Clinical usefulness of HDL cholesterol as a target to lower risk of coronary heart disease

Summary of evidence and recommendations of an expert group*

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Abstract

Multiple lines of evidence show that high-density lipoproteins (HDL) protect against coronary heart disease (CHD), and that low blood levels of HDL cholesterol (HDLc) indicate high risk of a coronary event. Major epidemiological studies show that a low HDLc is a strong predictor of CHD, and this relationship occurs at any level of low-density lipoprotein cholesterol (LDLc) or triglycerides, demonstrating independence. When the HDLc level is raised by drug therapy, coronary atherosclerosis is decreased and CHD events are lessened. Increases in HDLc are in fact independently correlated with coronary angiographic and clinical benefit. HDL stimulates the removal of cholesterol from cells in the vascular wall. The cholesterol is taken up by HDL and shuttled in part to the liver for excretion in the bile.

Experiments in transgenic mice provide proof that increased HDL secretion protects against atherosclerosis caused by an atherogenic diet or genetic hyperlipidaemia. In humans, HDL has direct beneficial effects on coronary arterial vasodilation. This compelling scientific evidence thus justifies HDLc as a target to reduce risk of CHD. An international group of experts in epidemiology, clinical and basic science formed a consensus that an HDLc concentration of 1.0 mmol/L (40 mg/dL) is a realistic clinical guideline for patients at high risk of a coronary event. Specific diet and drug therapies were recommended.

Key words: coronary heart disease, high-density lipoproteins, epidemiology, treatment.

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Introduction

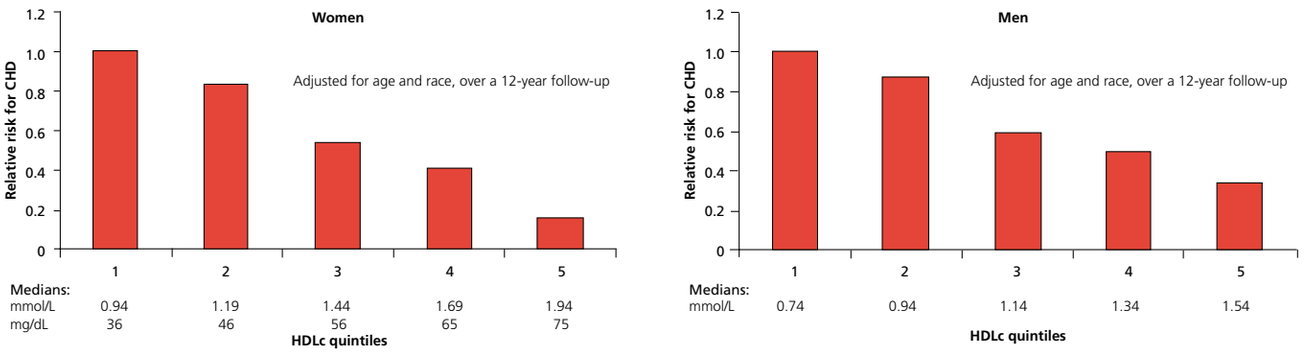
Low high-density lipoprotein cholesterol (HDLc) often occurs in the presence of other risk factors. Lack of exercise and overconsumption of high-carbohydrate foods depress HDLc. When energy expenditure does not keep up with rampant intake, so encouraged by intense competition among food companies to commandeer consumers' digestive systems, obesity is the consequence. Obesity is expanding rapidly in incidence, and Britain has one of the steepest trajectories worldwide. Diabetes and insulin resistance in adulthood can be nearly entirely attributed to such adipogenic tendencies, humans being genetically programmed to store fat as much as possible.

Obesity, insulin resistance and diabetes cause other serious metabolic problems, especially high triglyceride levels, and elevated concentrations of highly atherogenic triglyceride-rich lipoprotein remnants (chylomicrons and very low-density lipoprotein [VLDL]) indicated, (imperfectly) by high triglyceride levels. These linked metabolic disorders are called 'the metabolic syndrome'.

There is debate among experts about whether obesity or insulin resistance is the proximal insult that ignites this metabol-

*The expert group on HDL cholesterol is listed in *Am J Cardiol* 2002;**90**:139-43, from which this article is adapted and updated.

Figure 1. The relative risk of CHD in the Atherosclerosis Risk in Communities (ARIC) study in women and men



Key: CHD = coronary heart disease; HDLc = high density lipoprotein cholesterol

Adapted from Sharrett AR *et al*.[6]

ic conflagration. Obesity and insulin resistance are not perfectly correlated, and it is well known to clinicians that some fortunate obese people have normal glucose tolerance whereas some unfortunates who are just mildly overweight have insulin resistance. In either obesity or diabetes, metabolism of chylomicrons and VLDL is sluggish since the key enzyme effecting triglyceride hydrolysis, lipoprotein lipase, is low. This reduces HDL, since HDL itself is formed from components of chylomicron and VLDL metabolism as they circulate through the vasculature. This pathway, one of several that modulate HDL concentrations, links a high triglyceride with a low HDL concentration.

Although early mathematical attempts to unravel the relative importance of each element in this constellation may have been confounded by the biological interrelationships that bind them together, low HDLc turned out to confer independent risk, since its impact was not found to be secondary to these other associated conditions. In other words, depressed levels of HDLc herald increased risk for coronary heart disease (CHD) at all levels of low-density lipoprotein cholesterol (LDLc) and triglycerides, in people with diabetes and in non-diabetics, in men and women, and in the secondary as well as the primary prevention setting.

Epidemiology

The relationship between HDLc and the incidence of CHD is curvilinear (figure 1).[1-6] Men and women both experience higher CHD incidence with low HDLc (figure 1), but the strength of the relationship may be greater in women than in men as found in both the Atherosclerosis Risk In Communities (ARIC) study[6] and a meta-analysis of four prospective studies in the US.[3] Meta-analysis of the US studies determined that an increase in HDLc of 0.026 mmol/L (1 mg/dL) equates with a relative risk reduction in the incidence of coronary events by 2% in men and 3% in women.[7] A greater sensitivity in women to the anti-atherogenic effects of HDL was not found in the very large Apolipoprotein-related Mortality Risk (AMORIS) study in Sweden,[5] and this remains an unresolved point until other very large epidemiological studies in women are completed. Regression dilution bias in studies that rely on a single estimate of HDLc may even underestimate the strength of this relationship.

Prevalence of low HDLc

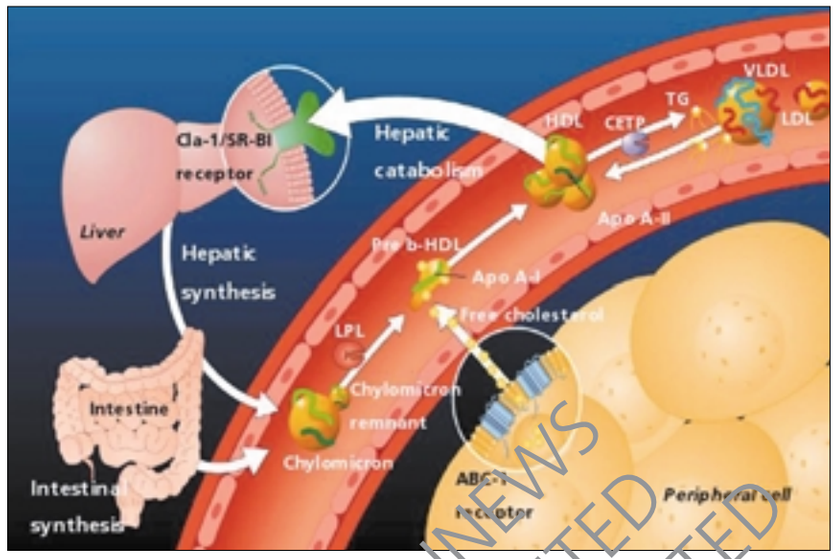
If we take HDLc < 1.0 mmol/L (< 40 mg/dL) as a threshold for increased risk, as recommended by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP-III) then 35–40% of men and about 15% of women in the general population are at increased risk.[8] There is considerable debate as to whether the same risk level of HDLc applies to women and men. Although NCEP ATP-III designated an HDLc < 1.0 mmol/L as a risk threshold for both sexes, the same group designated HDL < 1.29 mmol/L (< 50 mg/dL) in women as one of the components of the metabolic syndrome, whereas 1.0 mmol/L was retained for men for this diagnosis.[9] The panel may have heeded the stronger effect of HDLc levels in women, and the reality that a normal HDLc for a woman is at least 0.26 mmol/L (10 mg/dL) higher than for a man.

In the Prospective Cardiovascular Münster (PROCAM) study 33% of men who developed CHD had HDLc values < 0.91 mmol/L (35 mg/dL).[1] Low HDL even gains in importance over total cholesterol in predicting CHD mortality in older men and women: in those aged over 70 years, people with HDL < 0.91 mmol/L accounted for 30% of the coronary death.[10] In another survey of 8,500 men with CHD, 63% had HDLc values < 1.0 mmol/L.[11] Furthermore, about 25% of men with CHD had a very low HDLc (< 0.91 mmol/L) and a distinctly high LDLc (> 4.14 mmol/L [> 160 mg/dL]). These recent surveys show that average LDLc values (3.41 mmol/L [132 mg/dL]) in men with CHD were not substantially different from LDLc values in men without CHD, whereas HDLc levels were about 10–20% lower in those with CHD compared to those without. A similar conclusion is likely for women.[12]

HDL metabolism and its anti-atherosclerosis effect

Multiple lines of evidence suggest that HDL has a direct benefi-

Figure 2. HDL metabolism and reverse cholesterol transport



Key: ApoA-I = apolipoprotein A-I; LPL = lipoprotein lipase; TG = triglyceride; HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; VLDL = very low-density lipoprotein cholesterol; CETP = cholesterol ester transfer protein; SR = scavenger receptor

cial effect on the arterial wall. Apolipoprotein A-I (apoA-I), the major protein in HDL, activates the mobilisation of cholesterol ester stores in macrophages, leading to the reduction of the cholesterol content of this major cell type in atherosclerosis.[13] At least two specific receptors, ABC-1 and SRB-1, participate in mediating this protective effect.[13,14] Intravenous infusion of HDL in rabbits prevents atherosclerosis.[15] Introduction and expression of the human apoA-I gene in mice prevents diet-induced atherosclerosis,[16] and stimulates the regression of pre-existing atherosclerosis.[17,18] HDL appears to deliver cholesterol to the liver for excretion. Again, SRB-1 mediates both of these effects.

This HDL function is termed, reverse cholesterol transport and is shown in figure 2. HDL, in the form of recombinant human apoA-I liposomes, when infused into hypercholesterolaemic humans, produced net cholesterol excretion from the body, directly demonstrating the stimulation of reverse cholesterol transport.[19] Direct infusion of recombinant apoA-I Milano liposomes into hypercholesterolaemic apolipoprotein E-deficient mice resulted in reduction in plaque lipid and macrophages.[20]

In addition to its major role in reverse cholesterol transport, HDL has other functions that may contribute to the ability to protect against CHD. Examples include anti-inflammatory and antioxidant properties.[21,22] HDL directly suppressed vascular inflammation in a porcine model.[23] In this study, injection of HDL reduced E-selectin expression in vascular endothelium. In hypercholesterolaemic humans, intravenous infusion of HDL normalised endothelium-dependent vasodilation.[24] These experiments demonstrate that HDL employs several means of protecting against atherosclerosis. They also strongly support the findings from epidemiology and clinical trials that the apparent clinical benefit of raising HDLc is not secondary to its relationship to other coronary risk factors.

Raising HDLc by diet and lifestyle modification

It is well established that diet and lifestyle modifications can help to increase low HDLc.

- Smoking lowers HDLc levels, and smoking cessation is critical to preventing CHD.
- Aerobic exercise and strength training both increase HDLc.
- Weight loss in overweight people raises HDLc but clinicians should be aware of temporary reductions in HDLc during active weight loss.[25] Low-fat high-carbohydrate diets lower HDLc and raise triglycerides. This may be particularly important to patients with diabetes or the metabolic syndrome. Unsaturated fats or oils, rather than carbohydrates, are recommended to replace saturated fat, since by taking these measures HDLc and triglyceride levels are preserved.[26,27] A high fibre content or carbohydrate-rich foods that have a low glycaemic index attenuate the hypertriglyceridaemic but not the HDL-lowering effect of carbohydrate.[28,29]
- Alcohol in any form raises HDLc in a strict dose-dependent manner, and moderate quantities such as one to two alcoholic beverages per day are associated with reduced total and coronary mortality.[30] However, the benefits of alcohol must be weighed against the problems of potential excess.

Clinical studies

Coronary artery stenosis

Angiographic trials utilising all the major lipid-regulating drug

Figure 3. High density lipoprotein cholesterol (HDLc) is a risk factor in statin-treated patients

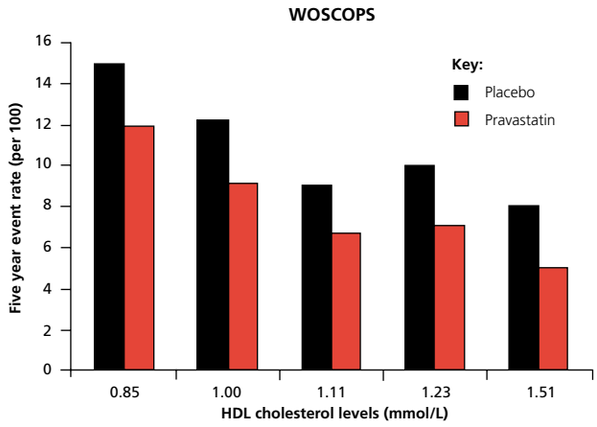


Figure taken from WOSCOPS trial[51]

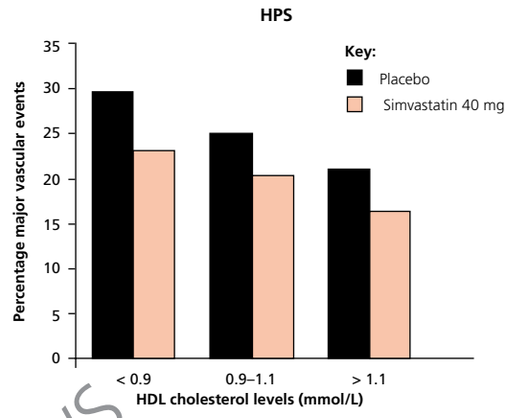


Figure taken from Heart Protection Study[49]

classes, including fibrates,[31-33] resins,[34-36] niacin[35,36] and statins[37-39] have shown raised HDLc, as well as reduced LDLc, and found a reduction in the progression rate of coronary narrowing. Moreover, in certain of these trials, increases in HDLc during therapy predicted a slowing of the progression in coronary narrowing, independent of changes in LDLc, apoB or triglycerides.[34,36]

Coronary heart disease events

Several clinical trials have demonstrated that increases in HDLc during therapy were associated with a reduced incidence of coronary events, independent of decreases in LDLc or triglycerides. This has been apparent in the Lipid Research Clinics study of cholestyramine,[40] as well as in major statin[41] and fibrate trials.[42,43]

HDLc in the large-scale statin trials

The large-scale trials of statins unequivocally demonstrate reduction in cardiovascular events,[44-49] and, in most of them, all-cause mortality.[44,45,47,49] Analysis of several statin trials found that the majority of the event reduction could be attributed to LDL reductions[41,50-52] with little, if any, attributable to HDL changes. Statin treatment reduced coronary events in patients whose HDLc concentrations were low or high.[49,51,53,54] Nonetheless, the strong relationship between baseline HDLc and subsequent event rates was present in statin-treated patients.

For example, in the West of Scotland Coronary Prevention Study (WOSCOPS) coronary event rates decreased as baseline HDLc concentrations increased, with a slope that was nearly identical in the pravastatin- and placebo-treated patients (figure 3).[51] The Heart Protection Study (HPS) also found that in the simvastatin group a low HDL increased risk by just as much as it did in the placebo group (figure 3).[49] The same conclusion emerged from a pooled analysis of the large placebo-controlled trials of pravastatin.[54]

This result, that statins do not alter the CHD risk associated with HDLc, is not surprising in view of the independent effects of HDLc and LDLc on CHD risk. Thus, although statin trials have consistently shown that statins reduce coronary events in patients with low HDLc and average to high LDLc, patients on statin therapy with low HDLc continue to have a greater risk than those with higher HDLc, indicating that other treatments will be necessary to make additional progress in prevention.

HDLc in the large-scale fibrate trials

It is well established that fibrates raise HDL by increasing the synthesis of apoA-I and apoA-II by the liver.[55] In addition, fibrates accelerate lipolysis of triglyceride-rich lipoproteins, leading to the formation of HDL from the association in plasma of the lipolysis products, apoA-I, apoA-II, phospholipids and cholesterol. The molecular mechanism for these actions is activation of peroxisome proliferator-activated receptor (PPAR) alpha which increases the transcription of genes related to HDL metabolism and reverse cholesterol transport, including SRB-1 and ABC-1, as already discussed.

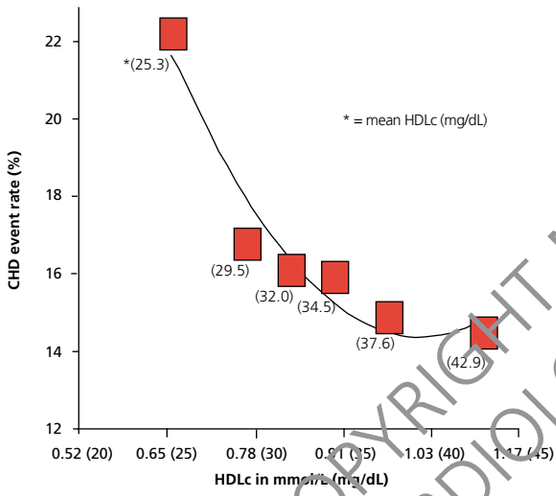
Helsinki Heart Study

The Helsinki Heart Study was a primary prevention trial with gemfibrozil in hyperlipidaemic men. Gemfibrozil caused a 34% reduction of coronary events.[42] The largest increases in HDLc with gemfibrozil occurred in patients with the lowest baseline levels of HDLc. The highest risk and greatest reduction in the incidence of coronary events was seen in those patients with the lowest HDLc at baseline (1.08 mmol/L or < 42 mg/dL). Many epidemiological studies confirmed the high risk associated with low HDLc.[1-7,56] Finally, the changes in plasma lipids were evaluated in terms of the effects on coronary events in a meticulous multiple regression analysis. Each 1% increase in HDLc was associated with a 3% reduction in coronary events, independently of changes in LDLc and triglycerides (table 1).[42]

Table 1. The relative contributions of low density lipoprotein cholesterol (LDLc) and high density lipoprotein cholesterol (HDLc) to reduction in coronary heart disease (CHD)

	Percentage reduction in CHD =		
	% decrease in LDLc	+	% increase in HDLc
● 4S (statin)[41]	2%		1%
● LRC (resin)[40]	2%		1%
● HHS (fibrate)[42]	2%		3%

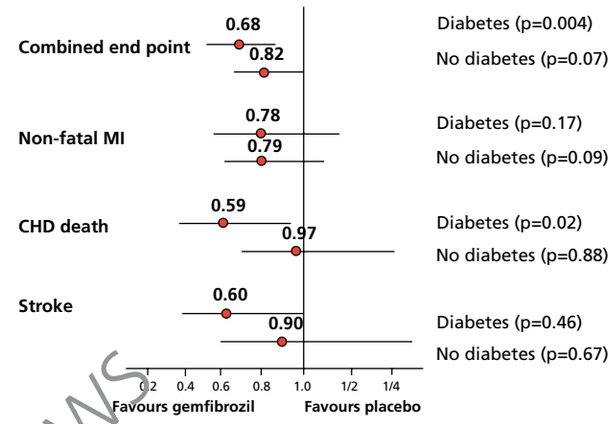
Figure 4. The relation of CHD events to HDLc during gemfibrozil treatment in the VA-HIT study[57]



Key: CHD = coronary heart disease, HDLc = high density lipoprotein cholesterol

Adapted from *Am J Cardiol* 2002;**90**:139-43, with permission

Figure 5. A sub-analysis of VA-HIT, showing major cardiovascular events in patients with and without diabetes



Key: CHD = coronary heart disease, MI = myocardial infarction

Adapted from Rubins *et al*.[58]

VA-HDL Intervention Trial (VA-HIT)

The VA-HIT investigators were particularly interested in the substantial numbers of patients who had a lipid phenotype of low HDL with low LDL. Such patients were generally not included in statin trials at that time, and they experience a greater risk for a coronary event than those with a moderately high LDLc and an average HDLc, characteristics of patients in the Cholesterol And Recurrent Events (CARE) and Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) secondary prevention trials.[54,57] The high rate of recurrent coronary events in the VA-HIT patients reflected the high prevalence of features of the metabolic syndrome (or insulin resistance syndrome), including abdominal obesity, diabetes, hypertension and high fasting plasma insulin levels.[57,58]

The investigators hypothesised that fibrate therapy would reduce coronary events in patients by raising HDL while leaving LDL unchanged, thereby providing a direct test of the HDL theory.[57] The baseline mean HDLc was 0.83 mmol/L (32 mg/dL) and the mean LDLc was 2.87 mmol/L (111 mg/dL), both lower values than have been found in any other lipid trial. Associated with this, gemfibrozil significantly reduced major CHD events (non-fatal myocardial infarction [MI] or CHD deaths) and cerebrovascular events (stroke or Transient Ischaemic Attack [TIA]).[57,59] The HDLc concentration, but not LDLc or triglycerides, during gemfibrozil treatment was highly inversely predictive of coronary events (figure 4); the increase in HDLc was associated with reduced coronary events. These findings support the hypothesis that the HDL-raising effect of fibrates is at least in part responsible for event reduction.[43] These results are consistent with findings in trials of other fibrates, bezafibrate and fenofibrate, showing reduction in progression of coronary artery stenosis.[33,60]

Fibrate therapy may have a special role in the treatment of patients with the high-risk features of the metabolic syndrome most often resulting from abdominal obesity – which can be readily assessed by the measurement of waist circumference – or insulin resistance. In support of this concept, the Helsinki Heart Study found that risk reduction in the gemfibrozil group was related to the body mass index (BMI) it was greatest in the obese (BMI > 30 kg/m^2), intermediate in the overweight (BMI 26–30), and least in the lean (BMI $\leq$ 25).[61] Risk reduction in the overweight and obese was further potentiated by the presence of dyslipidaemia or hyperglycaemia. In VA-HIT, similar findings were recently reported regarding the enhanced coronary event reduction in patients with diabetes or high fasting insulin concentrations (figure 5)[58] or with BMI of $\geq$ 26.

Nicotinic acid (niacin)

Niacin is also known to increase HDLc significantly in a dose-dependent manner. The molecular mechanisms are not fully understood. Niacin does not increase the synthesis by the liver of

Key messages

- Depressed levels of HDLc are a strong predictor of coronary heart disease at any level of LDLc or triglyceride, and also in patients who are being treated with statins
- Using HDLc < 1.0 mmol/L (40 mg/dL) as a threshold level, about 35–40% of men and 15% of women are at increased risk
- There is continuing debate about whether the same risk level of HDLc applies to women and men, and whether raising HDL should be given additional emphasis in women
- Diet and lifestyle modifications can help to raise low HDLc levels
- Fibrates and, in some patients, niacin may be considered as initial therapy for patients with cardiovascular disease or at high global risk who have low HDLc and low-risk LDLc

apoA-I but it inhibits uptake of apoA-I by the liver, thereby raising the plasma apoA-I concentration.[62,63] Niacin also does not alter the uptake by the liver of cholesterol esters from HDL, leaving unanswered the question of whether reverse cholesterol transport is affected.[63] The Coronary Drug Project showed that niacin prevented recurrent coronary events and cerebrovascular events in patients with MI.[64] However, risk reduction due to niacin in this study has been explained by its total cholesterol-lowering effect, according to a quantitative review of clinical trials[40] and a meta-regression analysis.[65] Since increases in HDLc were not quantitated in the Coronary Drug Project, it is not possible to determine directly the contribution of changes in HDLc to the beneficial effect of niacin.

Nonetheless, it is reasonable to hypothesise that increases in HDL cholesterol contribute to niacin's beneficial effect on coronary and cerebrovascular events. In the Familial Atherosclerosis Treatment Study (FATS) angiographic study, increases in HDL during combination therapy with niacin and lovastatin were associated with improvement in disease progression.[36] Since lovastatin has only a small effect on HDL, it is likely that this association is related to the niacin component of the treatment. Niacin has a dose-dependent effect on HDL; for example an increase of approximately 25% is seen with 1,500 mg of the new extended release formulation, Niaspan®,[66] which represents an ideal balance between reasonable efficacy and avoidance of the adverse effects that occur with higher doses. Smaller doses of niacin have less effect, i.e. a 15% increase in HDL is seen with 1,000 mg.

HDLc target level

Although a continuous inverse relationship is present between HDLc and coronary events, the risk curve for coronary events flattens considerably as HDLc increases above an 'average' concentration, i.e. 1.0 mmol/L (40 mg/dL).[1-6] Thus, HDLc of ≥ 1.0 mmol/L (40 mg/dL) is a convenient goal for HDL-raising therapy. A single HDLc goal is proposed for women and for men. Although women have higher average HDLc concentrations than men, the shape of the HDL risk curve is similar to that seen in men (figure 1).

Summary of the Expert Group's recommendations

Ample evidence supports the importance of HDLc for CHD risk. Raising low HDLc should be considered important, as is lowering LDLc, to prevent CHD. Increased prominence should be given to HDLc as an intervention target.

Therefore, we propose that:

- An HDLc of 1.0 mmol/L or greater be recommended as a goal for patients with cardiovascular disease and those without clinical cardiovascular disease but at high global risk, and especially in those with type 2 diabetes or features of the metabolic syndrome, most particularly abdominal obesity with high fasting insulin values.
- Lifestyle changes that include smoking cessation, weight loss, a diet moderate in unsaturated fat (rather than a low-fat diet) and regular exercise should be encouraged to reach this HDLc goal.
- Consideration be given to a fibrate as initial therapy for patients in these categories with a low HDLc and low-risk LDLc, defined as below the threshold for LDL-lowering drug treatments according to recognised guidelines (e.g. NCEP < 3.4 mmol/L for secondary prevention). Niacin may also be considered in appropriate patients.
- These recommendations would apply both to patients who do not require statin therapy to reduce LDLc, and to those who are being treated with statins in accordance with current national or international guidelines.

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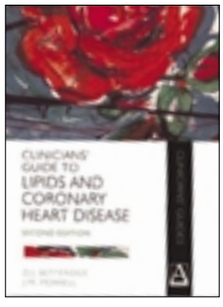
Book review



Clinicians' guide to lipids and coronary heart disease, 2nd edition
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Lipid metabolism, as the authors highlight, has not captured the popular medical imagination. Yet the past two decades have witnessed huge strides in our understanding of lipoprotein biology and of the pathophysiology of atherosclerosis. Equally, through application of new therapies, very substantial clinical benefits from treatment of hyperlipidaemia have been demonstrated. In this rapidly moving field, many physicians and allied professionals should appreciate a distillation of this proliferation of information in a readable and accessible text. This book makes a timely contribution.

The book's approach is practical and it is thoughtfully put together. Presented in four sections it covers topics ranging from lipoprotein metabolism to epidemiology, diagnosis and screening to therapeutic interventions and major trials. Readers will be interested to revisit the controversial early trials, where, not much more than a decade ago, cholesterol reduction was perceived to be potentially hazardous. There are dedicated sections covering nurse-led clinics and general lipid management in primary care and the UK National Service Framework for Coronary Heart Disease. Great effort has been made to address practical considerations, including a series of case studies derived from the authors' personal experience. The book consistently draws on a robust evidence base and is clearly and abundantly illustrated throughout.

The revised second edition is up to date in its discussion of newly available agents (e.g. evidence relating to the use of ezetimibe and rosuvastatin), recent trials and guidelines (e.g. Heart Protection Study, ATPIII), and current issues, such as the 'pleiotropic' effects of statins. The discussion does not shy away from more thorny issues: critical consideration is given to current guidelines and limitations are identified – e.g. should there be target levels for LDL-cholesterol? When should HDL be treated? Do the guidelines match the evidence? The authors strike an excellent balance between detail – of which there is much – whilst maintaining clarity, focus and readability. As a result, this book works well as both a systematic review and a well-indexed reference text.

Overall, this is an exceptionally well presented, authoritative and practical book of particular benefit to practising physicians.

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