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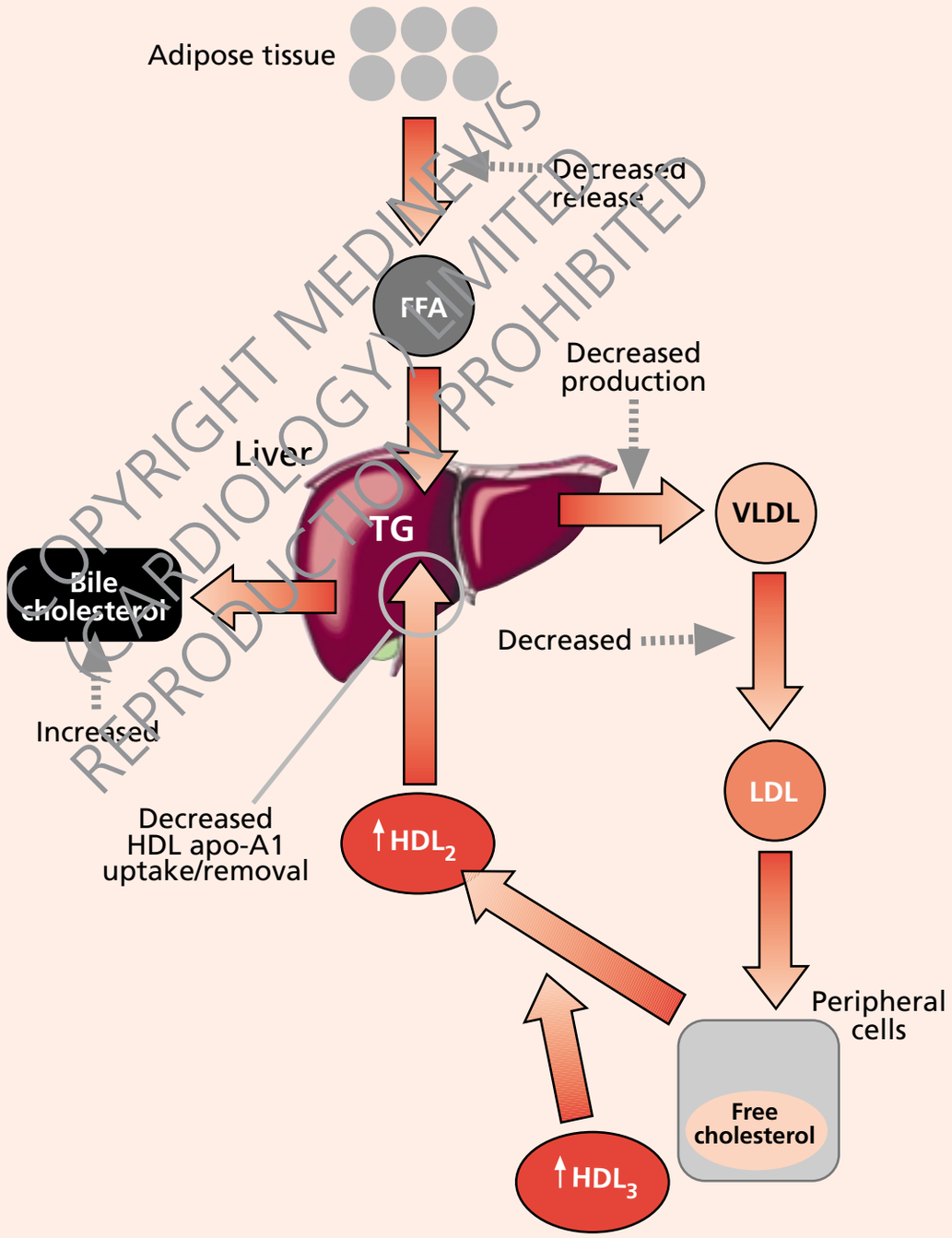

IMPROVED CARDIOVASCULAR RISK REDUCTION: THE EVIDENCE FOR RAISING HDL CHOLESTEROL

SUPPLEMENT 2
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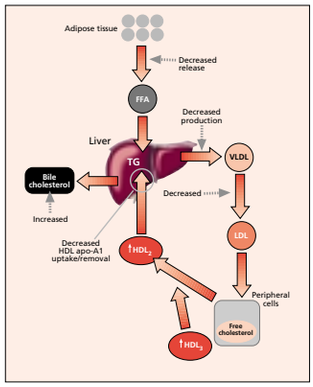

Front cover: Simplified diagram of the mechanism of action of nicotinic acid.
(Adapted from Knopp RH. *Am J Cardiol* 1998;**82**(12A):27U)

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Symposium introduction

GERD ASSMANN

High-density lipoprotein (HDL) cholesterol is an important molecule in cardiovascular disease. In myocardial infarction (MI) survivors, low levels of HDL are commonly found. For example, in the Prospective Cardiovascular Münster (PROCAM) study, coronary angiography was performed, and HDL and low-density lipoprotein (LDL) levels were measured, in 1,293 MI survivors and 11,402 controls.[1] Lipoprotein measurements show that the LDL level was on average 50 mg/dl higher in MI survivors aged 30–39 years as compared to age-matched controls (figure 1).

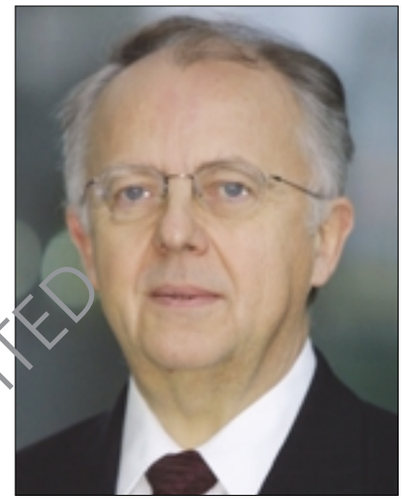
On examination of the PROCAM study population, it was apparent that most of the MI survivors in the study experienced their MI at the age of 60 years or older. Among these older individuals the HDL level seemed to have a more pronounced impact than the LDL level: in MI patients the HDL cholesterol level was on average 15 mg/dl lower than in controls, whereas the LDL level was only 3 mg/dl higher.

These findings indicated that the HDL level might have a significant impact on the development of myocardial infarction. Indeed, further research showed that HDL might be important prospectively as a risk factor for MI.

If the frequency distribution of HDL data from the PROCAM study are examined – this included 325 men aged 35–55 years with newly developed fatal or non-fatal MI, with a follow-up period of 10 years – the distribution pattern of HDL cholesterol differs markedly between cases and controls (figure 2). These and other epidemiological data suggest that individuals with low HDL cholesterol concentrations, e.g. below 40 mg/dl, are at particular risk of myocardial infarction. It should be noted, however, that available epidemiological data include only a limited number of individuals with very low (e.g. < 20 mg/dl) or very high (e.g. > 70 mg/dl) HDL cholesterol values. By implication, prognosis for risk of cardiovascular disease should be based upon the family history of such individuals or the identification of the genetic origins rather than on extrapolation of epidemiological data.

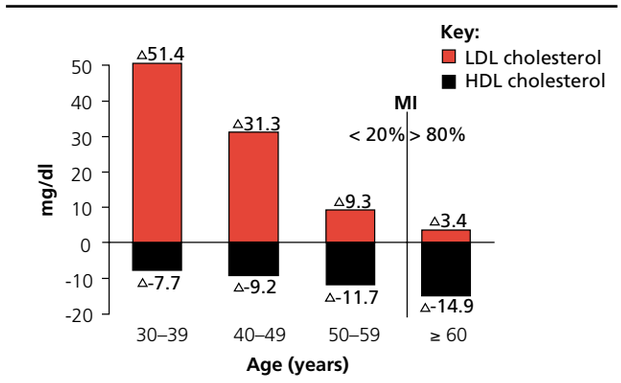
In about 95% of cases, those patients with low HDL levels (below 40 mg/dl) will also be found to have high serum triglycerides (TG). The combination of low HDL and high TG may be accompanied by obesity, insulin resistance, diabetes, metabolic syndrome and high global risk of cardiovascular disease (figure 3).

In the more unusual circumstances where the patient has low HDL but normal or only slightly elevated TG (which occurs in about 5%), it is worth making the effort to find the molecular origin of the low HDL, searching for mutations and polymorphisms



Gerd Assmann

Figure 1. Lipoprotein cholesterol in coronary angiography patients



Patients with coronary artery disease and myocardial infarction (MI) (n=1,293) *vs.* controls (n=11,402)

Br J Cardiol 2004;**11**(suppl 2):S1–S2

University of Münster, Germany, and Chairman of the International Task Force for the Prevention of Coronary Heart Disease
Gerd Assmann, Head and Director of the Institute of Arteriosclerosis Research

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Figure 2. Frequency distribution of HDL cholesterol in men with (CHD +) or without (CHD -) coronary events in the PROCAM-Study

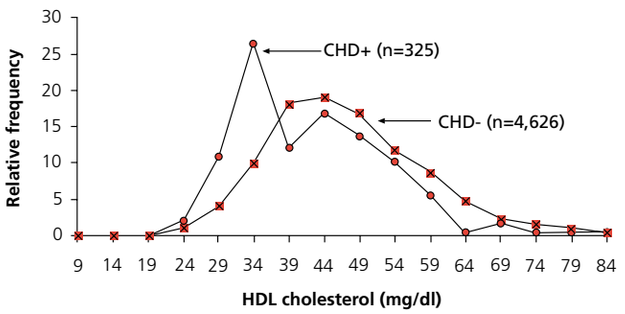
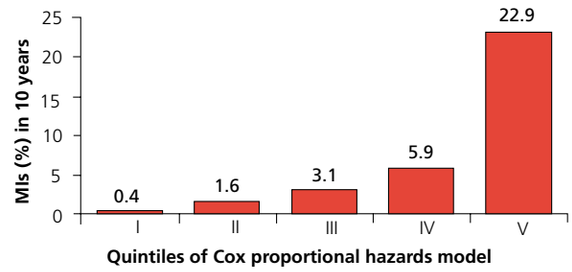
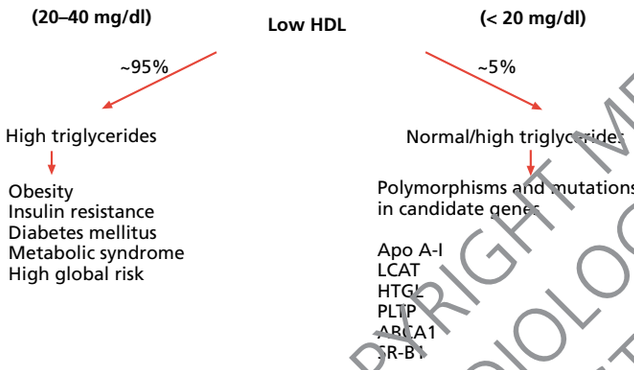


Figure 4. The PROCAM algorithm



Independent variables were: age, systolic blood pressure, LDL-C, HDL-C, triglycerides, diabetes mellitus, smoking, family history of MI.

Figure 3. Heterogeneity of low HDL



in candidate genes. Systematic studies among more than 1,000 individuals with very low HDL cholesterol have identified mutations in apo-lipoprotein A-1, LCAT, HTGL, ABCA1 and SR-B1 (figure 3). It is not known exactly how mutations in these candidate genes affect the risk of atherosclerosis.

The significance of low HDL levels in MI can be derived from the PROCAM algorithm (figure 4).[3] Examination of the data on 325 fatal and non-fatal MIs shows that age, systolic blood pressure, LDL, HDL, TG, diabetes, smoking, and a family history of MI seem to be independent predictors of future events. They are also significant risk factors, and age is the most important of all on mathematical ranking. In this algorithm, age ranks above LDL, smoking and HDL. In turn, HDL ranks above systolic blood pressure, diabetes, the TG level, and a family history of MI.

Management guidelines suggest that patients with a greater than 20% risk of MI over the next 10 years should be identified. Their LDL levels should be brought to below 100 mg/dl, and perhaps also their levels of HDL and other lipoproteins should be normalised in order to decrease their overall CHD risk.

References

1. Assmann G, Cullen P, Schulte H. The Münster Heart Study (PROCAM). Results of follow-up at eight years. *Eur Heart J* 1998;**19**(suppl A):A2-11.
2. Assmann G, Schulte H. Results and conclusions of the Prospective Cardiovascular Münster Study. In: Assmann G, Ed. *Lipid metabolism disorders and coronary heart disease*. München: MMV Medizin Verlag, 1993:19-67.
3. Assmann G, Cullen P, Schulte H. Simple scoring system for calculating the risk of acute coronary events based on the 10-year follow-up of the Prospective Cardiovascular Münster (PROCAM) Study. *Circulation* 2002; **105**:310-15.

Reducing the risk of atherosclerosis: the role of high-density lipoprotein cholesterol

PETER LIBBY

Abstract

High-density lipoprotein (HDL) cholesterol exerts beneficial effects regardless of the low-density lipoprotein (LDL) level. HDL is believed to affect reverse cholesterol transport by removing excess free cholesterol from the arterial wall. Progress in understanding the mechanism of action of HDL has been made recently with the identification of the molecular defect in Tangier disease. (This is a rare genetic disease that is characterised by a cholesterol transport deficit.) Furthermore, there have also been advances in the understanding of the direct pathway of metabolism of cholesterol through HDL, with discovery of a receptor known as scavenger receptor B-1.

HDL also has an anti-inflammatory effect because it may be a carrier of antioxidant enzymes that can break down oxidised lipids.

Therapeutic options are needed to boost the protective properties of HDL. Beneficial effects may be obtained from inhibition of cholesteryl ester transfer protein, and from using combination therapy with a statin plus niacin or fibrate.

Key words: high-density lipoprotein, reverse cholesterol transport, antioxidant enzymes, cholesteryl ester transfer protein, niacin.

Br J Cardiol 2004;**11**(suppl 2):S3–S6

Peter Libby

Introduction

Daily medical practice should lend attention not only to the risk factors for atherosclerosis but also to some of the endogenous defence mechanisms that may reduce this chronic and ubiquitous disease.

High-density lipoprotein (HDL) cholesterol is one of the most important and potent combatants against atherosclerosis. It exerts its beneficial effect by changing the biology of the arterial lesion, and it does so regardless of the low-density cholesterol (LDL) level. There has been a tendency towards complacency about cardiovascular disease since the statins, whose principal effect is lowering of the LDL level, came onto the market. However, data from the Framingham Heart Study clearly show that, regardless of the LDL level and even at low LDL levels, there is a very potent and continuous reduction in risk of coronary artery disease with increasing levels of HDL.[1]

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Reverse cholesterol transport

There are two major ways in which HDL alters the biology of the arterial wall. First, it affects reverse cholesterol transport by aiding the efflux of lipid from the artery wall. Second, it has an antioxidant effect by acting as a carrier for antioxidant enzymes and detoxifying oxidised lipid in the atherosclerotic plaque.

Reverse cholesterol transport removes excess free cholesterol from cells in peripheral tissues, particularly from macrophages in the arterial wall, and returns cholesterol to the liver for excretion into the bile. HDL is involved in this process through two pathways – one the direct pathway and the other by transferring cholesterol through VLDL and LDL (figure 1).

One of the great new insights into the mechanisms of reverse cholesterol transport occurred in 1999 with deduction of the molecular defect in a rare genetic disease, Tangier disease.[2-4] Patients with Tangier disease have a low HDL level due to rapid catabolism. There is foam cell accumulation causing orange tonsils, which are

Figure 1. Reverse cholesterol transport

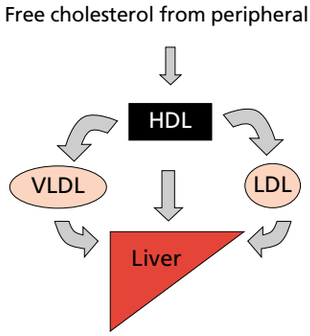
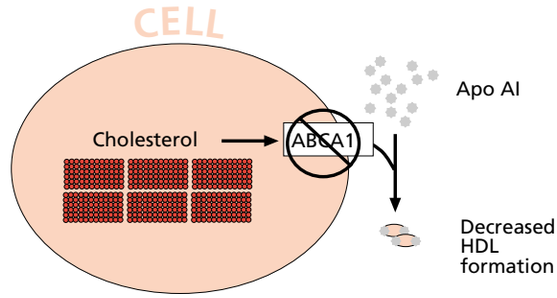
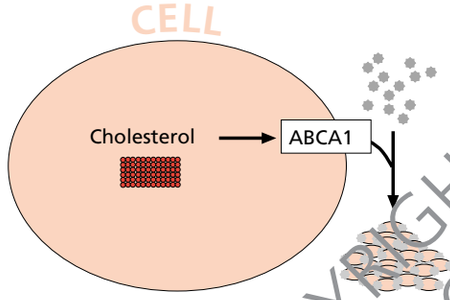


Figure 3. Tangier disease, which is caused by mutations in ABCA1



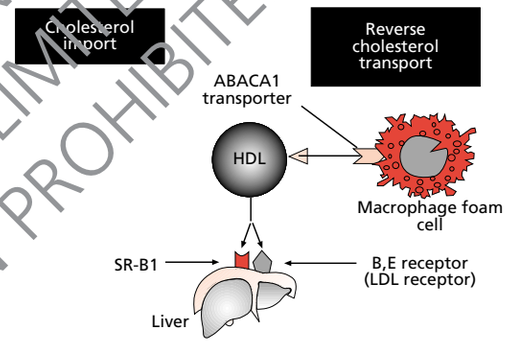
Adapted from Young SG, Fielding CJ. *Nat Genet* 1999;**22**:316-18.

Figure 2. ATP-binding cassette transporter (ABCA1) furnishes cholesterol for HDL formation



Key: Apo AI = apolipoprotein AI; HDL = high density lipoprotein
Adapted from Young SG, Fielding CJ. *Nat Genet* 1999;**22**:316-18.

Figure 4. The flux of cholesterol through HDL



merely accumulations of cholesterol-laden macrophages. In many cases, patients have premature coronary artery disease.

Mutations in an ATP-binding cassette transporter, known as ABCA1, cause Tangier disease. The protein encoded by ABCA1 is a key gatekeeper influencing the transport of excess cholesterol out of the peripheral cell. It is the key molecule in loading cholesterol onto apolipoprotein A1 to form HDL, that will then take part in the rest of the steps of lipoprotein metabolism. This is shown in figure 2.[5]

A genetic defect in ABCA1 results in a malfunction in cholesterol transport. Cholesterol builds up inside the cells, with lipid-laden macrophages manifest as visibly orange tonsils, and in atheromatous plaques. The apo-A1 is rapidly catabolised and is excreted through the kidneys. Decreased amounts of HDL are formed and HDL levels are very low, usually below 10 mg/dl. The molecular pathways in Tangier disease (figure 3) contrast with those under normal conditions (figure 2).

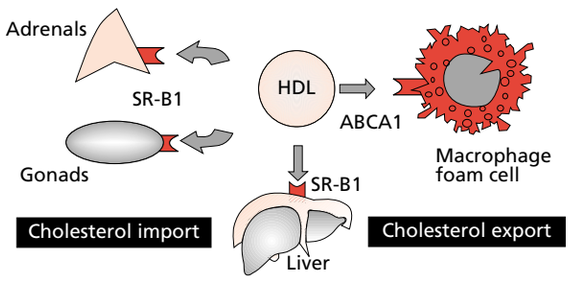
Atherosclerotic plaque contains LDL particles and inflammatory cells such as T lymphocytes and lipid-filled macrophages. In contact with such plaques, the HDL particle becomes more spherical as it takes up cholesterol. It also picks up apolipoprotein E synthesised by the macrophages, a functionally important step that helps to target the HDL particle for metabolism.

There have also been great advances in our molecular understanding of the direct pathway of metabolism of cholesterol through HDL. Researchers at the Massachusetts Institute of Technology discovered a receptor that binds HDL particles, known as scavenger receptor B-1 (SR-B1).[6] SR-B1 is a transmembrane protein that binds the HDL particle and allows it to unload cholesterol and to deliver it to cells. The SR-B1 receptor is expressed on cells such as the hepatocyte.

Figure 4 shows the flux of cholesterol through HDL. Through the ABCA1 transporter, the HDL particle is loaded with cholesterol. It can then go through either apolipoprotein E, which binds to the B,E receptor (LDL receptor); or through the SR-B1 receptor, thereby targeting the cholesteryl ester for metabolism by the liver and excretion through the bile.

The SR-B1 receptor has an important physiological role in delivery of cholesterol biosynthesis of the steroid hormones (figure 5). A lot of HDL metabolism occurs in the adrenals and the

Figure 5. Delivery of HDL to the adrenals and gonads



Adapted from Libby P. HDL-C and reducing the risk of atherosclerosis: a mechanistic review. *Clinician* 2000;**18**:3-8.

Figure 7. Effects of niacin on myocardial infarction (MI) and coronary death in the Coronary Drug Project

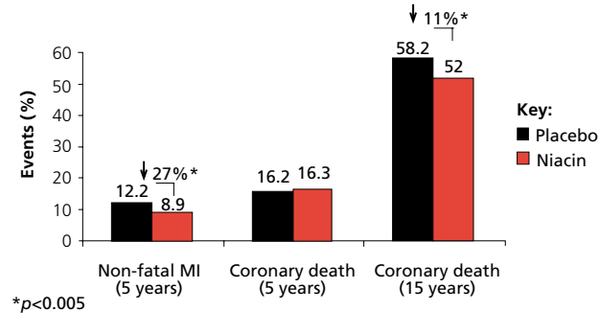
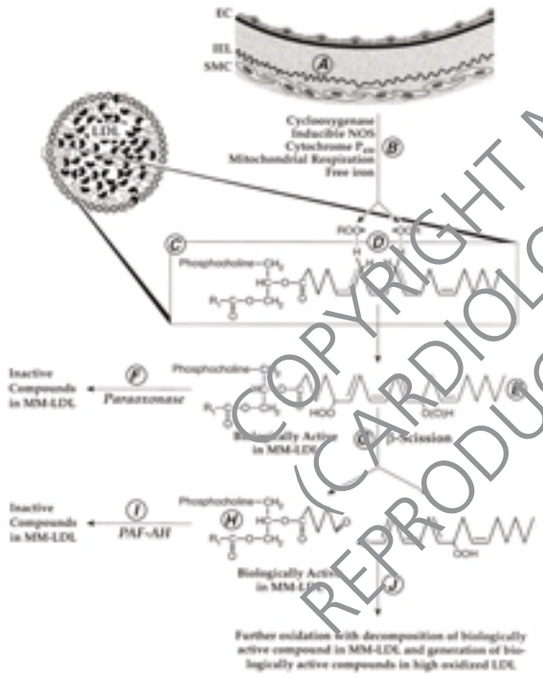


Figure 6. Destruction of biologically active lipids by HDL



gonads, and the SR-B1 delivers the cholesterol that is a substrate for the sex steroids and adrenal steroids.[7]

HDL modifies the biology of the arterial wall and atheroma not only by affecting cholesterol metabolism but also by an anti-inflammatory effect. Inflammation participates integrally in atherosclerosis at all stages, from initiation through progression and to ultimate complications such as rupture. HDL is one of the very important endogenous brakes put on this inflammatory process.

Much of the work in this area has been conducted by Dr Alan Fogelman's group at the University of California in Los Angeles, with Mohamad Navab and Aldons Lusis. The group has pointed out that HDL can be a carrier of antioxidant enzymes that can break down active, oxidised, pro-inflammatory lipids. These enzymes are known as paraoxonase and platelet activating factor (PAF) acetylhydrolase, the latter an enzyme specialising in metabolising phospholipids.

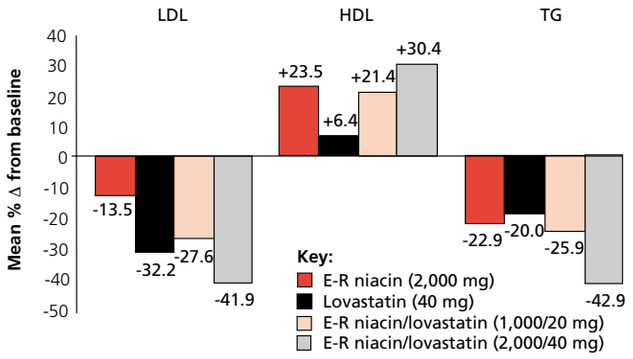
Figure 6 shows a hypothetical model for the mechanism by which HDL destroys biologically active lipids in mildly oxidised LDL.[8] Multioxygenated phospholipids may be substrates for paraoxonase in HDL. If paraoxonase concentrations are low or lipid peroxide levels are excessive, oxidatively fragmented phospholipids may be substrates for the second line of defence, PAF-AH. Its action hydrolyses these biologically active lipids into molecules that do not evoke inflammatory responses in endothelial cells. This biochemical pathway provides a mechanism for ridding the body of toxic oxidised phospholipids, potentially important instigators of the inflammatory process in atherosclerotic plaque.

How can these endogenous protective mechanisms be utilised to help patients in daily practice? How can HDL levels be influenced, and is it certain that raising the HDL will confer clinical benefit? It is known that lowering LDL by whatever pathway, whether by statins, resins, plasmapharesis or intestinal bypass surgery, confers benefit. But the metabolism of HDL is much more complex.

The control of lipids through lifestyle measures such as diet and exercise is fundamental in the practice of prevention of cardiovascular disease. Unfortunately, however, it is difficult to change diet and exercise in the majority of patients to an extent that lowers the patients' level of risk down to current targets. Other ways to bring down their risk are needed.

Cholesteryl ester transfer protein (CETP) inhibition may raise HDL levels. What is CETP, and what does it do? The cholesterol-enriched HDL particle can transfer cholesteryl ester to LDL particles by a CETP-dependent mechanism. Under normal circumstances, when the plasma TG level is not elevated, the CETP decreases the cholesteryl ester in HDL and transfers it to the apoB-containing proteins. However, high triglyceride levels favour enrichment of LDL in cholesteryl ester and triglycerides.[9]

Figure 8. Effect of extended release (E-R) niacin and lovastatin on lipids in primary hypercholesterolaemia



Data from Hunninghake DB *et al. Clin Cardiol* 2003;**26**:112-18.

These particles become excellent substrates for hepatic lipase that can process them into small dense LDL and HDL. They can also become substrates for lipases and contribute to the small dense lipoprotein particles that are particularly atherogenic and that are particularly associated with diabetes.[9]

Thus raising the HDL by inhibiting CETP may not necessarily give clinical benefit. It is a very complex pathway, and the steadystate plasma level of HDL may not reliably reflect flux through the reverse lipid transport pathway or clinical outcome.

Could raising the plasma HDL level with nicotinic acid (niacin) be of clinical benefit? The Coronary Drug Project was conducted in 8,431 men in the US between 1966 and 1975.[10] It studied dithyroxine, clofibrate, oestrogen and niacin. On five-year follow-up, niacin reduced non-fatal MI by 27% ($p<0.005$) and on 15-year follow-up, niacin reduced coronary death by 11% ($p<0.005$) (figure 7). The median survival time from entry into the study was 13.03 years for patients given niacin, compared with 11.40 years for patients given placebo ($p=0.0012$). Mortality rates began to diverge at month 72. Thus in this study, niacin was shown to have beneficial effects.

The combination of statins with nicotinic acid may be used to obtain beneficial changes in the lipid profile. Figure 8 shows increases in HDL and decreases in TG and LDL seen in patients with primary hypercholesterolaemia who were treated with extended-release niacin and lovastatin.[11]

Thus the combination may be an achievable way to manipulate lipoproteins, and it is encouraging that it emerges from an evidence base from the statin trials showing that monotherapy with statins is protective, and evidence from the Coronary Drug Project showing that niacin gives a decrease in cardiovascular events. Combinations of statins with fibrates may likewise raise HDL and lower cardiovascular event rates. The safety and efficacy of this approach require urgent evaluation in clinical trials.

This is an exciting time in our understanding of HDL metabolism. In 2003 three reports of the molecular identification of nicotinic acid receptors were published.[12,13] A G-protein coupled receptor binds nicotinic acid and other compounds with related biology, particularly in adipose tissue, and is supposed to be involved in mediating its pharmacological effects. By focusing on the molecular receptor for nicotinic acid, we may be able to benefit our patients by manipulating HDL levels while minimising the symptoms previously associated with high-dose nicotinic acid therapy.

References

1. Castelli W. Cholesterol and lipids in the risk of coronary artery disease. The Framingham Heart Study. *Can J Cardiol* 1988;**4**(suppl A):5a-10a.
2. Brooks-Wilson A, Marcil M, Clee SM *et al*. Mutations in ABC1 in Tangier disease and familial high-density lipoprotein deficiency. *Nat Genet* 1999; **22**:336-45.
3. Bodzioch M, Orso E, Klucken J *et al*. The gene encoding ATP-binding cassette transporter is mutated in Tangier disease. *Nat Genet* 1999;**22**:347-51.
4. 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.
5. Young SG, Fielding CJ. The ABCs of cholesterol efflux. *Nat Genet* 1999; **22**:316-18.
6. Acton S, Rigotti A, Landschulz K *et al*. Identification of scavenger receptor SR-B1 as a high density lipoprotein receptor. *Science* 1996;**271**:518-20.
7. Libby P. HDL-C and reducing the risk of atherosclerosis: a mechanistic review. *Clinician* 2000;**18**:3-8.
8. Navab M, Berliner JA, Watson AD *et al*. The yin and yang of oxidation in the development of the fatty streak: a review based on the 1994 George Lyman Duff Memorial Lecture. *ATVB* 1996;**16**:831.
9. Barter PJ, Brewer HB, Chapman MJ *et al.* Cholesteryl ester transfer protein: a novel target for raising HDL and inhibiting atherosclerosis. *ATVB* 2003;**23**:160.
10. Coronary Drug Project Research Group. Clofibrate and niacin in coronary heart disease. *JAMA* 1975;**231**:360-81.
11. Hunninghake DB, McGovern ME, Koren M *et al*. A dose-ranging study of a new, once-daily, dual-component drug product containing niacin extended-release and lovastatin. *Clin Cardiol* 2003;**26**:112-18.
12. Wise A, Foord SM, Fraser NJ *et al*. Molecular identification of high and low affinity receptors for nicotinic acid. *J Biol Chem* 2003;**278**:2849-74.
13. Soga T, Kamohara M, Takasaki J *et al*. Molecular identification of nicotinic acid receptor. *Biochem Biophys Res Comm* 2003;**303**:364-9.

Beyond LDL cholesterol reduction: what do the trials tell us?

CHRISTIE BALLANTYNE

Abstract

Statins have been shown to lower the level of low-density lipoprotein (LDL) cholesterol and to reduce the risk of coronary heart disease (CHD) death and non-fatal myocardial infarction (MI) in primary and secondary prevention trials. People with low high-density lipoprotein (HDL) cholesterol are in fact at high risk of CHD. Statins raise HDL by 5–10%, fibrates by 10–15%, and niacin by 15–25%. Data from the Coronary Drug Project showed that niacin treatment reduced the risk of non-fatal MI/death from CHD, compared to placebo. The HDL-Atherosclerosis Treatment Study, an angiographic study carried out in CHD patients with low HDL, is discussed. The advantages and disadvantages of adding niacin or a fibrate to a statin are also discussed.

Key words: high-density lipoprotein cholesterol, statins, fibrates, niacin.

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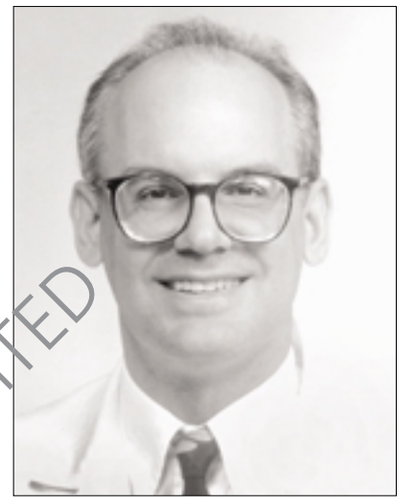


Christie Ballantyne

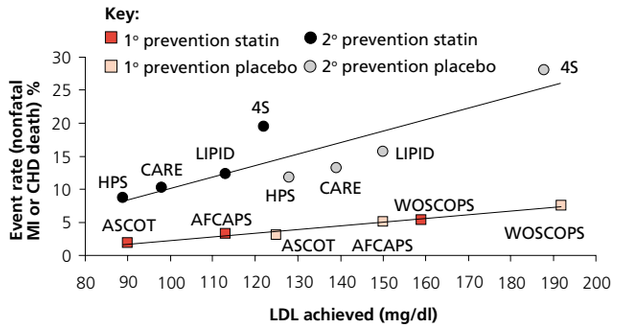
Introduction

Numerous primary and secondary prevention trials indicate that statins are highly effective in a wide range of patients. The data show (figure 1) a consistent reduction in clinical events (non-fatal myocardial infarction [MI] or coronary heart disease [CHD] death) across a wide range of achieved low-density lipoprotein (LDL) cholesterol levels. In the US, guidelines state that the optimal level of LDL is below 100 mg/dl, and results from the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)[1] seem to indicate a similar level. Perhaps, as further results come in from currently ongoing trials, the ideal level will turn out to be lower still.

The epidemiological data shed some light on this topic. For example, the Atherosclerosis Risk in Communities (ARIC) study[2] was conducted among 12,339 middle-aged men and women in the US. It was shown that the relative risk of cardiovascular events in both men and women in the quintile with the highest LDL (median 4.78 mmol/L [185 mg/dl] for men and 4.84 mmol/L [187 mg/dl] for women) was approximately twice the risk in the quintile with the lowest LDL levels (figure 2).

Much has been written about the risk of a low HDL. The guidelines say that, in men, levels should be above 1.05 mmol/L (40 mg/dl) but the HDL cutoff point in women is still under debate. Using HDL data from the ARIC study,[2] the median HDL for

Figure 1. Primary and secondary prevention trials with statins



Adapted from Ballantyne CM. *Am J Cardiol* 1998;**82**:3Q–12Q.

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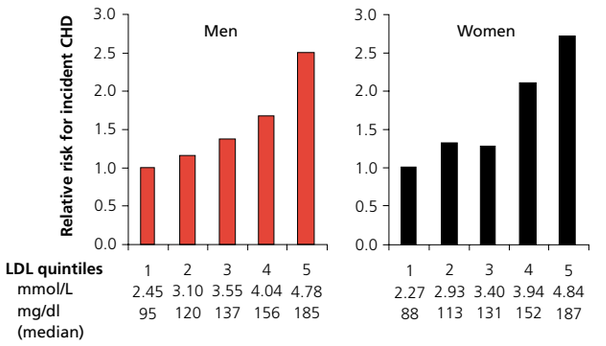
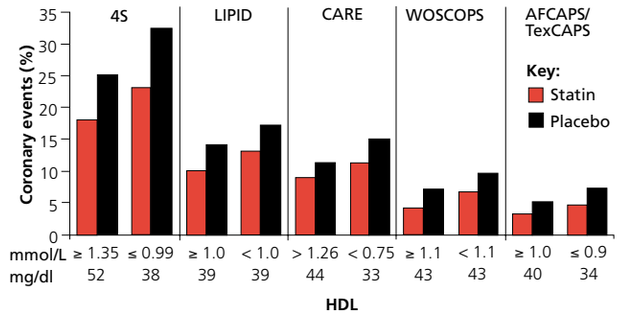
Figure 2. What is the optimal LDL? Data from ARIC



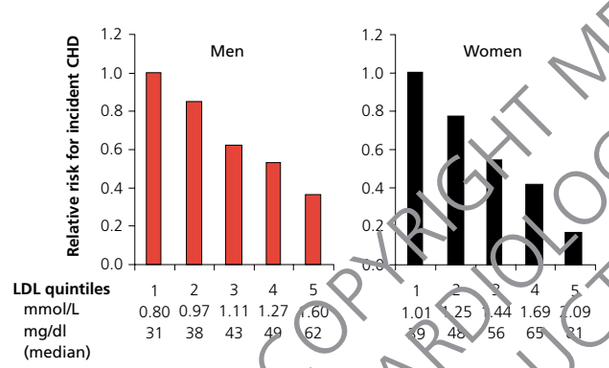
Adapted from Sharrett AR *et al. Circulation* 2001;**104**:1108-13.

Figure 4. Comparison of trials in which statin therapy reduced the coronary risk associated with low HDL



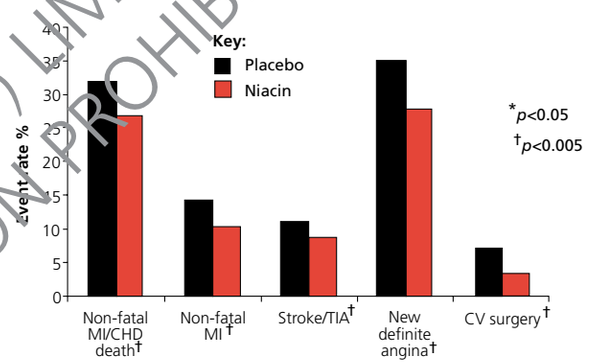
Adapted from Ballantyne CM *et al. Circulation* 1999;**99**:736–43.

Figure 3. What is the optimal HDL? Data from ARIC



Adapted from Sharrett AR *et al. Circulation* 2001;**104**:1108-13.

Figure 5. Cardiovascular outcomes in the Coronary Drug Project at six years



Key: MI = myocardial infarction; CHD = coronary heart disease; TIA = transient ischaemic attack

men in the lowest HDL quintile was 0.80 mmol/L (31 mg/dl) (figure 3) while in the highest HDL quintile, the median HDL level was 1.60 mmol/lL (62 mg/dl). At these higher levels of HDL, the risk of CHD events was reduced by more than 60%.

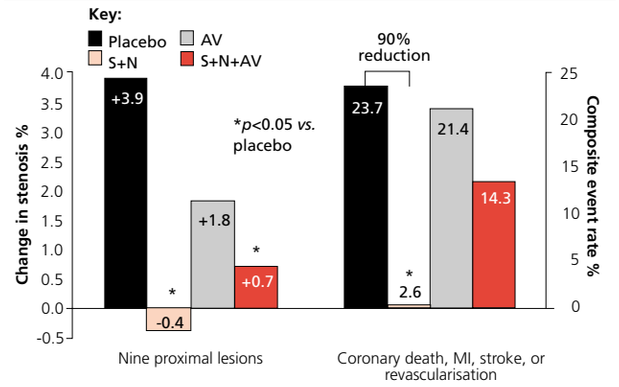
For women, the median HDL in the lowest HDL quintile was 1.01 mmol/L (39 mg/dl) and in the highest quintile it was 2.09 mmol/L (81 mg/dl). The risk differential between the quintiles was even more marked in women than in men: those with the highest HDL levels had a greater than 80% reduction in CHD events. Since treatment options for HDL are limited, there is a long way to go before these optimal HDL levels are achieved in the population.

What can be done to reduce the high risk of heart disease in people with low plasma HDL? The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)[3] was a primary prevention trial using lovastatin. The participants in this trial had fairly low levels of HDL, and there was a consistent benefit in terms of events with lovastatin treatment. Interestingly, greater benefit with statin therapy was seen in patients with the lowest HDL levels.

The beneficial effects of statin treatment in reducing the CHD risk associated with low levels of HDL have been shown in a number of trials (figure 4). In every trial, individuals with low HDL had very high event rates on placebo, and they all had a reduction in events with statin treatment. Two of the newer trials, the Heart Protection Study (HPS)[4] and Prospective Study of Pravastatin in the Elderly at Risk (PROSPER),[5] show the same thing.

However, it is apparent from the HPS that if a statin is used in a patient who has low HDL levels, the coronary event rate is reduced – but it is still higher than the event rate in a placebo-treated patient who had a higher basal HDL level. In the long term, the probability of having a recurrent event may be as high as 50% over 10 years in very high risk patients.

Figure 6. Angiographic and clinical end points in the HDL-Atherosclerosis Treatment Study



Key: S = simvastatin; N = niacin; AV = antioxidant vitamins

Table 1. The effect of once-daily extended-release niacin on blood lipids

Dose	HDL	LDL	TG
500 mg	↑ 10%	↓ 3%	↓ 5%
1,000 mg	↑ 15%	↓ 9%	↓ 12%
1,500 mg	↑ 22%	↓ 14%	↓ 28%
2,000 mg	↑ 26%	↓ 17%	↓ 35%

In the catheter laboratory, interventional cardiologists treat coronary disease aggressively, said Dr Ballantyne. It is logical and consistent therefore that cardiologists should be equally aggressive in treating the disease process itself.

How can atherosclerosis be influenced? Possibilities include lowering LDL, lowering lipoprotein (a) (Lp[a]), lowering triglycerides and raising HDL. Different treatment modalities achieve these ends to differing extents. Data show that the statins raise HDL by 5–10%; fibrates by 10–15%; and niacin by 15–35%.[6] In the VA-HIT study,[7] for example, gemfibrozil had very little effect on LDL levels. It raised HDL modestly, it reduced triglycerides by 30% and it significantly reduced the end point of non-fatal MI or CHD death. Clearly, then, it is possible to reduce events without reducing LDL: there are other lipoprotein fractions of clinical significance.

Niacin may have advantages over other treatment modalities since it improves levels of HDL, triglycerides and Lp(a). In the Coronary Drug Project (CDP),[8] niacin treatment was compared with placebo. There was a 10% reduction in total cholesterol with niacin versus placebo, and a 26% reduction in triglycerides from baseline over five annual follow-up visits. The HDL undoubtedly went up but, interestingly, the trialists did not measure HDL because they were not convinced at that time (1975) that it was important.

Looking at cardiovascular outcomes in the CDP at six years (figure 5), the relative hazard of non-fatal MI/CHD death was 0.82 ($p<0.005$) in patients treated with niacin as compared to those treated with placebo. All the other categories showed trends in favour of niacin treatment: the relative hazard of non-fatal MI was 0.70; of stroke/TIA was 0.78; of new definite angina was 0.75; and of cardiovascular surgery was 0.46.

There is concern about niacin and blood glucose levels in diabetic patients. However, quartile analysis of baseline fasting blood glucose in the CDP showed an impressive reduction in incidence of non-fatal MI at six years with niacin treatment across all quartiles of glucose at baseline. There was also a significant reduction in total mortality at 15 years with niacin treatment.[9]

Why has niacin not been used more? In the 1980s patients in our Lipid Clinic were treated with 3 g or more of niacin plus 8 g three times daily of cholestyramine to bring down their LDL levels. Patients alternated between being flushed and constipated, and were pleased when the statins were launched. In Europe it seems that everybody gave up completely on niacin when the statins came into use, but in the US clinicians are rethinking why and how to use niacin.

The improved formulation of niacin as a once-daily extended-release formulation may be helpful in this regard. The dose-response pattern is given in table 1. It is, however, interesting that there is a ceiling effect: HDL is not raised much more if niacin in greater (2,500 and 3,000 mg) than recommended doses (1,000–2,000 mg) is tried.

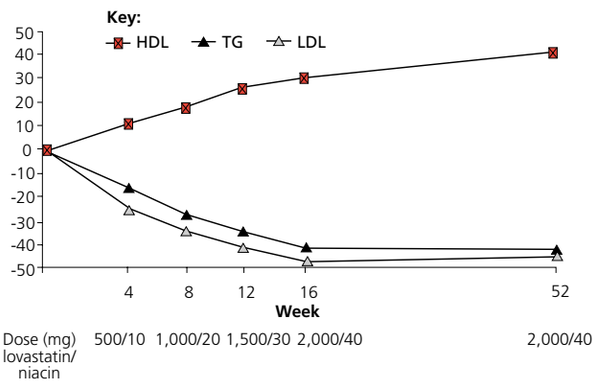
The HDL-Atherosclerosis Treatment Study (HATS)[11] was an angiographic study carried out in 160 CHD patients with low HDL (≤ 35 mg/dl in men, ≤ 40 mg/dl in women) and with LDL ≤ 145 mg/dl. They were randomised to: simvastatin 10–20 mg/day plus niacin 2–4 g/day, antioxidant vitamins (E, C, beta carotene and selenium), simvastatin plus niacin plus vitamins, or placebo. The primary end points were mean per-patient three-year change in percent stenosis in nine coronary segments, and the time to first event (coronary death, MI, stroke or revascularisation).

The effects on lipids were good in HATS. The plasma LDL level fell by 40% in patients treated with simvastatin and niacin, while plasma HDL rose by 30% and HDL_2 by 60%. The antioxidant vitamins blunted these beneficial effects, especially the effects on HDL levels (figure 6).

Turning to the angiographic end point, there was a small amount of regression of stenosis in the coronary vessels of patients treated with simvastatin plus niacin. The 0.4% regression of atherosclerosis was modest, but none of the statin trials have shown regression with monotherapy. The composite clinical event rate was 23.7% with placebo treatment and 2.6% with simvastatin plus niacin treatment. This is a 90% reduction compared to placebo ($p<0.05$) but it has to be interpreted with caution because the number of patients was small; it was an angiographic study, and it was not powered to be an event trial.

Kashyap and colleagues[12] investigated the safety and efficacy of once-daily niacin extended-release plus lovastatin in a multicentre study of 814 men and women. The doses of both agents were increased every four weeks so that by week 16, patients were taking 2,000 mg niacin plus 40 mg lovastatin; this dosage

Figure 7. Efficacy of once-daily niacin-ER/lovastatin combination (n=814)



Adapted from Kashyap ML *et al. Am J Cardiol* 2002;**89**:672.

Table 2. The pros and cons of combination therapy with niacin or a fibrate and a statin

Pros	Cons
Better ↓ TG and ↑ HDL	Increased cost and complexity
May ↓ LDL more (niacin or fenofibrate)	Increased myositis risk (fibrate)
↓ Lp(a) (niacin)	Potential for other drug interactions
↑ LDL particle size	Lack of event trials with combination treatment with either fibrate or niacin plus a statin
Angiographic data	

was maintained for one year. Effects on the lipoprotein fractions are shown in figure 7. At one year follow-up, there were no cases of drug-related myopathy and the incidence of ALT and AST elevation was the same as that seen with statin treatment alone. There was an approximately 5% incidence of hyperglycaemia. The dropout rate due to flushing in this study was 10%, but this effect can be minimised by taking the niacin at night, with a snack and with aspirin beforehand.

The advantages and disadvantages of adding niacin or a fibrate to a statin are given in table 2. Translating evidence from clinical trials for management of individual patients is a personal decision for the clinician, but patients with atherosclerosis have a high event rate even after they are treated with statins. Thus the pros of combination treatment tend to outweigh the cons.

In summary, patients with high global risk for CHD benefit from aggressive reduction of LDL with statins. High-risk patients benefit from lipid-modifying therapy with fibrates and with niacin, agents that raise HDL and reduce TG. Additional trials are needed to examine the benefits of combination therapy with niacin or fibrate plus statin in high-risk patients.

References

1. Sever PS, Dahlöf B, Poulter NR *et al*. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003;**361**:1149-58.
2. Sharrett AR, Ballantyne CM, Coady SA *et al.* Coronary heart disease prediction from lipoprotein cholesterol levels TG, lipoprotein (a), apolipoprotein A-1 and B, and HDL density subfractions: the ARIC study. *Circulation* 2001;**104**:1108-13.
3. 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.
4. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,356 high-risk individuals: a randomised, placebo-controlled trial. *Lancet* 2002;**360**(9326):7-22.
5. Shepherd J, Blauw GJ, Murphy MB *et al*. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002;**360**:1623-30.
6. Belalcazar LM, Ballantyne CM. Defining specific goals of therapy in treating dyslipidaemia in the patient with low high-density lipoprotein cholesterol. *Progr Cardiovasc Dis* 1998;**41**:151-74.
7. 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. *N Engl J Med* 1999;**341**:410-8.
8. Coronary Drug Project. Clofibrate and niacin in coronary heart disease. *JAMA* 1975;**231**:360-81.
9. Canner PL, Furberg C, McGovern ME. Niacin decreases myocardial infarction and total mortality in patients with impaired fasting glucose or glucose intolerance: results from the Coronary Drug Project. *Circulation* 2002;**106**:11-636.
10. Goldberg AC. Clinical trial experience with extended-release niacin (Niaspan): dose-escalation study. *Am J Cardiol* 1998;**82**:35U-38U.
11. Brown BG, Zhao X-Q, Schaub A *et al*. Simvastatin and niacin, antioxidant vitamins and the combination for the prevention of coronary disease. *N Engl J Med* 2001;**345**:1583-92.
12. 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.

Dyslipidaemia and diabetes – the clinical realities

JOHN BETTERIDGE

Abstract

The risk of cardiovascular disease is increased 2–4 fold in patients with diabetes, and this increased risk is apparent even before the glucose levels reach the stage of diagnosis of diabetes. Type 2 diabetes is often accompanied by dyslipidaemias and other parameters of the metabolic syndrome.

Dyslipidaemia in diabetes is present at the time of diagnosis and persists despite best efforts at glycaemia control. Dyslipidaemia in diabetics is characterised by low levels of HDL and high levels of triglyceride relative to controls. The HDL is altered in concentration, and is probably dysfunctional as well. Despite statin therapy the high risk persists in these patients: combination therapy has the potential to reduce vascular risk further.

Key words: diabetes, dyslipidaemia, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol.

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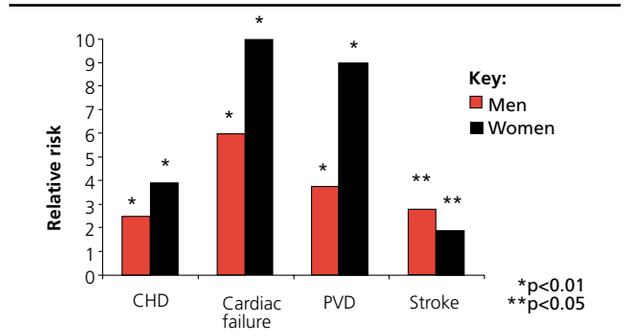
John Betteridge

Introduction

The major challenge for clinicians who treat patients with type 2 diabetes, and for the patients themselves, is the prevention of macrovascular disease. It is the largest cause of morbidity and mortality in patients with type 2 diabetes: most studies show that the risk of cardiovascular disease is increased 2–4 fold. There is a higher case fatality from myocardial infarction (MI) for diabetic patients. In addition, patients with type 2 diabetes are at substantially increased risk of stroke and peripheral disease. All this argues for primary prevention in these patients. Coronary intervention is beneficial in patients with diabetes but nevertheless they have reduced survival post-MI, post-bypass graft and particularly post-angioplasty.

The Framingham Study, which followed up patients with diabetes for 30 years, showed that the relative risks of all manifestations of atherosclerosis-related disease – coronary heart disease (CHD), cardiac failure, peripheral vascular disease and stroke – are markedly increased in patients with diabetes (figure 1).[1] Interestingly, the relative risk seems to be higher in diabetic women, though it is not yet known why.

Figure 1. The Framingham Study: cardiovascular events in patients (ages 35–64) with diabetes



Key: CHD = coronary heart disease; PVD = peripheral vascular disease
Adapted from Wilson PWF and Kannel WB[1]

The FINMONICA Myocardial Infarction Register Study Group compared the cardiovascular mortality in individuals who had suffered an MI, both those who did have diabetes (n=620) and those who did not have diabetes (n=3,445).[2] The data show that there is an increase in death prior to hospitalisation in diabetic men

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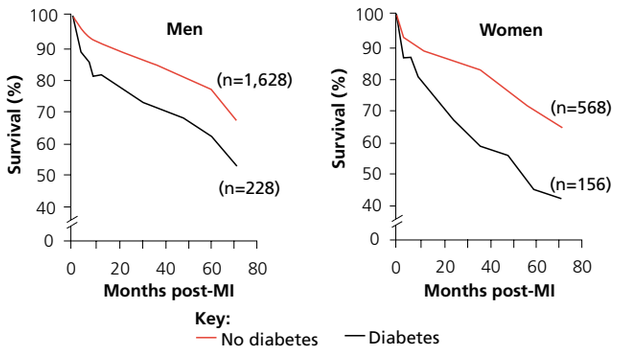
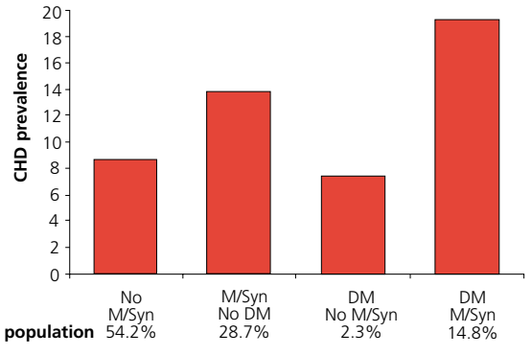
Figure 2. Survival post-MI in diabetic and non-diabetic men and women



Adapted from Sprafka JM *et al. Diabetes Care* 1991;**14**:537.[4]

Figure 3. Prevalence of CHD in the US population (> 50 years) in relation to metabolic syndrome and type 2 diabetes



Key: M/Syn = metabolic syndrome; DM = diabetes

(28.6% *vs.* 22.1%). Furthermore, there is a higher death rate in both men and women with diabetes in the first 28 days after hospitalisation (15.4% *vs.* 9.6% in men; 22.7% *vs.* 9.0% in women). At one year, there is still increased frequency of death in diabetic men (9.1% *vs.* 4.2%) and women (11.1% *vs.* 2.8%).

The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study[3] looked at aspirin versus aspirin plus clopidogrel in acute coronary syndromes (ACS). A total of 2,840 patients with diabetes were randomised within 24 hours of onset of ACS without ST segment elevation. The primary outcomes were death from cardiovascular disease, non-fatal MI or stroke after 3–12 months. The risk of events was nearly twice as great in diabetic patients compared to non-diabetic patients in the aspirin-only group.

Diabetes is a risk factor in the longer term, too. The Minnesota Heart Survey looked at survival post-MI in diabetic and non-diabetic men and women.[4] Among MI survivors discharged from hospital, the risk of death was 40% higher in diabetics after six years of follow-up (figure 2). This is a major challenge for cardiologists.

A paper from Scandinavia published last year cast interesting light on the subject. Norhammar *et al.* performed a glucose tolerance test in 181 individuals coming into the Coronary Care Unit who were not known to be diabetic.[5] By hospital discharge 35% were found to have impaired glucose tolerance and 31% to have (newly diagnosed) diabetes. This was not a case of stress-induced hyperglycaemia, since three months later, 40% of patients were found to have impaired glucose tolerance and 25% were found to have diabetes.

Not only are patients with known diabetes at increased risk: patients are at increased risk even before their glucose levels and their clinical symptoms and signs reach the stage of diagnosis of diabetes. This has been shown by the Nurses Health Study,[6] which looked at cardiovascular risk in a total of 117,629 female nurses who were free of diagnosed cardiovascular disease at baseline and who were followed up for 20 years. If the risk of cardiovascular disease for women who did not develop diabetes during the course of the study was 1.0, then the relative risk was 5.02 for those who had diabetes at baseline. For those who developed diabetes during the course of the study, the relative risk was 3.71, and the relative risk was 2.82 for those who became diabetic later on.

In most individuals, type 2 diabetes is part of the clustering of risk factors that is termed metabolic syndrome. There are many definitions of metabolic syndrome. The Adult Treatment Panel III of the National Cholesterol Education Program (NCEP) clinical definition of metabolic syndrome[7] states that metabolic syndrome is present when three or more of the following risk determinants are present:

- Abdominal obesity
- Raised triglycerides
- Low HDL
- Hypertension
- Raised fasting glucose (> 6.1 mmol/L) (> 110 mg/dl)

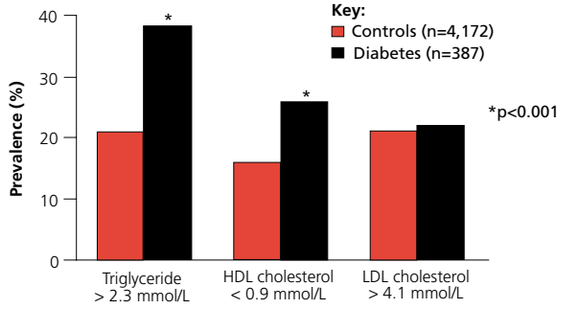
The World Health Organization definition also includes a measure of insulin resistance.

The problem with this definition is that it needs to be adapted to the population that is being dealt with – in the Far East, for example, it is unlikely that men would reach a waist circumference of 40 inches (101 cm) (the cutoff for the definition of abdominal obesity).

The prevalence of CHD in the US population over the age of 50 years in relation to diabetes and metabolic syndrome, using NHANES III data, is about 44% when rated according to NCEP criteria.[8] Those without metabolic syndrome, regardless of diabetes status, had the lowest CHD prevalence (8.7% without diabetes, 7.5% with diabetes). People with diabetes but without metabolic syndrome had a similar CHD prevalence compared to those without metabolic syndrome. Those patients who had metabolic syndrome without diabetes had 13.9% CHD prevalence, and those patients who had both diabetes and metabolic syndrome had the highest prevalence of CHD (19.2%) (figure 3).

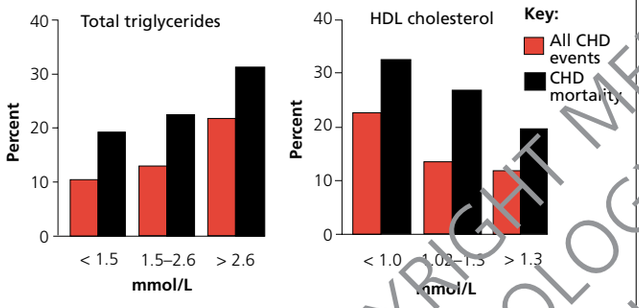
Thus the impact of cardiovascular disease is considerable in

Figure 4. Diabetic dyslipidaemia in the PROCAM study



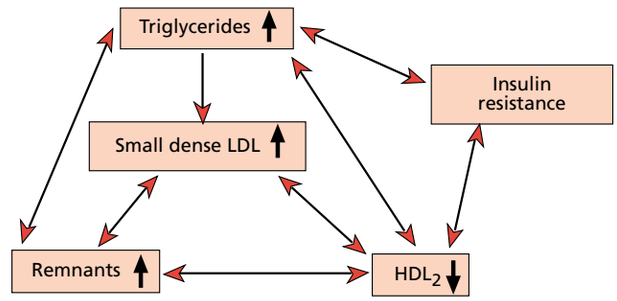
Adapted from Assmann G *et al.* (1994).[9]

Figure 5. Seven-year incidence (%) of CHD in type 2 diabetes



Adapted from Lehto S *et al. Diabetes* 1997;**46**:1354-9.[11]

Figure 6. Diabetic dyslipidaemia



patients with diabetes. There are many possible explanations for the premature excessive atherosclerosis that is seen in diabetes:

- Hyperglycaemia
- AGE proteins
- Oxidative stress
- Insulin resistance/hyperinsulinaemia
- Dyslipidaemia
- Hypertension
- Haemostatic abnormalities

Dyslipidaemia in type 2 diabetes is important because it is present at the time of diagnosis of diabetes, it persists despite best efforts at glycaemia control and it is a major cardiovascular risk factor. Its severity depends on genetic factors, diet and lifestyle, other primary and secondary dyslipidaemias, drugs, nephropathy and glycaemia control. It is extremely important to control dyslipidaemia in diabetic patients.

Figure 4 shows that LDL levels are not raised in diabetics compared to non-diabetics when dyslipidaemia is found. In the PROCAM study,[9] diabetics had an increased frequency of low HDL (that is, below 35 mg/dl, 0.9 mmol/L) and high triglycerides (TG) (here > 203 mg/dl, 2.3 mmol/L) in comparison to controls. (That is not to say that total cholesterol and LDL are not important risk factors in diabetes, just that plasma levels in diabetics do not differ greatly from those seen in controls.)

The accuracy of that statement is shown by data from the enormous Multiple Risk Factor Intervention Trial (MRFIT),[10] which followed up approximately 300,000 men. In this study about 5,000 men with diabetes were monitored to ascertain the relationship between serum cholesterol and 12-year cardiovascular mortality. It was found that, at each cholesterol level (< 4.7, 5.2–5.7, 6.2–6.7, and > 7.2 mmol/L; < 180, 200–219, 240–259 and > 280 mg/dl, respectively), the risk in the person with diabetes was two to three times higher than that in the person without diabetes.

TG and low HDL levels, particularly the HDL_2 subfraction, are also important factors affecting CHD risk in diabetic patients. Data from Finland on the seven-year incidence of CHD in type 2 diabetes[11] show that all CHD events and CHD mortality rise with increasing TG levels (figure 5). The HDL level is inversely correlated with, and predicts, risk: as HDL levels increase, all CHD events and CHD mortality decrease, and low levels of HDL are an important risk factor in patients with diabetes.

Figure 6 shows the characteristics of diabetic dyslipidaemia. Interestingly, qualitative changes in LDL are seen: although the total LDL as measured is the same, the LDL particle is altered and becomes smaller and denser. In addition, there is an accumulation of cholesterol-rich remnant particles.

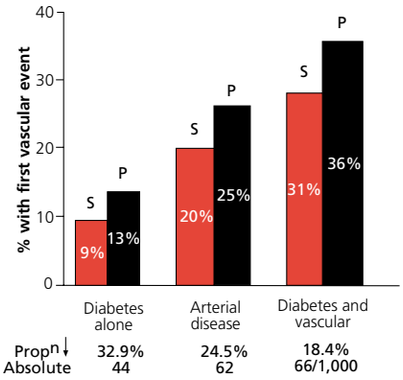
In the smaller LDL particles, there is less polar lipid than in large, buoyant LDL. This affects the accessibility of apo B-100, which is the major protein of LDL. In the more exposed region of apo B, there is a higher affinity for glycosaminoglycans (GAG). This is of particular interest because small dense LDL is more likely to bind to GAG when LDL penetrates the wall of the artery.[12]

The absolute concentration of LDL in itself can be misleading in subjects with small dense LDL. For a given plasma LDL level, the number of LDL particles is increased if they are small and dense. Each LDL particle contains one molecule of apo B, and therefore the apo B concentration increases in direct relation to the number of LDL particles.[13]

Table 1. CHD prevention trials with statins in diabetic patients: subgroup analyses

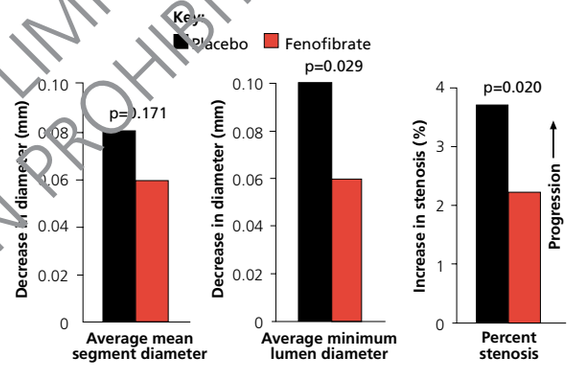
			CHD % RR	
			Overall	Diabetes
Primary prevention				
AFCAPS/TexCAPS	Lovastatin	155	37	43 (NS)
HPS	Simvastatin	2,913	24	20 (p<0.0001)
ASCOT-LLA	Atorvastatin	2,532	36	24 (NS)
Secondary prevention				
CARE	Pravastatin	586	23	25 (p=0.05)
4S	Simvastatin	202	32	55 (p=0.002)
LIPID	Pravastatin	782	24	19 (NS)
4S reanalysis	Simvastatin	483	32	42 (p=0.001)
HPS	Simvastatin	3,050		18.4 (<0.0001)
Overall				
ALLHAT	Pravastatin	3,648	9	11 (p=NS)

Figure 7. HPS: absolute benefit in cohort of diabetic patients



Adapted from *Lancet* 2003;**361**:2005-16.[15]

Figure 8. DAIS: angiographic changes



Adapted from *Lancet* 2001;**357**:905-10.[17]

HDL has been studied in some detail by groups in Finland.[14] In type 2 diabetes, there is characteristically a reduction in large HDL particles. The distribution changes from relatively high amounts of the larger HDL 2B and 2A particles seen in non-diabetics to relatively high amounts of the smaller HDL 3B and 3C particles in diabetics.

Thus the HDL is altered in composition in diabetic patients, particularly the HDL_2 fraction, and it is probably dysfunctional as well. How may it be dysfunctional, and thereby reduce the potential for all protective effects of HDL? Not only is HDL size decreased, but so is the number of HDL particles. This leads to a decreased residence time of HDL in the plasma, and decreased transport of antioxidative enzymes. Further, the apo A can be glycated, and this will affect its conformation and its binding to receptors. HDL in diabetes is probably dysfunctional in terms of its ability to be involved in reverse cholesterol transport. All this leads to an increase in risk of atherosclerotic disease.

Patient management

What are the consequences for treatment of diabetic patients? There is overwhelming evidence of benefit with statins in the non-diabetic population. Table 1 shows results from the primary and secondary CHD prevention trials with statins: in these trials, patients with diabetes have roughly the same benefit in terms of CHD reduction as individuals without diabetes. Results from the ALLHAT trial, which are included in the table, show that if there is not much effect on cholesterol (as happened in ALLHAT), then there is not much effect on risk. In the UK, the Collaborative Atorvastatin Diabetes Study (CARDS) has just been terminated prematurely because of overwhelming evidence of benefit from the statin.

Statins are clearly important in reducing risk, but diabetic patients remain at high risk even with statin treatment. The Heart Protection Study[15] showed the effects of simvastatin 40 mg/day on five-year rates of a first major vascular event – non-fatal MI, coronary death, stroke or revascularisation (figure 7). Among patients with diabetes and vascular disease, 36% of those on placebo treatment had a first vascular event, compared with 31% on statin alone. In individuals with diabetes alone, 13% of placebo-treated patients and 9% of statin-treated patients experienced a first vascular event.

In VA-HIT,[16] which used gemfibrozil, there was substantial benefit in the diabetic cohort using a drug that primarily increases HDL and lowers TG, with little effect on LDL. (Results were a 32% reduction in CHD events, a 41% reduction in CHD death, and a 40% reduction in stroke using the fibrate among the diabetic subgroup.) It seems that there is benefit beyond effects on LDL in patients with diabetes. Similarly, in the Diabetes Atherosclerosis Intervention Study (DAIS),[17] an angiographic study, fenofibrate was associated with less progression of the average minimum lumen diameter and percent stenosis in individuals with diabetes (figure 8).

Future directions

Clinicians are dealing with a very high-risk population when they treat diabetic individuals. Even those without symptomatic cardiovascular disease are at high risk, while those with symptomatic disease are at very high risk. The high risk persists despite statin therapy: the five-year risk of vascular events on simvastatin treatment in the Heart Protection Study remained at 31%. There is evidence of benefit through manipulating fractions other than LDL in diabetes, as has been seen from VA-HIT and DAIS. Combination therapy to improve the overall lipid profile by raising HDL and lowering TG has the potential to reduce vascular risk further in diabetes.

References

1. Wilson PWF, Kannel B. The Framingham Study. In: *Hyperglycaemia, diabetes and vascular disease.* Oxford: 1992.
2. Miettinen H, Lehto S, Salomaa V *et al*. Impact of diabetes on mortality after the first myocardial infarction. The FINMONICA myocardial infarction register study group. *Diabetes Care* 1998;**21**:69-75.
3. The Clopidogrel in Unstable angina to prevent Recurrent Events trial investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST segment elevation. *N Engl J Med* 2001;**345**:494-502.
4. Sprafka JM, Burke GL, Folsom AR, McGovern PG, Hahn LP. Trends in prevalence of diabetes in patients with myocardial infarction and effect of diabetes on survival. The Minnesota Heart Survey. *Diabetes Care* 1991;**14**:537-43.
5. Norhammar A, Tenerz A, Nilsson G *et al*. Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes: a prospective survey. *Lancet* 2002;**359**:2140-4.
6. Hu FB, Stampfer MJ, Haffner SM *et al*. Elevated risk of cardiovascular disease prior to clinical diagnosis of diabetes. The Nurses Health Study. *Diabetes Care* 2002;**25**:1129-34.
7. National Cholesterol Education Program Adult Treatment Panel III guidelines. www.nhlbi.nih.gov/guidelines/cholesterol
8. Alexander GM, Landsman PB, Teutsch SM, Haffner SM. NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants aged 50 years and older. *Diabetes* 2003; **52**:1210.
9. Assmann G, Schulte H. Relationship of HDL-C and triglyceride to incidence of atherosclerotic coronary artery disease (the PROCAM experience). *Am J Cardiol* 1992;**70**:733-7.
10. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-year cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 1993;**16**:434-44.
11. Lehto S, Ronnemaa T, Haffner SM *et al*. Dyslipidemia and hyperglycemia predict coronary heart disease events in middle-aged men with NIDDM. *Diabetes Care* 1997;**46**:1354-9.
12. Hurt-Camejo E, Camejo G, Peilot H, Oornik K, Kovanen P. Phospholipase A2 in vascular disease. *Curr Opin Lipidol* 2000;**11**:465-71.
13. Sniderman AD, Scantlebury T, Cianflone K. Hypertriglyceridemic hyperapo B: the unappreciated atherogenic dyslipoproteinemia in type 2 diabetes. *Ann Intern Med* 2001;**135**:447-59.
14. Syvanne M, Ahola M, Lahdenpera S. HDL subfractions in NIDDM and coronary artery disease. *J Lipid Res* 1995;**36**:573-82.
15. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5,963 people with diabetes: a randomised, placebo-controlled trial. *Lancet* 2003;**361**:2005-16.
16. Rubins HB, Robins SJ, Collins D *et al*. Diabetes, plasma insulin, and cardiovascular disease: subgroup analysis from the Department of Veterans Affairs HDL Intervention Trial (VA-HIT). *Arch Intern Med* 2002;**162**: 2597-604.
17. Diabetes Atherosclerosis Intervention Study investigators. Effect of fenofibrate on progression of coronary artery disease in type 2 diabetes: the DAIS study, a randomised study. *Lancet* 2001;**357**:905-10.

New strategies for raising HDL in daily practice: international recommendations

JOHN CHAPMAN

Abstract

Atherogenic lipid phenotypes characterised by low levels of high-density lipoprotein cholesterol (HDL) are common, and are typical of individuals with metabolic syndrome, type 2 diabetes, mixed hyperlipidaemia and hypertriglyceridaemia. It is recommended that low levels of HDL should be raised since interventional trials such as VA-HIT suggest a reduction in coronary heart disease events when HDL is raised.

Therapeutic options for raising HDL include monotherapy with statins, fibrates and niacin. The combination of extended-release niacin with a second lipid-lowering agent may offer new therapeutic possibilities.

Niacin inhibits adipose tissue hormone-sensitive lipase, leading to decreased free fatty acid flux to the liver. As a result, hepatic production of triglyceride-rich lipoproteins is decreased. Equally, the intravascular remodelling of LDL and HDL is normalised. Thus niacin could be helpful in conditions when dyslipidaemic parameters other than LDL need clinical attention.

Key words: high-density lipoprotein cholesterol, recommendations, statins, fibrates, niacin.

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Introduction

The low high-density lipoprotein (HDL) syndrome is highly prevalent. The North American NHANES III survey[1] indicated that 35% of adult men and 15% of adult women display a plasma HDL below 40mg/dl (1.04 mmol/L). Rubins and colleagues screened 8,500 patients from the Veterans Administration network in preparation for the Veterans Administration HDL cholesterol Intervention Trial (VA-HIT).[2] They observed that 63% of men in the coronary heart disease cohort displayed a low HDL level. Furthermore, the Cholesterol and Recurrent Events (CARE) trial[3] demonstrated that 40% of post-MI women also exhibited low HDL levels.

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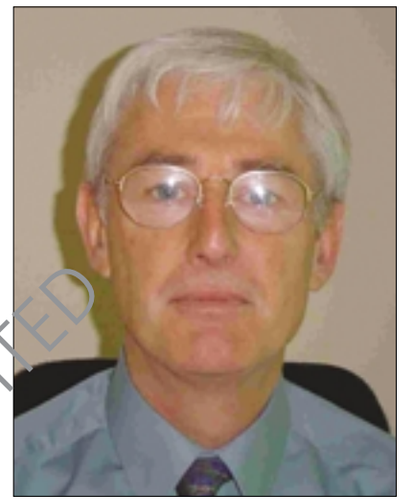
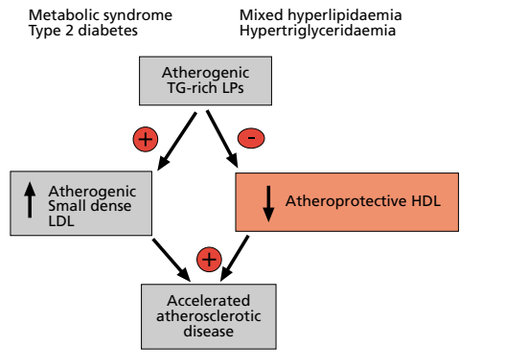


John Chapman

Figure 1. Low HDL phenotypes



Metabolic syndrome, type 2 diabetes, mixed hyperlipidaemia and hypertriglyceridaemia are all lipid phenotypes which occur frequently and in which one of the major characteristics is a low HDL level (figure 1). The metabolism of HDL is intimately linked to that of the apo B-containing lipoproteins. Indeed, it is established that elevated levels of triglyceride-rich lipoproteins are typically associated with elevated concentrations of atherogenic small dense LDL

Figure 2. Metabolic syndrome: definition of clinical criteria: NCEP ATPIII guidelines

Subjects displaying ≥ 3 criteria

- **Low HDL-C:**
  - **Men < 40 mg/dl (1.04 mmol/L)**
  - **Women < 50 mg/dl (1.29 mmol/L)**
- Abdominal obesity:
  - waist circumference: men > 102 cm; women > 88 cm
- Hypertriglyceridaemia: > 150 mg/dl (1.69 mmol/L)
- High BP: ≥ 130/85 mmHg
- High fasting glucose: > 110 (≥ 6.1 mmol/L) and < 125 mg/dl

Figure 3. Relation of CHD events to HDL achieved with gemfibrozil in the VA-HIT trial

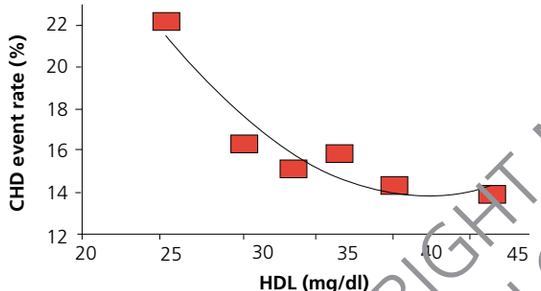


Figure 4. Therapeutic options for HDL raising across a wide range of low HDL phenotypes

Monotherapy: HDL elevation

Statins: ≤ 10% (CARE; HPS; LLA-ASCOT)
Fibrates: ≤ 10% (VA-HIT; DAIS; HHS)
Niacin (IR): up to 35%

Combination therapy: HDL elevation

Resin (colestipol) + niacin (IR):
+ 37% (CLAS-I) + 43% (FATS)
Statin + niacin (IR): + 30% (HATS)
Statin + fibrate: up to 25%
Statin + resin (colestipol): ≤ 15%

and, inversely, with subnormal levels of atheroprotective HDL. These three characteristics favour accelerated atherogenesis.

Low HDL is a key criterion of the metabolic syndrome as defined in the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III guidelines (figure 2).[4] For men the threshold is 40 mg/dl (1.04 mmol/L) and for women it is higher, at 50 mg/dl (1.29 mmol/L). In pre-menopausal women HDL is typically about 20% higher than that of males of a similar age, which explains the higher suggested threshold in the ATP guidelines.

In 2002, Frank Sacks and a number of other internationally recognised researchers made some key recommendations with respect to HDL-raising therapy, which were published in the *American Journal of Cardiology*.[5] This Expert Group recommended an HDL of 40 mg/dl (1.04 mmol/L) or greater as a goal for patients with cardiovascular disease and those without cardiovascular disease but at high global risk, and especially those presenting with type 2 diabetes or metabolic syndrome. These recommendations apply both to patients who do not require statins to reduce LDL, and equally to those on statin treatment.

Subsequently, the American Diabetes Association recommended in 2002 that optimal HDL levels for adults (both men and women) who present with type 2 diabetes should be greater than 45 mg/dl (1.15 mmol/L).[6]

What is the relationship between drug-mediated elevation in HDL and clinical benefit? Figure 3 depicts results from the VA-HIT intervention trial, in which the relationship of CHD events to HDL levels achieved on gemfibrozil treatment is shown in a population that consisted largely of individuals with metabolic syndrome. Dramatic clinical benefit was observed when HDL was raised from 20 mg/dl (0.51 mmol/L) or so up to the range 40–45 mg/dl (1.04–1.15 mmol/L). However, raising the HDL above 40 mg/dl (1.04 mmol/L) did not appear to bring significant additional benefit in this trial. This relationship is especially relevant in clinical practice given the fact that it specifically includes only those patients who took their medication. The results of the VA-HIT trial are consistent with the suggestion that an HDL target of 40 mg/dl constitutes a therapeutic target in this population.

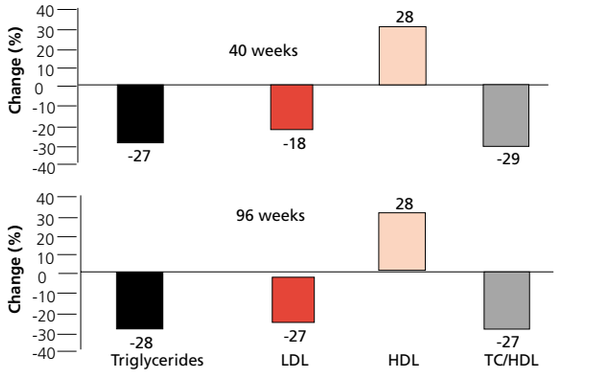
When interpreting such data, it is relevant that the profile of HDL particles induced by fibrates is distinct from the profile produced by statins, and therefore the clinical benefit resulting from HDL elevation in fibrate trials cannot be superimposed on that observed in clinical trials in which statins were used as lipid-lowering agents.

Therapeutic options for raising HDL

Therapeutic options for raising HDL are shown in figure 4. Monotherapy with statins typically raises HDL by less than 10%, as seen in CARE,[3] the Heart Protection Study[7] and the lipid-lowering arm of ASCOT.[8] In the major fibrate trials using gemfibrozil and fenofibrate, that is VA-HIT,[2] DAIS[9] and the Helsinki Heart Study,[10] there was an on-trial benefit approaching 10%. By contrast, monotherapy with the immediate-release formulation of niacin raises HDL by up to 35% in a number of different lipid phenotypes, according to 1980s data.[11]

With respect to combination therapy, the combination of the resin colestipol plus immediate-release niacin induced elevation of 37% in HDL in the CLAS-1 study[12] and a 43% rise in the FATS study.[13] In the HATS trial,[14] treatment with statin plus immediate-release niacin resulted in a 30% increase in HDL. Statin plus fibrate combinations have been shown to induce a < 25% rise in HDL, while association of statin plus resin typically results in a < 15% increment rise in HDL. Thus niacin rep-

Figure 5. Effect of Niaspan™ monotherapy (< 3 g/day) on lipid profile in hypercholesterolaemia



Adapted from Capuzzi *et al. Am J Cardiol* 1998;**82**:74U-81U

Figure 6. Metabolic basis of an atherogenic low-HDL phenotype

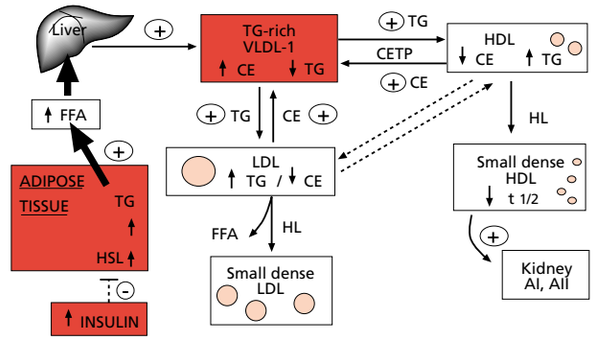
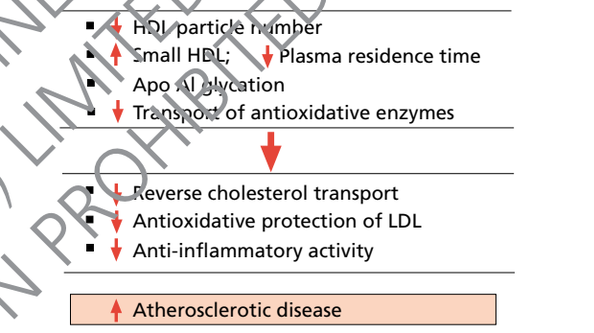


Figure 7. Dysfunctional HDL in type 2 diabetes



resents an interesting and efficacious therapeutic approach for raising HDL, especially in the context of combination therapy.

New developments in the pharmacology of niacin include the identification of high and low affinity receptors for nicotinic acid which are expressed primarily in adipose tissue and the spleen.[15,16] These receptors act to inhibit adenylyl cyclase, which results in diminution of cyclic AMP levels and the inhibition of the phosphorylation of a number of target proteins. In adipose tissue, for example, the phosphorylation of hormone-sensitive lipase (HSL) is attenuated, resulting in inhibition of enzyme activity and therefore of triglyceride hydrolysis.

Extended-release niacin (Niaspan™) as monotherapy has been shown to have satisfactory efficacy and safety.[17] For example, in a recent study in which Niaspan™ was used as monotherapy in hypercholesterolaemic individuals, a reduction of 28% in triglyceride levels over a 96-week period plus a 27% reduction in LDL levels was observed. In addition, the HDL levels were raised by 28% and, in turn, the TC:HDL ratio was reduced by 27% (figure 5).

Morgan *et al.* looked at the effects of Niaspan™ 2 g/day on lipoprotein subclass distribution in primary hypercholesterolaemia.[18] These studies revealed that large HDL_2 particles, which are rich in apo A1, were preferentially increased (by 75–89%) with niacin treatment, though intravascular remodelling of the more dense HDL_3 subclass also occurred. A major reduction in levels of atherogenic dense LDL was observed, involving a shift to more buoyant particles; in addition, a preferential reduction in large VLDL, i.e. VLDL-1, was documented.

How does niacin exert beneficial effects on HDL metabolism in atherogenic dyslipidaemia? The metabolic basis of an atherogenic low-HDL phenotype is represented in figure 6. Niacin inhibits hormone-sensitive lipase (HSL), and as a result the release of free fatty acids (FFA) by adipose tissue is attenuated. As a consequence, both hepatic synthesis of TG and hepatic secretion of VLDL are diminished, leading to reduction in the production of precursor VLDL particles for intravascular LDL formation. The core composition of LDL is normalised and there is a shift from small dense LDL to larger, more buoyant LDL. Under these conditions, a reduction in CETP-mediated transfer of triglyceride to HDL may result. Thus, niacin has a number of beneficial effects in the treatment of dyslipidaemia.

One of the key features of both type 2 diabetes and metabolic syndrome (figure 7) involves a reduced number of HDL particles, which are also dysfunctional as they exhibit decreased residence time in plasma and reduced transport of antioxidative enzymes. One of the major therapeutic goals for the future then will be normalisation of the biological activity of such dysfunctional HDL particles.

The mechanism of action of niacin on lipoprotein metabolism as we currently understand it can be summarised as follows:

- Inhibition of adipose tissue HSL, leading to decreased FFA flux to the liver
- Decreased production of TG-rich lipoproteins in the liver, notably large VLDL (i.e.VLDL-1)
- Normalised intravascular remodelling of LDL and HDL

Importantly, in *in vivo* turnover studies, Shepherd and colleagues [19] showed that the residence time of HDL is prolonged in the plasma of individuals treated with niacin, and that large HDL particles enriched in apo AI are preferentially formed. The HDL subfraction containing apolipoprotein A-1 without apolipoprotein

Figure 8. Effects of ER-niacin/statin combination in patients with combined hyperlipidaemia with low HDL (percentage changes)

	Niacin 2 g/day n=72	Rosuvastatin 10 mg/day Niacin 2 g/day n=72
TG	-26	-41
Non-HDL-C	-11	-38
LDL	-0.1	-36
Apo.B	-9	-34
HDL	+12	+24
Apo.AI	+7	+11

Adapted from Capuzzi *et al. Am J Cardiol* 2003;**91**:1304-10

A-II (LP-AI) may be more antiatherogenic than HDL particles containing apolipoprotein A-I and A-II (LP-AI + AII). In this context it is relevant that Sakai *et al.*[20] have recently shown that niacin selectively increases LP-AI compared with LP-AI + AII particle concentration in patients with low HDL levels. Such action appears to be mediated by decreased hepatic removal of LP-AI particles, which are more efficient in reverse cholesterol transport, suggesting an additional mechanism by which niacin mediates its antiatherogenic properties.

Very recently, Ganji *et al.*[21] demonstrated that niacin selectively inhibits the uptake/removal of HDL apolipoprotein A1-containing particles by human hepatocytes (Hep G2 cells) in an *in vitro* model.

Thus, the therapeutic goals in individuals with atherogenic low HDL dyslipidaemia, in order to normalise or decrease their accelerated atherogenesis, are reduction of both the concentrations of atherogenic cholesterol-rich lipoproteins, and hence cholesterol influx into the arterial wall, improvement of the anti-atherogenic function of HDL particles, and finally an increase in their concentration (that is, particle numbers). In this way, accelerated atherogenesis may be attenuated or even normalised.

The combination of niacin and statin provides additional antiatherogenic effects on blood lipids, improving levels of a number of lipid fractions. In a study by Capuzzi *et al.*[22] rosuvastatin 10 mg/day was added to extended-release niacin 2 g/day. The data shown in figure 8 reveal that HDL rose by 12% with niacin and by 24% upon treatment with niacin plus statin; TG levels fell by 26% and 41%, respectively, while the LDL level was reduced by 36% on statin treatment alone.

Conclusions

Atherogenic low HDL phenotypes are common, especially in individuals with premature coronary disease. International recommendations concur with respect to the importance of raising low HDL. Typically, extended-release niacin alone raises HDL levels as much as, or more than, other lipid-lowering agents used as monotherapy. Use of a combination of extended-release niacin plus statin together induces larger increases in HDL and apo AI than those seen with either agent given alone. This results in clinical benefit, as exemplified by the recent HATS clinical end point trial.

The combination of extended-release niacin and a second lipid-lowering agent may offer new therapeutic possibilities, though it must be borne in mind that more regular and frequent patient follow-up will be required.

References

1. NHANES III survey. www.cdc.gov/nchs/nhanes.htm
2. Rubins HB, Robins SJ, Iwane MK *et al*. Rationale and design of the Department of Veterans Affairs High-density lipoprotein Intervention Trial (VA-HIT) for secondary prevention of coronary artery disease in men with low HDL cholesterol and desirable LDL-C. *Am J Cardiol* 1993;**71**:45-52.
3. Sacks FM, Pfeffer MA, Moye LA *et al*. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. CARE trial investigators. *N Engl J Med* 1996;**335**:1001-09.
4. National Cholesterol Education Program Adult Treatment Panel III guidelines. www.nhlbi.nih.gov/guidelines/cholesterol
5. Sacks FM. Expert Group on high-density lipoprotein cholesterol. The role of HDL-C in the prevention and treatment of coronary heart disease: expert group recommendations. *Am J Cardiol* 2002;**90**:139-43.
6. American Diabetic Association. Management of dyslipidaemia in adults with diabetes mellitus. *Diabetes Care* 2002;**25**(suppl 1):S74-7.
7. 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**(9326):7-22.
8. Sever PS, Dahlof B, Poulter NR *et al*. Rationale, design, methodology and baseline demographics of participants of the Anglo-Scandinavian Cardiac Outcomes Trial. *J Hypertens* 2001;**19**:1139-47.
9. Diabetes Atherosclerosis Intervention Study investigators. Effect of fenofibrate on progression of coronary artery disease in type 2 diabetes: the DAIS study, a randomised study. *Lancet* 2001;**357**:905-10.
10. Frick MH, Elo O, Haapa K *et al*. Helsinki Heart Study: primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. *N Engl J Med* 1987;**317**:1237-45.
11. Saucan L, Brinton EA. LPAI and niacin. New views of an antiatherogenic duo. *Arterio Thromb Vasc Biol* 2001;**21**:1707-09.
12. Blankenhorn DH, Nessim SA, Johnson RL *et al*. Beneficial effects of combined colestipol-niacin therapy on coronary atherosclerosis and coronary venous bypass grafts. *JAMA* 1987;**257**:3233-40.
13. Brown G, Albers JJ, Fisher LD *et al*. Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. *N Engl J Med* 1990;**323**:1289-98.
14. Brown BG, Zhao X-Q, Clait A *et al*. Simvastatin and niacin, antioxidant vitamins and the combination for the prevention of coronary disease. *N Engl J Med* 2001;**345**:1583-92.
15. Tunaru S, Kero J, Schaub A *et al*. PUMA-G and HM74 are receptors for nicotinic acid and mediate its anti-lipolytic effects. *Nature Med* 2003;**9**: 352-5.
16. Wise. Molecular identification of high and low affinity receptor for nicotnic acid. *J Biol Chem* 2003;**278**:9869-74.
17. Capuzzi DM, Guyton JR, Morgan JM *et al*. Efficacy and safety of an extended-release niacin (Niaspan): a long-term study. *Am J Cardiol* 1998; **82**:74U-81U.
18. Morgan JM, Capuzzi DM, Guyton JR. A new extended-release niacin (Niaspan): efficacy, tolerability and safety in hypercholesterolaemic patients. *Am J Cardiol* 2003;**91**:1432-6.
19. Shepherd J. Effects of nicotinic acid therapy on plasma high-density lipoprotein subfraction distribution and composition and on apolipoprotein a metabolism. *J Clin Invest* 1979;**63**:858-67.
20. 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. *ATVB* 2001;**21**:1783.
21. Ganji SH, Kamanna VS, Kashyap ML. Niacin and cholesterol: role in cardiovascular disease (review). *J Nutr Biochem* 2003;**14**:298-305.
22. Capuzzi DM, Morgan JM, Weiss RJ *et al*. Beneficial effects of rosuvastatin alone and in combination with extended-release niacin in patients with a combined hyperlipidaemia and low HDL-C levels. *Am J Cardiol* 2003; **91**:1304-10.

Summary points

- HDL particles exert multiple antiatherogenic actions.
- Low HDL-C is a principal characteristic of type 2 diabetes and metabolic syndrome.
- There is strong evidence of clinical benefit when HDL is raised in atherogenic low-HDL dyslipidaemias.
- Minor (<10%) elevations in HDL-C induced by statins and fibrates have been associated with reductions in cardiovascular morbidity and mortality.
- Niacin induces marked elevation in HDL in low-HDL-C phenotypes.
- Combination therapy, using statin plus fibrate or statin plus niacin, exerts additive effects on the lipid profile and facilitates lipid management.
- Combination therapy takes advantage of complementary mechanisms of action, low doses and a potential reduction in side effects.
- Available evidence suggests that statin plus niacin combinations, as in the HATS study, induce not only regression of atherosclerosis but also reduction in cardiovascular events.