette transporter 1 (ABC1)[20], is associated with defective transfer of cholesterol onto ApoA-I, causing a marked acceleration of its fractional catabolism rate. Consequently, two patients may have similar levels of HDL-C and ApoA-I but may have very different mechanisms as well as compositional changes responsible for that level, and hence have different predispositions for ASCVD.

In addition to its role in reverse cholesterol transport, HDL-C has several other potentially significant proposed roles, including increasing fibrinolysis[21], antioxidant to LDL[22], anti-inflammatory, nitric oxide promoting, and also in decreasing platelet aggregability via prostacyclin[23], all contributing to decreasing the risk of atherothrombotic disease.

THERAPEUTIC CONSIDERATIONS IN A PATIENT WITH ISOLATED LOW HDL CHOLESTEROL

Before concluding that the patient has idiopathic isolated low HDL-C, the clinician should rule out and manage all secondary causes from history and appropriate tests. Lipid disorders associated with hypertriglyceridaemia and the metabolic syndrome, diabetes mellitus, obesity, use of drugs

like beta-adrenergic blockers, thiazide diuretics, androgens, progestins, isotretinon, and disorders like chronic renal failure and advanced liver failure, need to be considered. Lifestyle characteristics like cigarette smoking, sedentary lifestyle and diets low in fat are also associated with low HDL-C. Rare genetic disorders like fish eye disease, Tangier disease, lecithin cholesterol acyl transferase (LCAT) deficiency and ApoA-I deficiency are other possible causes of this abnormality.

Lifestyle measures

The typical patient under consideration is one who has HDL-C of <1.0 mmol/L, LDL-C <3.4 mmol/L and fasting triglycerides <2.2 mmol/L. First line management should be to prescribe lifestyle measures which include caloric restriction to achieve ideal body weight, regular physical aerobic exercise, cessation of cigarette smoking and adherence to a healthy diet, e.g. National Cholesterol Education Program (NCEP) step-two diet. For every unit of sustained decrease in body mass index (BMI), HDL-C increases by about 0.02 mmol/L[24]. Low fat diets lower both LDL-C and HDL-C, with the effect on LDL-C being greater than on HDL-C in many but not all individuals. Such diets are well known to be associated with low ASCVD incidence[25]. More recently, in obese women with BMI >30-35 kg/m^2, a calorie restricted diet, with very low daily carbohydrate intake over a six-month period, was associated with a 13% raising of HDL-C[26]. It is however unclear which type of HDL-C (i.e. Lp A-I or Lp AI+AII) is raised by such diets.

Moderate amount of exercise significantly raises HDL-C. Joggers who run 16 km per week experience a 10% rise in HDL-C after 10 months[27], a result more impressive than some pharmacological agents. Kraus et al studied the effect of the amount and intensity of exercise in overweight men and women[28]. It was shown that over a six-month period, low amount (equivalent of jogging 19.2km/week) and moderate intensity exercise at 40-55% peak oxygen consumption is associated with a 1% increase in HDL-C, and low amount and high intensity at 65-80% peak oxygen consumption was associated with a 0.6% increase in HDL-C and high amount (equivalent of jogging 32 km/week) with high intensity causes a HDL-C rise of nearly 10%. This data and others reinforce the importance of both intensity and amount of exercise in raising HDL-C. Another very important lifestyle measure that is modifiable is cigarette smoking. This has been shown in trials to cause a 0.13 mmol/L to 0.23 mmol/L drop in HDL-C[29], hence the importance of encouraging cessation.

Drug therapy

Pharmacological therapy should be considered for a patient with isolated HDL-C based on coronary risk profile. Considering current evidence, an argument can be made to initiate pharmacotherapy to raise HDL-C to above 1.0 mmol/L, when hygienic measures have failed, in the following four groups of patients:

- Patients with underlying ASCVD (based on convincing evidence from studies like the VA-HIT)[15].
- Patients without clinical ASCVD but with DM. The East-West study showed that patients with DM but without pre-existent clinical ASCVD to have a risk of developing myocardial infarction equivalent to patients without DM but already having pre-existent clinical ASCVD[30]. It is from such data that DM is considered a coronary risk equivalent in many guidelines[4,5]. The American Diabetes Association (ADA) in a consensus statement recommends optimal LDL-C <2.6 mmol/L and HDL-C >1.0 mmol/L for men and >1.1 mmol/L for women, and a desirable Tg level <1.7 mmol/L; these are difficult to achieve on nonpharmacological measures alone, and are often not possible even with monotherapy.
- Patients with the metabolic syndrome. Here, patients characterised by presence of obesity, glucose intolerance/insulin resistance, dyslipidaemia, and raised blood pressure, are at an intermediate risk of developing ASCVD, and about 20% have a high risk of ASCVD (>20% in 10 years). These patients need to be considered for pharmacological therapy as part of the global approach to risk reduction.
- Patients with two or more vascular risk factors (e.g. positive family history of premature coronary disease, hypertension, smoking) have a moderately high risk of developing a clinical event, and they too should be considered for pharmacotherapy.

The Framingham Study[31] and the Physicians Health Study[32] have shown that TC to HDL-C ratio is a better predictor of ASCVD than TC, LDL-C, HDL-C or Tg alone. In patients with desirable TC levels, the main culprit for an increased ratio will be the low HDL-C level. Thus, merits of raising a low level of HDL-C cannot be overemphasised.

Table IV. Summary of drugs raising HDL cholesterol levels.

Agent	HDL ⇑ (%)	Mechanism	LDL ⇓ (%)	Tg ⇓ (%)	Outcome 1⁰ prevention (events)	Outcome 2⁰ prevention (angiogram)	Outcome 2⁰ prevention (events)
Fibrates[4,8,15,34]	10-20	PPAR-α agonist. Increased rate of synthesis of ApoA-I, ApoA-II	5-20	20-50	Reduced coronary events and mortality	Reduction of progression of atherosclerosis	Reduction in coronary events and mortality
Niacin[4,11-13]	15-35	Reduction in fractional catabolic rate of ApoA-I, ApoA-II	5-25	20-50	No trials	Regression, reduction in rate of progression	Reduction in coronary events and mortality from all-cause
Statins[4,9,18,43]	5-15	Inhibition of CETP activity	18-55	7-30	Reduced coronary events and mortality	Reduction in rate of progression of atherosclerosis	Reduction in coronary events and mortality from all-cause
CETP inhibitors[47]	46-106	Inhibition of CETP activity	8-17	0-26	No trials	No trials	No trials
Oestrogen[51,52]	5-13	Increased rate of synthesis of ApoA-I, ApoA-II	12-14	6-10⇑	No trials	No trials	No benefit seen in completed trials

PPAR: Peroxisome proliferator activated receptor.

CETP: Cholesteryl ester transfer protein.

AGENTS RAISING HDL-C LEVELS

There are a number of agents that can potentially raise HDL-C levels. These are summarised in Table IV and described below in more detail.

Fibric acid derivatives

This group of drugs produces reductions in TC, LDL cholesterol, apolipoprotein B, total Tg and Tg-rich lipoprotein (VLDL) in treated patients. In addition, increases in HDL and apoproteins ApoA-I and ApoA-II are also observed. Studies have shown that this group of drugs activate the peroxisome proliferator activated receptor (PPAR) -α, and this results in increased transcription of human ApoA-I, apart from being involved in the modulation of other lipoprotein modulatory events[33].

Fibric acid derivatives increase lipolysis, and eliminate Tg-rich particles from plasma by activating lipoprotein lipase and reducing production of Apo C-III (an inhibitor of lipoprotein lipase activity). The resulting fall in Tg produces an alteration in the size and composition of LDL from small, dense particles (which are thought to be atherogenic due to their susceptibility to oxidation), to large buoyant particles. These larger particles have a greater affinity for cholesterol receptors and are catabolised rapidly. Activation of PPARα also induces an increase in the synthesis of ApoA-I, A-II and HDL-C. Turnover studies on ApoA-I and A-II indicate that fibric acid derivatives like gemfibrozil increase their production rate without affecting the fractional catabolic rate in patients with low HDL-C and elevated Tg.

The benefits of gemfibrozil in primary prevention and secondary prevention studies, both angiographical and clinical outcome studies[8,12,14,15] have been highlighted earlier. Patients with Type 2 DM are an important group of patients with the lipid profile that we are discussing in this paper. Benefits of fibrates in this group of patients have been shown in studies like the Diabetes Atherosclerosis Intervention Study (DAIS), which proved by quantitative angiography that treatment with micronised fenofibrate corrected their lipid abnormalities and reduced the progression of coronary disease[34].

In clinical practice, several of our patients require combination therapy to reach the lipid goals. Whether combination therapy with statin and fibrate would produce synergistic effects and greater risk reductions compared with monotherapy with either drug in high-risk patients is unknown. Such a question is being investigated in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, which is designed to compare the effect of simvastatin monotherapy with the combination with fenofibrate in patients with DM. The first results from this study are expected in 2008.

Nicotinic acid (Niacin)

Niacin is a vitamin that also has a broad-spectrum lipid regulating activity. It increases HDL-C by

15-35%[4]. Niacin also decreases LDL-C, Tg, and Lp A. It is especially effective in patients with isolated low HDL-C, and clinical studies have demonstrated that niacin alone or in combination can slow or reverse the progression of atherosclerosis, and reduce cardiovascular event rates and total mortality in hypercholesterolaemic men with established ASCVD[11,13].

HDL turnover studies indicate that niacin increases plasma ApoA-I and ApoA-II by decreasing the fractional catabolic rate of ApoA-I and A-II and not by increasing their production rate. Comparing the effect of niacin and gemfibrozil on LpA-I and LpAI+AII particles in patients with low HDL-C, after 19 weeks it was seen that niacin, but not gemfibrozil, selectively increased LpA-I levels[35]. With data showing LpA-I to be more efficient than LpAI+AII in reverse cholesterol transport, this may indicate that niacin may be more potent in mediating reverse cholesterol transport than gemfibrozil.

Apart from its potent effect on HDL raising, niacin also decreases the production of ApoB containing lipoproteins, LDL, VLDL and LpA. Considerable evidence indicates that a large amount of synthesised Apo B is not secreted, but undergoes post-translational degradation in hepatocytes. Niacin by inhibiting Tg synthesis results in increased ApoB degradation, hence decreasing the secretion of ApoB containing VLDL particles[36,37]. As VLDL is converted to intermediate density lipoprotein (IDL) and then to LDL, the decrease in VLDL can also explain a decrease in LDL-C levels.

Although to date there are no clinical trials in the population of interest, niacin appears to be the ideal drug in the management of the group of patients discussed here, in view of its safety, efficacy and cost effectiveness. In the past however, vasodilatory mediated side effects like flushing, together with the need for frequent ingestion of three-times-daily dose of immediate release preparations limited the tolerability of niacin, leading to a problem with compliance. Active peptic ulcer disease, acute gout, and liver disease are contraindications to the use of niacin. Slow incremental titration, together with the use of aspirin, may reduce the flushing symptom to a more tolerable degree. Although the use of niacin was previously cautioned in patients with DM, it has recently been shown to be safe and effective in patients with type 2 DM with an HbA1c <9.0%[38].

An extended release niacin (niacin-ER) formulation, Niaspan (Kos Pharmaceuticals, Inc, Miami, Florida) is the only time-release niacin preparation approved by the Food and Drug Administration of the United States of America, to be taken once nightly. This is convenient, well-tolerated and particularly effective at raising HDL-C level. Guyton et al directly compared niacin-ER and gemfibrozil for the treatment of patients with low HDL-C[39]. In this randomised, double-blind trial which included 173 patients with baseline LDL-C ≤4.1 mmol/L and HDL-C ≤1.0 mmol/L, niacin-ER at a daily dose of 2,000mg provided a two-fold greater HDL-C increase (26% vs. 13%). Gemfibrozil achieved a greater reduction of Tg levels (40% vs. 29%), and compared to no favourable change in patients treated with gemfibrozil, patients on niacin-ER had a 20% decrease in Lp A levels, and up to 6% decrease in fibrinogen levels. These effects further support the broad-spectrum effects of niacin in the reduction of the risk of atherothrombotic disease.

As the mechanism of action of niacin on Tg, LDL-C and HDL-C is different from fibric acid derivatives, statins and resins, its combination will provide synergistic effects. Combinations of niacin with resins[11], fibric acid derivatives[40] and statins[13] have been shown to be effective and safe. In a long-term safety and efficacy study, 814 patients received a single tablet formulation of niacin-ER and lovastatin at bedtime after a low-fat snack[41]. The dose was initially 500 mg of niacin-ER component and 10mg of the lovastatin component, and was then titrated upward to 2,000mg/40mg or to the highest tolerated dose. The treatment phase of the study was 52 weeks, with a 48-week extension. Interim data at 52 weeks showed that therapy with this formulation resulted in an average percent change from baseline in LDL-C of -47%, HDL-C increased by a mean of 41% from baseline and Tg decreased by an average of 42% from baseline at 52 weeks. The safety profiles were comparable to that of other studies that included statins in the therapy. With the merits of combination therapy with statins and niacin proven before in clinical studies[13], such safe and convenient formulations will be of great importance for prevention of ASCVD.

HMG CoA reductase inhibitors

The major action of this group of drugs (statins) is to lower LDL-C levels by upregulating LDL receptors, thus facilitating LDL removal. A variable increase in HDL-C (approximately 3-10%) results but the mechanism underlying this is unclear, although there are reports to indicate that statins increase HDL-C by decreasing the activity of cholesterol ester transfer protein (CETP)[42]. Several clinical trials have proven the benefits of statins in both primary and secondary prevention, convincingly

reducing the risk of cardiovascular mortality and all-cause mortality, especially in patients with hypercholesterolaemia. It is clear that statins favourably modify lipoprotein profile, including the TC/HDL-C ratio, and are thus effective in reducing ASCVD risk, especially in patients with raised LDL-C levels. Based on their different mechanisms of action, statins can be used effectively in safe combinations with niacin, or cautiously with fibrates as mentioned earlier, especially when the LDL-C levels have not reached target.

The Pravastatin or Atorvastatin Evaluation and Infection-Thrombolysis in Myocardial Infarction 22 (PROVE IT) study looked at whether intensive LDL-C lowering (atorvastatin 80 mg daily) will reduce major coronary events, including mortality, more than "standard dose" LDL-C lowering with statin therapy (pravastatin 40 mg daily) in high-risk patients[43]. In this study, patients had a baseline median LDL-C and HDL-C levels of 2.7 mmol/L and 1.0 mmol/L, respectively. Results showed a 16% reduction in major coronary events in favour of the intensively treated group who achieved an on-treatment median LDL-C levels of 1.6 mmol/L. Data from this trial and others[18] have prompted the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP) in its recent report[44], to recommend that for patients with a very high risk of cardiovascular disease and events, targeting LDL-C levels of <1.8 mmol/L (<70mg/dl) instead of the previous target of <2.6 mmol/L (<100mg/dl) is a reasonable therapeutic option.

Looking again at the PROVE IT study, with regard to the patients discussed in this paper, it was interestingly noted that the benefits of aggressive statin therapy was more marked in the group with baseline HDL-C levels >1.0 mmol/L, compared to the group with low HDL-C levels. This leads one to speculate if combination therapy of a "standard dose" of a statin, with another agent with greater HDL-C raising effect, would have yielded better results in this subgroup.

Inhibitors of cholesteryl ester transfer protein

The inhibition of CETP is a novel method of raising HDL-C currently undergoing trials. CETP is a plasma glycoprotein that facilitates the transfer of cholesteryl esters from HDL-C to Apo-B containing lipoproteins. Humans with CETP deficiency due to molecular defects in the CETP gene have markedly-elevated plasma levels of HDL-C and ApoA-I[45], and this observation led to the idea that CETP inhibition might increase HDL-C levels. In animal models, inhibition of CETP resulted in increased HDL-C levels[46].

Brousseau et al examined the effects of a novel CETP inhibitor, torcetrapib, on plasma Lp in patients with a low level of HDL-C (<1.0 mmol/L) when given either alone or in combination with atorvastatin[47]. Treatment with 120mg of torcetrapib daily significantly increased plasma concentrations of HDL-C by 61%, and 46% in the atorvastatin and non-atorvastatin cohorts, respectively, and treatment with 120mg twice daily increased HDL-C by 106%. Torcetrapib not only increased the levels of HDL-C and ApoA-I, it also reduced the levels of LDL-C and ApoB, both when given alone and when given in combination with atorvastatin. In this 16-week trial, there was no serious adverse event, and neither was there any clinically significant change in biochemical or haematological values. These profound effects on plasma Lp in patients with low HDL-C levels by torcetrapib offer much promise. Ultimately, the question of whether CETP inhibition is effective in reducing ASCVD in humans will have to be resolved only by trials based on clinical end points.

HDL mimetic agents

This novel group of agents is those that mimic the effects of HDL, and this subject has gained great interest lately. Historically, it began in a little town in Italy, where it was observed that carriers of a variant form of ApoA-I, ApoA-I Milano, had very low levels of HDL-C (0.25-0.78 mmol/L), apparent longevity, and much less atherosclerosis and premature CHD than would be expected from such low HDL-C levels[48]. Subsequently, animal studies have shown that intravenous infusions of HDL or ApoA-I, or genetic overexpression of ApoA-I, significantly reduced progression and in some cases induced regression of pre-existent atherosclerosis[49].

The next logical approach will be to use intravenous ApoA-I infusion in humans, and as ApoA-I Milano was suggested to be more protective for CHD than wild type ApoA-I, Nissen et al used it in a recent trial[50]. These investigators studied the effect of intravenous recombinant ApoA-I Milano/phospholipid complexes (ETC-216) on atheroma burden in patients with acute coronary syndromes (ACS). This was a double-blind, randomised, placebo-controlled multicentre trial comparing the effect of ETC-216 or placebo on coronary atheroma burden measured by intravascular ultrasound (IVUS). Patients were given weekly infusions of ETC-216 or placebo, for five weeks. IVUS was performed within two weeks following ACS and repeated within two weeks of treatment. Significant regression of coronary atherosclerosis as measured by IVUS was documented in the group receiving ETC-216 when compared to placebo. The results of this study are indeed promising. Whether similar findings would be seen in infusion of

wild type ApoA-I is unknown. Though encouraging, the results require confirmation in larger clinical trials with morbidity and mortality end points.

Oestrogen

Oestrogen increases HDL-C and LpA-I levels largely by increasing production rates of ApoA-I containing particles without altering the fractional catabolic rate. Although they also lower LDL-C favourably, oestrogens increase production of VLDL and therefore increase Tg in some women. Based on the above, one would infer that a major mechanism of its presumed cardioprotective effect might be via increased reversed cholesterol transport. Although observational studies suggested benefits, the results of clinical trials have been less encouraging in patients with pre-existing ASCVD. Results of the Heart and Estrogen/progestin Replacement Study (HERS)[51], showed hormone replacement therapy (HRT) to give no overall reduction in coronary events.

The Women's Health Initiative (WHI) was one of the largest studies to study the effects of HRT on cardiovascular disease[52]. In this study, the combination of conjugated equine oestrogen and medroxyprogesterone was stopped when it was demonstrated that there was an excess number of new coronary events in the treated group. In addition, there was a small but increased risk of breast cancer. The oestrogen-only arm apparently did not show these effects and continues to show none. It is suggested that if oral oestrogen (with or without progestin) actually promotes atherosclerosis, this might be through its effect on promoting clotting and/or its effect in raising hs-CRP levels. Whatever the effect of exogenous hormones, HRT should not be used as a substitute or an adjunct to lipid lowering therapy.

Ethanol

Epidemiological and pathological studies indicate that light or moderate intake of ethanol (approximately equivalent of 1-3 oz. of 80-proof spirits, i.e. 12-36 g ethanol, 4-12 oz wine) is associated with evidence of protection of ASCVD[53]. A higher intake of ethanol is complicated with systolic hypertension and its sequelae, and alcoholic liver disease. The mechanism by which cardioprotection is achieved is not entirely clear, but it has been shown that intake results in the elevation of HDL-C and ApoA-I, LpA-I and LpAI+AII particle concentrations. Ethanol stimulates the production of ApoA-I and may act by enhancing reverse cholesterol transport.

Besides its beneficial effects on HDL-C levels, the cardioprotective effects of ethanol are also due to the lowering of LDL-C levels[54], and haemostatic changes which include a decrease in fibrinogen, inhibition of platelet aggregation, and plasminogen activator secretion[55]. Despite its potential benefits, alcohol is not recommended for raising HDL-C in clinical practice. The patient who takes alcohol must be strongly advised about moderation and be educated about the complications arising from abuse, in addition to the fact that ethanol intake makes it difficult for the obese patient to follow weight loss diets.

CONCLUSION

Recent trial evidence indicates that raising HDL-C has survival benefits in patients at a high risk of atherosclerotic disease and compels us to pay close attention to low HDL-C as an important risk factor, and to consider pharmacotherapy to raise low HDL-C in the appropriate patient. The advent of newer, well-tolerated preparations, together with the discovery of novel agents to raise HDL-C or mimic its actions, hold much promise for the management of patients with low HDL-C levels and for the reduction in the risk of ASCVD.

REFERENCES

1. Gordon DJ, Probstfield JL, Garrison RJ, et al. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. Circulation 1989; 79:8-15.
2. Miller GJ, Miller NE. Plasma-high-density-lipoprotein concentration and development of ischaemic heart-disease. Lancet 1975; 1:16-9.
3. Goldbourt U, Yaari S, Medalie JH. Isolated low HDL cholesterol as a risk factor for coronary heart disease mortality. A 21-year follow-up of 8000 men. Arterioscler Thromb Vasc Biol 1997; 17:107-13.
4. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001; 285:2486-97.
5. American Diabetes Association. Management of dyslipidemia in adult men with diabetes. Diabetes Care 2000; 23 (supp 1):S57-60.
6. Rubins HB, Robins SJ, Collins D, et al. Distribution of lipids in 8,500 men with coronary artery disease. Department of Veterans Affairs HDL Intervention Trial Study Group. Am J Cardiol 1995; 75:1196-201.
7. Martin MJ, Hulley SB, Browner WS, et al. Serum cholesterol, blood pressure, and mortality: implications from a cohort of 361,662 men. Lancet 1986; 2:933-6.
8. Manninen V, Huttunen JK, Heinonen OP, et al. Relation between baseline lipid and lipoprotein values and the incidence of coronary heart disease in the Helsinki Heart Study. Am J Cardiol 1989; 63:42-7H.
9. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA 1998; 279:1615-22.
10. Pasternak RC, Brown LE, Stone PH, et al. Effect of combination therapy with lipid-reducing drugs in patients with coronary heart disease and "normal" cholesterol levels. A randomized, placebo-controlled trial. Harvard Atherosclerosis Reversibility Project (HARP) Study Group. Ann Intern Med 1996; 125:529-40.
11. Stewart BF, Brown BG, Zhao XQ, et al. Benefits of lipid-lowering therapy in men with elevated apolipoprotein B are not confined to those with very high low density lipoprotein cholesterol. J Am Coll Cardiol 1994; 23:899-906.
12. Frick MH, Syvanne M, Nieminen MS, et al. Prevention of the angiographic progression of coronary and vein-graft atherosclerosis by gemfibrozil after coronary bypass surgery in men with low levels of HDL cholesterol. Lopid Coronary Angiography Trial (LOCAT) Study Group. Circulation 1997; 96:2137-43.

13. Brown BG, Zhao XQ, Chait A, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. N Engl J Med 2001; 345:1583-92.
14. Ruotolo G, Ericsson CG, Tettamanti C, et al. Treatment effects on serum lipoprotein lipids, apolipoproteins and low density lipoprotein particle size and relationships of lipoprotein variables to progression of coronary artery disease in the Bezafibrate Coronary Atherosclerosis Intervention Trial (BECAIT). J Am Coll Cardiol 1998; 32:1648-56.
15. Rubins HB, Robins SJ, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. N Engl J Med 1999; 341:410-8.
16. Robins SJ, Collins D, Wittes JT, et al. Relation of gemfibrozil treatment and lipid levels with major coronary events: VA-HIT: a randomized controlled trial. JAMA 2001; 285:1585-91.
17. Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease: the Bezafibrate Infarction Prevention (BIP) study. Circulation 2000; 102:21-7.
18. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002; 360:7-22.
19. Barkia A, Puchois P, Ghalim N, et al. Differential role of apolipoprotein A1-containing particles in cholesterol efflux from adipose cells. Atherosclerosis 1991; 87:135-46.
20. Rust S, Rosier M, Funke H, et al. Tangier disease is caused by mutations in the gene encoding ATP-binding cassette transporter 1. Nat Genet 1999; 22:352-5.
21. Saku K, Ahmad M, Glas-Greenwalt P, et al. Activation of fibrinolysis by apolipoproteins of high density lipoproteins in man. Thromb Res 1985; 39:1-8.
22. Henriksen T, Mahoney EM, Steinberg D. Interaction of plasma lipoproteins with endothelial cells. Ann N Y Acad Sci 1982; 401:102-16.
23. Yui Y, Aoyama T, Morishita H, et al. Serum prostacyclin stabilizing factor is identical to apolipoprotein A-I (ApoA-I). A novel function of Apo A-I. J Clin Invest 1988; 82:803-7.
24. Berns MA, de Vries JH, Katan MB. Increase in body fatness as a major determinant of changes in serum total cholesterol and high density lipoprotein cholesterol in young men over a 10-year period. Am J Epidemiol 1989; 130:1109-22.
25. Ornish D, Brown SE, Scherwitz LW, et al. Can lifestyle changes reverse coronary heart disease? The Lifestyle Heart Trial. Lancet 1990; 336:129-33.
26. Brehm BJ, Seeley RJ, Daniels SR, et al. A randomized trial comparing a very low carbohydrate diet and a calorie-restricted low fat diet on body weight and cardiovascular risk factors in healthy women. J Clin Endocrinol Metab 2003; 88: 1617-23.
27. Sagiv M, Goldbourt U. Influence of physical work on high density lipoprotein cholesterol: implications for the risk of coronary heart disease. Int J Sports Med 1994; 15:261-6.
28. Kraus WE, Houmard JA, Duscha BD, et al. Effects of the amount and intensity of exercise on plasma lipoproteins. N Engl J Med 2002; 347:1483-92.
29. Criqui MH, Wallace RB, Heiss G, et al. Cigarette smoking and plasma high-density lipoprotein cholesterol. The Lipid Research Clinics Program Prevalence Study. Circulation 1980; 62(4 Pt 2):IV 70-6.
30. Haffner SM, Lehto S, Ronnemaa T, et al. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998; 339:229-34.
31. Castelli WP, Abbott RD, McNamara PM. Summary estimates of cholesterol used to predict coronary heart disease. Circulation 1983; 67:730-4.
32. Stampfer MJ, Sacks FM, Salvini S, et al. A prospective study of cholesterol, apolipoproteins, and the risk of myocardial infarction. N Engl J Med 1991; 325:373-81.
33. Jin FY, Kamanna VS, Chuang MY, et al. Gemfibrozil stimulates apolipoprotein A-I synthesis and secretion by stabilization of mRNA transcripts in human hepatoblastoma cell line (Hep G2). Arterioscler Thromb Vasc Biol 1996; 16:1052-62.
34. Steiner G. Treating lipid abnormalities in patients with type 2 diabetes mellitus. Am J Cardiol 2001; 88:37N-40N.
35. Sakai T, Kamanna VS, Kashyap ML. Niacin, but not gemfibrozil, selectively increases LP-AI, a cardioprotective subfraction of HDL, in patients with low HDL cholesterol. Arterioscler Thromb Vasc Biol 2001; 21:1783-9.
36. Jin FY, Kamanna VS, Kashyap ML. Niacin accelerates intracelluar ApoB degradation by inhibiting triacylglycerol synthesis in human hepatoblastoma (HepG2) cells. Arterioscler Thromb Vasc Biol 1999, 19:1051-9.
37. Ganji SH, Tavintharan S, Zhu D, et al. Niacin noncompetitively inhibits DGAT2 but not DGAT1 activity in HepG2 cells. J Lipid Res. 2004; 45:1835-45.
38. Grundy SM, Vega GL, McGovern ME, et al. Efficacy, safety, and tolerability of once-daily niacin for the treatment of dyslipidemia associated with type 2 diabetes: results of the assessment of diabetes control and evaluation of the efficacy of niaspan trial. Arch Intern Med 2002; 162:1568-76.
39. Guyton JR, Blazing BA, Hagar J, et al. Extended-release niacin vs gemfibrozil for the treatment of low levels of high-density lipoprotein cholesterol. Niaspan-Gemfibrozil Study Group. Arch Intern Med 2000; 160:1177-84.
40. Zema MJ. Gemfibrozil, nicotinic acid and combination therapy in patients with isolated hypoalphalipoproteinemia: a randomized, open-label, crossover study. J Am Coll Cardiol 2000; 35:640-6.
41. Kashyap ML, McGovern ME, Berra K, et al. Long-term safety and efficacy of a once-daily niacin/lovastatin formulation for patients with dyslipidemia. Am J Cardiol 2002; 89:672-8.
42. Napoli C, Leccese M, Palumbo G, et al. Effects of vitamin E and HMG-CoA reductase inhibition on cholesteryl ester transfer protein and lecithin-cholesterol acyltransferase in hypercholesterolemia. Coron Artery Dis 1998; 9:257-64.
43. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med. 2004; 350:1495-504.
44. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 2004; 110:227-39. Erratum in: Circulation 2004; 110:763.
45. Brown ML, Inazu A, Hesler CB, et al. Molecular basis of lipid transfer protein deficiency in a family with increased high-density lipoproteins. Nature 1989; 342:448-51.
46. Gaynor BJ, Sand T, Clark RW, et al. Inhibition of cholesteryl ester transfer protein activity in hamsters alters HDL lipid composition. Atherosclerosis 1994; 110:101-9.
47. Brousseau ME, Schaefer EJ, Wolfe ML, et al. Effects of an inhibitor of cholesteryl ester transfer protein on HDL cholesterol. N Engl J Med 2004; 350:1505-15.
48. Sirtori CR, Calabresi L, Franceschini G, et al. Cardiovascular status of carriers of the apolipoprotein A-I(Milano) mutant: the Limone sul Garda study. Circulation 2001; 103:1949-54.
49. Rader DJ. High-density lipoproteins and atherosclerosis. Am J Cardiol 2002; 90:62i-70i.
50. Nissen SE, Tsunoda T, Tuzcu EM, et al. Effect of recombinant ApoA-I Milano on coronary atherosclerosis in patients with acute coronary syndromes: a randomized controlled trial. JAMA 2003; 290:2292-300.
51. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/protestin Replacement Study (HERS) Research Group. JAMA 1998; 280:605-13.
52. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA 2002; 288:321-33.
53. Beaglehole R, Jackson R. Alcohol, cardiovascular diseases and all causes of death: a review of the epidemiological evidence. Drug Alcohol Rev 1992; 11:275-90.
54. Marmot M, Brunner E. Alcohol and cardiovascular disease: the status of the U shaped curve. BMJ 1991; 303:565-8.
55. Malmendier CL, Delcroix C. Effect of alcohol intake on high and low density lipoprotein metabolism in healthy volunteers. Clin Chim Acta 1985; 152:281-8.
56. Langer RD, Criqui MH, Reed DM. Lipoproteins and blood pressure as biological pathways for effect of moderate alcohol consumption on coronary heart disease. Circulation 1992; 85:910-5.