THE MANAGEMENT OF DYSLIPOPROTEINAEMIA IN LANCASTER

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INTRODUCTION

Over the last 20 years the importance of abnormal concentrations of lipoproteins in the plasma as risk factors promoting the development of atherosclerosis, and hence cardiovascular disease, has been well recognised largely as a result of prospective epidemiological studies on defined populations. More recently dietary and drug intervention has demonstrated improvement in plasma levels of lipids over the long term, leading to a fall in the incidence of new cardio-vascular disease and to a slowing of progression in that which already existed. These studies have not, so far, demonstrated a decrease in overall mortality in treated as against control groups of patients, but morbidity is reduced. The pharma-ceutical industry has responded to the challenge with new and very powerful agents which, together with existing ones, offer the possibility of considerable reduction in both cholesterol and triglyceride. It seems opportune, therefore, to consider the evidence so far available, and indicate how this is being applied to our practice in Lancaster.

HOW DOES ATHEROSCLEROSIS DEVELOP?

Atherosclerosis begins when cholesterol ester accumu-lates in macrophages in the subendothelial region of the arterial wall. The macrophages then become recognisable as foam cells and aggregates of these cells form a fatty streak, the first sign of cholesterol deposition in the arterial lining recognisable by naked eye. Progression occurs as the macro-phages secrete growth factors and other chemical mediators possibly provoking endothelial damage together with replication of smooth muscle cells in the wall of the vessel which then migrate into the lesion. There may be recruitment of inflammatory cells, for example T lymphocytes, and adhesion of platelets to the endothelium with subsequent release of further chemical mediators such as platelet-derived growth factor, among others, adding to the local response. It is this mixed humoral and cellular response which leads to permanent damage in the intimal and medial coats of the arterial wall with fibrosis and calcification in addition to deposition of cholesterol.

Cholesterol accumulation in macrophages appears to be promoted by high concentrations of certain types of lipoprotein particles in the blood (very low density lipoproteins, VLDL; intermediate density lipoproteins, IDL; and low density lipoproteins, LDL) and probably by lowered concentration of others (high density lipoproteins, HDL). Lipoprotein particles are the vehicles in which water-soluble cholesterol esters and triglycerides are transported in the circulation cloaked in a surrounding membrane with a hydrophilic outer surface and a lipophilic inner surface. Structural proteins, the apo-proteins, are incorporated into the membrane and act as markers which label the particles enabling them to bind to specific receptor sites on the surface of cells.

HOW DO ATHEROGENIC LIPOPROTEINS ARISE?

VLDL, IDL (endogenous) and LDL from the liver

VLDL together with its products in the circulation IDL (endogenous) and LDL, serve to transport two different types of lipid from the liver into the bloodstream and hence to other tissues. These are triglyceride which is a source of energy, and cholesterol ester, which is an essential component of cell membranes and a precursor of steroid hormones. The liver secretes VLDL particles, which are rich in triglycerides and esterified cholesterol, labelled with the structural protein apo-B_{100}. The triglycerides are removed from these particles by lipases in the endothelium of capillaries and the free fatty acids released are taken up by cells to be used as a source of energy or, in the case of adipose tissue, to be stored as fat. VLDL are thus converted to IDL (endogenous) which contain less triglyceride. These are further processed by the removal of most of the remaining triglyceride until they become LDL particles containing the residual cholesterol ester. The apo-B_{100} label on these particles is then recognised by a specific receptor which is present on the surface of most cells in the body. The number of receptors present on its surface increases when a cell is short of cholesterol and decreases when it has a surfeit. Hence at any one time LDL cholesterol is directed into those cells which need it. Liver cells also have B_{100} receptors and hence can themselves gauge the amount of circulating LDL, and adjust the output of VLDL to maintain an adequate supply.

This balance of supply and demand can be distorted. For example an excessive supply of nutrients to the liver, over and above that which it can store as glycogen or fat within the liver cells, will stimulate the secretion of VLDL simply to dispose of the calories by transporting them as fat into adipose tissue. This excess may result from taking too much energy-containing food or drink, or from liberating energy from fat stores, as for example in diabetic ketosis. The increase in VLDL output from the liver results in more IDL (endogenous) and LDL in the blood than is required to satisfy peripheral cells' need for cholesterol. The concentration of all three types of particle will thus rise. Other examples are provided when the apo-B_{100} receptors on the peripheral and liver cell membranes do not function correctly, either as a result of genetic defect or some subsequent degradation of the apo-B_{100} protein marker, for example by oxidation or by combination with other peptides. The efficiency with which peripheral and liver cells recognise the presence of LDL in the blood is diminished and the liver produces more VLDL and the concentration of LDL rises further. The common factor in all these situations is an increased concentration of lipoprotein particles particularly the LDL. This is thought to trigger an increased uptake by macrophages which cannot break down cholesterol so it accumulates to form foam cells and the process of atherosclerosis begins. The mechanism of the increased uptake by macrophages is the subject of some controversy.

IDL (Exogenous) Derived from Chylomicra

Chylomicra, the triglyceride-rich particles produced in the small intestine from absorbed dietary fat, are probably not themselves atherogenic. They are, however, stripped of much of their triglyceride during their passage through the circulation by endothelial lipoprotein lipase and converted to IDL (exogenous) particles which gain an apo-E label on their surface. This process is similar thus far to the maturation of VLDL particles liberated from the liver. However, the IDL (exogenous) are not converted to particles analogous to LDL, but are normally removed from circulation directly by liver cells which have a further specific apo-E receptor on their surface. If apo-E protein is genetically altered, as in Type III hyperlipidaemia, it may bind less efficiently to the receptor on the liver cell and IDL (exogenous) accumulate being then taken up by macrophages which again become foam cells.

WHAT IS THE ROLE OF HDL PARTICLES?

HDL, which are small dense particles containing the structural protein apo-A, may be secreted from the liver and the small intestine and may perhaps arise also from fragments breaking off the membranes of other lipoproteins as they are processed in the circulation. When first produced they contain very little lipid. However, they have a high affinity for a plasma enzyme, lecithin cholesterol acyl transferase (LCAT), which esterifies free cholesterol when activated by the apo-A_1 protein in the particle. A small amount of free cholesterol present in the plasma in equili-brium with that in cell and lipoprotein membranes is esterified and carried into the core of the HDL particles. Some may also be transferred into other lipoproteins such as VLDL or IDL (endogenous), thus increasing their cholesterol concentrations and assisting their conversion to LDL.

Recently it has been suggested that this mechanism may enable reverse cholesterol transport to take place out of macrophages. In vitro studies have demonstrated that HDL particles may attach to cultured cells in a way which suggests receptor-ligand binding, remove free cholesterol from the cell membranes and mobilise esterified cholesterol stored within the cells. This has been proposed as a model for the removal of cholesterol from macrophages and perhaps reduction of the amount of cholesterol in atherosclerotic lesions, with take-up by HDL particles and transfer back to the liver.

A SIMPLE CONCEPT OF ATHEROGENESIS

We have, therefore, a simple model for atherogenesis in which cholesterol from IDL (exogenous) and LDL particles is laid down in macrophages in the endothelial lining of arteries. In addition we have a simple model for the reversal of some of the components of the atherosclerotic lesion, namely the removal of cholesterol by reverse cholesterol transport with HDL particles as the vehicle. Stimulation of net removal of cholesterol from the established lesion at any stage of progression beyond the simpliest fatty streak may lead to an increase in the size of the lumen but will still leave a diseased arterial wall. Programmes for preventing atherosclerosis should, therefore, aim either to prohibit cholesterol uptake by macrophages in the first place or to promote the removal of cholesterol from foam cells before the lesion progresses.

This model could explain why the majority of epidemiological studies show that low HDL cholesterol is as significant a risk factor in the development of atherosclerosis as high LDL cholesterol. It must be said, however, that the reverse cholesterol transport hypothesis, though rapidly gaining ground, is not universally accepted.

HOW CAN WE ESTABLISH THE PRESENCE OF ATHEROGENIC LEVELS OF LIPOPROTEIN IN A PATIENT?

The risk of atherosclerosis is increased in patients with raised plasma levels of LDL, IDL and possibly VLDL concentrations and also with decreased HDL, especially the subfraction HDL_2. Means of estimating the concentration of each of these are available without recourse to time-consuming and expensive ultracentrifugation on density gradients. As always, however, laboratory results must be treated with caution as they can be subject to serious errors. These may include sampling error which may arise from day to day variation in the patient's actual blood concentration, systematic error arising from differences between laboratories using different methods and random error within a single laboratory. The combination of all three can produce differences as much as 2 to 3 mmol/l in total cholesterol in the same patient in different laboratories at different times. Errors like this can result in serious miscalculation of a patient's risk. It is sensible, therefore, to repeat lipid determinations two or three times before starting expensive or time-consuming treatment.

Total Cholesterol as a proxy for LDL Cholesterol Concentration

Much of the epidemiological data obtained relates total cholesterol rather than LDL cholesterol to atherosclerosis risk because the latter is more difficult to measure. The relationships are very similar and total cholesterol is a good proxy for LDL cholesterol. Several groups have examined these relationships and indicated the degree of risk associated with particular concentrations of total cholesterol. They have recommended strategies for treatment at certain levels, but these are not all mutually consistent. In Lancaster the categories shown in Table 1 are suggested as indicators of risks and guides to treatment. It is probable that above 8.5 mmol/l the risk rises more rapidly still as does the proportion of patients with inherited disorders of lipoprotein metabolism.

Risk Level	Risk Ratio	Range of Total Cholesterol (mmol/l)
Low	1	<5.2
Slight	1 – 2	5.2 – 6.5
Moderate	2 – 4	6.5 – 7.8
High	>4	>7.8

Table 1

Total Triglyceride as a Proxy for VLDL Triglyceride Concentration

The total triglyceride concentration in a sample of blood taken after an overnight fast (14 hours) is a good proxy for the concentration of VLDL triglyceride under most circumstances. Error can occur in patients with persistent chylomicronaemia or persistence of IDL (exogenous) particles but these can be distinguished in the laboratory. The risk of high VLDL is by no means as well defined as in the case of cholesterol, and it appears to affect women more than men. It has been difficult to separate this risk from that of a low HDL cholesterol since in most patients HDL cholesterol and VLDL triglyceride have a reciprocal relationship. It is suggested that the categories indicated in Table 2 be used as provisional indicators of risk in Lancaster.

Risk Level	Range of Total Triglycerides (mmol/l)
Low	<0.2
Slight	2.0 – 2.5
Moderate	2.5 – 5.0
High	>5.0

Table 2

Total Cholesterol and Total Triglycerides together as a Proxy either for an increase in both LDL or VLDL or for the Persistence of IDL (Exogenous) Particiles

If both total cholesterol and total triglycerides are raised in a fasting specimen at least two possibilities arise. The commonest is an increase in both LDL and VLDL particles, known as combined hyperlipidaemia. Less commonly there may be an accumulation of IDL (exogenous) particles arising from chylomicra in association with defects in the apo-E protein marker responsible for binding to the liver receptor prior to removal from circulation. This can often be resolved by electrophoretic separation of the lipoproteins in the laboratory.

HDL Cholesterol Determination as a Proxy for the Concetration of HDL Particles in Circulation

The relationship between HDL cholesterol and atherosclerosis is confused by two factors. In the first place the inverse relationship between HDL cholesterol and VLDL triglycerides in many patients has given rise to different interpretations, some preferring to stress the importance of low HDL cholesterol as the independent risk, and some the raised triglycerides. In the second place, methods commonly used in the USA to measure HDL cholesterol (heparin-manganese precipitation) give higher results than those used in the UK (phospho-tungstate-magnesium precipitation). Much of the epidemiological data using the former method, therefore, cannot be directly transferred to the United Kingdom. Table 3 attempts to reconcile this by allowing for the difference and also demonstrates the inter-relationship of total cholesterol risk and HDL cholesterol risk. Provided the HDL cholesterol is greater than 1.39, the total cholesterol is not a great risk unless it is grossly raised. On the other hand if the HDL cholesterol is below 0.86 a total cholesterol below 5.2 may well be a problem. Between these extremes the risks from high total cholesterol and low HDL cholesterol appear to interact. The data do not permit extrapolation beyond the limits of 4.0 and 7.5 for total cholesterol and 0.5 and 1.6 for HDL cholesterol because the number of subjects in follow up is too small.

		HDL cholesterol (mmol/l)			
		<0.86	0.86 – 1.10	1.11 – 1.39	>1.39
Total cholesterol mmol/l	<5.2	3.5	1	1	1
	5.2 – 5.9	3.5	1.5	1	1
	5.91 – 6.7	3.5	3.0	1.5	1
	>6.7	4.0	3.0	2.5	1

Table 3 – Risk ratio associated with combination of total cholesterol and HDL cholesterol

HOW DO WE TREAT PATIENTS WITH ATHEROGENIC LEVELS OF LIPOPROTEIN?

The place of dietary management

About 65% of the population of the UK have atherogenic levels of lipoprotein. Many of these will respond well to a diet and this must always be the first line of treatment. The main features of an appropriate diet are:

i) Reduction of total fat intake to provide about 30% of total daily calories.

ii) Reduction of the proportion of calories as saturated fat to 10% and its replacement with 10% mono-unsaturates (such as oleic acid in olive oil) and with 10% polyunsaturates (such as linoleic acid in soya bean oil and eicosopentanoic acid in fish oil).

iii) Reduction in the amount of cane sugar, and of alcohol if excessive, particularly when triglycerides are raised.

The aims of the diet are to restore the lipoprotein concentrations to the lowest possible risk and to reduce obesity if present. The stringency of the diet depends on the degree of dyslipoproteinaemia and on the degree of obesity. Patients with slight risk (total cholesterol 5.2-6.5, triglycerides 2-2.5, HDL cholesterol 1.11-1.39 and Body Mass Index (BMI) less than 25) may be permitted a modest reduction. Those with more severe risk (total cholesterol 6.5-8.5, triglycerides 2.5-5, HDL cholesterol less than 0.86 and BMI greater than 28) will need more severe reduction in saturated fat and calories. The dietetic changes should be accomplished in the primary health care setting with the help of dieticians in the more severe cases. Provided the patient adheres to the low fat diet, there is usually a steady improvement over a period of at least six and possibly twelve months. During this time regular follow-up every two or three months is helpful to encourage the patient to continue. If the lipids do not respond, the weight will show whether this is because of a diet-resistant hyperlipidaemia or because of non-compliance. The effectiveness of the diet is judged by the degree of lowering of total cholesterol and triglycerides, by the rise in HDL cholesterol and the fall in BMI. These should be as great as possible and preferably bring the lipids within the lowest risk ranges (total cholesterol less than 5.2, triglycerides less than 2, HDL cholesterol greater than 1.39 and BMI less than 25). If, after prolonged diet, these are not attained, drug treatment may be appropriate if the residual risks are great and at this stage specialist advice may be sought.

The Place of Management of Other Cardiovascular Risks Factors

At the initial consultation the presence of other risk factors must be assessed. These may be reduced, for example cigarette smoking, hypertension, obesity and idleness; alleviated, for example insulin resistance with or without frank diabetes mellitus; or accepted, for example male sex, advanced years and a personal or family history of cardiovascular disease. During the months of dieting these risks should be reduced as much as possible. If a patient stops smoking, dietary response may be less than good. This is acceptable in the short term because a non-obese smoker has a threefold greater risk of heart disease than an obese non-smoker, and giving up smoking may increase HDL cholesterol by up to 15%.

CONDITIONS ASSOCIATED WITH DIET-RESISTANT DYSLIPOPROTEINAEMIA

Not all patients who conform to a diet and lose weight respond with a sufficient lowering of blood fats during the initial six-month period. Sometimes this is associated with medical conditions such as hypothyroidism, nephrotic syndrome, chronic renal failure, diabetes mellitus or paraproteinaemias. When these are excluded the remaining patients usually have one of the many types of inherited

disorder of lipid metabolism. These are the cases most suitable for referral to a specialist clinic for investigation and initial drug treatment if appropriate. They are frequently associated with extreme levels of total cholesterol and triglycerides; hence the option must remain to refer cases with total cholesterol over 8.5 and triglycerides over 5 mmol/l for specialised advice immediately.

HOW CAN WE MANAGE DIET-RESISTANT DYSLIPOPROTEINAEMIA?

It is important to re-assess the remaining risks in patients who have not responsed to diet. These will comprise the levels of total cholesterol, triglycerides and HDL cholesterol on a fasting specimen of blood together with the presence of the other remaining risk factors such as male sex, advanced age, presence of established vascular disease in the patient or close relative, diabetes mellitus, uncontrolled hypertension or continued cigarette smoking. These risks multiply rather than summate when combined together, hence the total risk to a patient may be very significant indeed. If no other risk factor is present save for residual hypercholesterolaemia, drug treatment may only be advised if the levels are relatively high. On the other hand if many risks are present, even a mild degree of hyperlipidaemia might be worth treating. In principle the risks of drug therapy must be judged against the risks of doing nothing and only if the balance of risk is firmly in favour should drugs be offered. There is great danger of using even relatively safe drugs on a large population since uncommon side effects will then have a significant prevalence. If a decision is made to use a drug, the safest one which is appropriate to the lipoprotein abnormality should be used, starting with the smallest possible therapeutic dose. If complete control is not established it should be increased at three-monthly intervals until maximum dose is achieved. If control cannot be achieved another drug may be substituted or an additional one introduced in combination. Combination therapy must be chosen carefully to avoid possible interactions between the two drugs.

WHAT DRUGS ARE AVAILABLE FOR TREATING DYSLIPOPROTEINAEMIA?

There are seven types of drug which may be used to treat hyperlipidaemia. Four act mainly on LDL cholesterol (resins, HMG-CoA reductase inhibitors, probucol, and neomycin) and three mainly on VLDL and IDL triglycerides (fibrates, nicotinic acid-like compounds, and fish oils). Some of these may increase HDL cholesterol (resins, HMG-CoA reductase inhibitors, fibrates and nicotinic-like compounds), some may decrease it (probucol).

Ion Exchange Resins

Colestipol and cholestyramine act by binding bile acids in the intestine and preventing recirculation through the biliary system. The liver cells respond by converting more cholesterol into bile acids, producing a relative cholesterol depletion. The number of B_{100} receptors on their surfaces then increases and more LDL particles are captured from circulation in the plasma thus reducing total and LDL cholesterol. Even if the receptors or the apo-B_{100} marker are altered to reduce their mutual affinity it may be partially compensated by the increase in the receptor numbers. These drugs will produce a lowering of up to 20% in total cholesterol but in some patients this requires high dosage which may be associated with constipation and sometimes dyspepsia.

These drugs are remarkably free of toxic side effects, though they often provoke an increase in VLDL triglycerides. They are considered safe in children, pregnant women and women who may become so.

HMG-CoA Reductase Inhibitors (Statins)

Lovastatin, pravastatin and simvastatin are drugs which produce competitive inhibition of the rate limiting step in cholesterol synthesis in the body.

These are usually formulated to confine their action to the liver as much as possible, this being the source of plasma cholesterol. They produce relative cholesterol depletion and hence an increase in the LDL receptor numbers on liver cell surfaces, as do the resins, with resulting increase in LDL uptake and reduction in plasma cholesterol.

They are highly effective, producing a reduction of up to around 40% in total cholesterol and they are easy to take. In some cases they provoke morning headaches but most patients tolerate them easily.

The drugs have been found to be relatively free of serious side effects over a period of two to four years but raised liver enzymes (AST, ALT and GammaGT) and muscle enzymes (CK) occur in a few patients. Rarely severe hepatic damage and severe myopathy have been noted with one death due to rhabdomyolysis when one of the drugs was used together with cyclosporin.

They are not suitable for administration to women who are pregnant or who are likely to become so as they may be teratogenic. They are licensed for administration to patients with a cholesterol greater than 7.8 and who do not respond to other treatments or are intolerant of them. They may well remain reserved for those severe cases who do not respond to other drugs particularly in late middle aged patients, until their long term safety becomes more apparent.

Proubcol

This drug may lower cholesterol by up to 20% in hypercholesterolaemic subjects but its mode of action is not fully understood. It probably becomes involved in the cell and lipoprotein membranes and may act as an anti-oxidant preventing damage to the apo-B protein. It certainly seems to accelerate the apo-B receptor mediated removal of LDL cholesterol in plasma and to reduce its deposition into macrophages.

The drug is easy to take but may produce diarrhoea, flatulence, abdominal pain, nauseau and vomiting. This often remits and it is rare for the patient to have to discontinue therapy.

Its safety in pregnancy is not certain, hence it must be given to women only in association with adequate contraception. It must be discontinued at least six months before a planned pregnancy because of its long half life in the body.

It may also be associated with prolonged QT intervals in the ECG and is not recommended for patients with recent myocardial damage, dysrhythmia, or heart block.

It does produce lowering of HDL cholesterol often of a disconcerting degree but despite this xanthelasmata and xanthomata often become less conspicuous.

Neomycin

Long term administration of neomycin by mouth can lower cholesterol in familial hypercholesterolaemia by up to 30% by precipitating cholesterol in the intestinal lumen. It always affects the LDL cholesterol particularly but sometimes it may lower HDL cholesterol. It frequently produces nausea and diarrhoea especially in the long term. It is, however, one of the only two drugs which will lower the concentration of a potentially atherogenic modification of LDL particles, Lp(a).

Fibrates

Bezafibrate, clofibrate, fenofibrate and gemfibrozil are the representatives of these drugs currently available in the United Kingdom. They are thought to have slight HMG-CoA reductase inhibiting properties rather like the statin drugs but to a much lesser degree. Some may also inhibit the synthesis of fatty acids in the liver. They all stimulate lipases in the endothelium of blood vessels thus speeding the maturation of VLDL and LDL and may result in an LDL particle containing even less triglyceride than usual, which is more easily cleared by apo-B_{100} receptors.

They are extremely effective in reducing VLDL particles and often produce a consequent rise in HDL cholesterol. Probably because of the more rapid clearing of LDL particles, bezafibrate, fenofibrate and gemfibrozil also reduce LDL particles and hence total cholesterol concentration. They are also effective in reducing fibrinogen in plasma, perhaps reducing the tendency of thrombosis to occur.

They are well tolerated but may produce gastro-intestinal side effects such as nausea and abdominal distention, impotence and myosits. Clofibrate is associated with an increase in gallstones.

Animal studies have shown that high dosage of fibrate drugs may provoke development of liver tumours and its degree of teratogenicity is not clear, hence they are best not used in pregnancy.

Nicotinic Acid-like Compounds

Nicotinic acid, nicofuranose and a cipimox are the members of this group available in the United Kingdom. They act by reducing the availability of free fatty acids from adipose tissue and depriving the liver of raw materials to construct triglycerides and hence VLDL. They also result in an increase of HDL_2 cholesterol probably by decreasing breakdown, and also reduce the concentration of Lp(a) as does neomycin.

Unfortunately these are not always well tolerated, being associated with flushing, though this may be reduced by taking aspirin prior to taking the drug. They also may produce skin rashes, gasto-intestinal effects, increased uric acid, hyperglycaemia and liver damage, and in some cases severe hepatic necrosis has been described particularly after self-medication.

Fish Oils

Oily fish contains triglycerides rich in long chain polyunsaturated fatty acids with the ω3 confirmation as distinct from ω6 in polyunsaturated vegetable oils. These have the property of lowering triglycerdes in plasma as a result of reduction in VLDL synthesis in the liver, reducing plasma fibrinogen concentration, altering platelet function with reduced stickiness, and stimulating the production of prostaglandins, prostacyclines and thromboxanes of unusual structure which are less damaging to endothelium than normal. These may together act to reduce atherosclerosis and thrombosis. However, some authorities claim that these oils may be harmful because they may easily by auto-oxidised in vivo to form toxic products, while others point to the increase in LDL cholesterol levels usually seen when patients take them. Their place in the management of hyperlipidaemia remains uncertain.

WHAT DRUGS SHOULD WE USE IN TREATMENT OF HYPERLIPIDAEMIA?

If the disorder is predominantly of total and LDL cholestrol (Type IIA) resins are the first drug choice because of their proven effectiveness and safety record. If the disorder is predominantly of VLDL triglycerides or IDL (exogenous) triglycerides (Type IV and Type III) the fibrates are the drug of choice. If the disorder is associated with raised cholesterol and triglycerides the choice is open between resins and fibrates with the final choice depending on which appears to be the greater problem, the cholesterol or the triglycerides, after an appropriate period of dieting.

It is preferable to reserve probucol for combination therapy in resistant cases of hypercholesterolaemia and fish oils for combination therapy in resistant hypertriglyceridaemia not associated with high LDL cholesterol. Nicotinic acid-like compounds may be used in combination therapy with cholestyramine in Type IIA and IIB hyperlipoproteinaemia, and in combination with fibrates in Type IIB and Type IV hyperlipoproteinaemia. The frequency with which flushing occurs may make this drug unpopular with patients.

The place of HMG-CoA reductase inhibitors at the moment is in the management of patients with cholesterol over 7.8 mmol/l who do not respond to other forms of treatment or who cannot tolerate them. These indications may become much more liberal as experience with the drugs accumulates and their long term safety is proved.

WHAT IS TO BE GAINED BY TREATING HYPERLIPOPROTEINAEMIA?

Between 1960 and 1980 the average cholesterol in the USA declined by about 0.7 mmol/l in association with changes in dietary habits. Since 1968 there has been a 30% reduction in coronary heart disease mortality with a similar reduction in its incidence. More formal trials of lipid lowering strategies have been carried out over the last 20 years. These have included primary prevention trials, in which subjects have no previous history of coronary heart disease prior to entry in the study, and secondary prevention trials in which subjects who have had previous coronary heart disease are specifically recruited. The primary prevention studies have included ones in which diet alone was used and others in which diet was used together with various drugs (clofibrate, cholestyramine and gemfibrozil) used singly. All produced a lowering of cholesterol between 9 and 20%, some with lowered triglyceride, some with raised triglyceride, and some with increased HDL cholesterol. They all produced a lowering of mortality from coronary heart disease ranging from 19 to 45%. None produced a reduction in total mortality. The clofibrate trial produced an increase in total mortality from all causes by 25%.

Secondary prevention trials have used nicotinic acid alone and nicotinic acid with clofibrate. These have demonstrated a

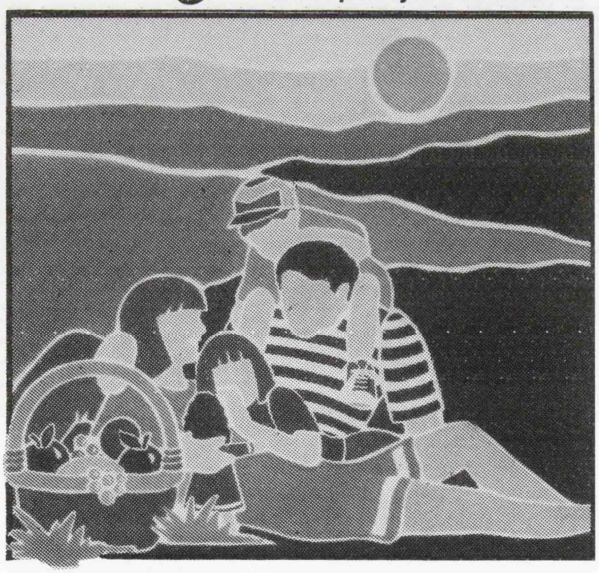
fall in total cholesterol of between 9 and 13% and falls in triglycerides of between 19 and 27%. There was a reduction in coronary heart disease mortality of 12 to 36% and a fall in total of all cause mortality of between 11 and 26%. A further series of trials conducted more recently has examined the effect of lipid lowering agents on angiographic appearance of coronary arteries. One study demonstrated that progression of lesions was reduced from around 30% in the control subjects treated with diet alone to around 10% in subjects treated with diet plus cholestyramine. In the second study colestipol was used with nicotinic acid, and the number of cases demon-strating progression fell from nearly 60% in the control group to 40% in the treated group. In this study regression occurred and increased from 2% in the control group to 16% in the treated group.

CONCLUSIONS

There is strong evidence for the thesis that certain plasma lipoproteins act as risk factors for the development of atherosclerosis and coronary heart disease in the population at large. There is epidemiological evidence that long term modification in diet can reduce the risk from these lipoproteins and can influence the incidence of coronary heart disease in populations. There is further evidence that drug treatment which will further reduce the lipoprotein risk can produce significant reduction in coronary heart disease to the extent that 1% fall in total cholesterol, and 1% rise in HDL cholesterol, will each provoke a 2% reduction in coronary heart disease incidence in a trial group as compared with controls. There is evidence in patients who have already had a myocardial infarction, that treatment with lipid lowering drugs will reduce the subsequent incidence of a second myocardial infarction and will reduce all cause mortality in the group. There is further evidence that treatment with lipid lowering drugs will slow progression of established arterial disease demonstrated on coronary artery angiography, and in some cases will result in regression.

Unfortunately the examination of all risks only increases the probability that an individual patient will have coronary heart disease at some time in the future. The degree of certainty remains poor. Approximately 60% of all myocardial infarctions in the country will be drawn from fairly high risk groups but 40% will not. Equally a considerable number ascribed to a high risk group will not develop coronary heart disease. We desperately need more precise indicators of risk so that we can know which patients require treatment and which can be left with mild non-pharmacological risk reduction manoeuvres. Further research is required into the cause and natural history of both atherosclerosis and thrombosis. In the meantime it seems likely that there are benefits to be gained if, as a population, we adopt simple manouevres to reduce our risks, for example by not smoking, by eating sensibly and by controlling blood pressure and blood fats where appropriate. We must, nevertheless, always remember our prime aim which is to do no harm to patients.

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