Management of hyperlipidaemia

Why, when and how to treat

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Introduction

For the last 50 years, there has been a seemingly endless debate in scientific, clinical and epidemiological journals and conferences round the world about the 'lipid hypothesis' and the role of cholesterol in the pathogenesis of coronary heart disease. Evidence accumulated in recent years has dispelled much of the earlier controversy and we can now conclude that the presence of atherogenic lipoproteins in the plasma is central to the causation of coronary heart disease.

Atherosclerosis and coronary heart disease

The data incriminating raised concentrations of plasma low density lipoproteins in the pathogenesis of atherosclerosis, and hence coronary heart disease, are overwhelming and come from experimental, genetic, epidemiological and clinical evidence.

For many years it has been recognised that induction of atherosclerosis occurs in experimental animals as a result of raising plasma low density lipoproteins. High concentrations of plasma low density lipoproteins in individuals who are homozygous or heterozygous for familial hypercholesterolaemia, where there are reduced or absent low density lipoprotein receptors on cell membranes, leads to accelerated and severe coronary atherosclerosis and premature coronary heart disease. There is a persuasive and consistent positive epidemiological relationship between raised low density lipoproteins in communities with a high incidence of coronary heart disease in contrast to those with a low incidence. Finally, individuals with raised plasma low density lipoproteins have an increased relative risk of coronary heart disease.

Of course, there are many unanswered questions. We still do not know how raised low density lipoproteins in the plasma leads to atherosclerosis. What evidence we have suggests that the process begins with penetration of low density lipoproteins from the arterial lumen through the endothelium where oxidation occurs with uptake by monocyte-macrophages. The influences that favour oxidation, the involvement of unstable longchain polyunsaturated fatty acids, liable to undergo peroxidation, and the role of locally available antioxidants are all under active investigation. The importance of inflammatory responses, and the role of cytokines in the macrophage-endothelial interactions, have yet to be resolved.

We do not yet understand the factors influencing the high density lipoprotein-dependent reverse transport system and the mechanisms through which cholesterol leaves the arterial wall; how are extracellular crystals of cholesterol mobilized and removed from the endothelial space; what is the role of apoprotein A1 and of the cholesterol transferase proteins in promoting this efflux; and how might high density lipoprotein be raised pharmacologically?

In the light of the results of recent clinical trials, these uncertainties should not be seen in any way as an obstacle to establishing and implementing interventional strategies to reduce raised low density lipoproteins concentrations in those with overt coronary heart disease and those at risk for coronary heart disease.

Why treat hyperlipidaemia?

While these questions will provide research programmes for years to come, there is sufficient strong evidence to make clear recommendations for the management of hyperlipidaemia with the likelihood that a greater degree of prevention of coronary heart disease will be possible than ever before. The evidence comes from three
sources — regression trials, a definitive secondary prevention trial and a new and seminal primary prevention trial.

Atheroma regression trials

There can no longer be any doubt that marked reduction of raised plasma low density lipoprotein cholesterol slows progression and induces regression of coronary atheroma in coronary heart disease patients, albeit a minority. The 12-year outcome of the POSCH study\(^\text{[1]}\), which used regional ileal bypass surgery to reduce hypercholesterolaemia, is particularly convincing with clear angiographic and clinical benefits. The results of several shorter regression trials\(^\text{[2-3]}\) using statins support the results of the POSCH trial. The extent of the changes is small, however, and amount to improvements of 0.1-0.2 mm or less in minimal and mean arterial diameters; this needs to be judged in the context that a 50% arterial occlusion equals about 2 mm intrusion into the lumen and they take some years to become evident. Not all the regression trials have demonstrated a concurrent clinical benefit. Most have been too small and were not designed with the statistical power to demonstrate a result in clinical events; in general, the smaller the trial and the less well it was blinded the quicker the apparent improvement. The large clinical trials suggest that benefit of cholesterol-lowering occurs earlier than might be expected from some of these regression trials. Marked reduction of low density lipoprotein concentrations may also lead to relatively rapid improvement in endothelial function\(^\text{[6]}\) and less platelet adhesiveness\(^\text{[7]}\) as well as increased stability of vulnerable lesions.

Secondary prevention trial

A randomized clinical trial, the 4S\(^\text{[8,9]}\), was conducted over a period of 5-4 years in 4444 patients with angina pectoris or previous myocardial infarction, serum cholesterol 5.5–8.0 mmol. l\(^{-1}\) (210–310 mg. d.l\(^{-1}\)) and serum triglycerides ≤ 2.5 mmol. l\(^{-1}\) (c 220 mg. d.l\(^{-1}\)). This study demonstrated that, compared with placebo-treated patients, simvastatin (20 mg daily in 63% and 40 mg daily in 37% of patients) produced a 30% reduction in the relative risk of deaths from all causes (\(P=0.0003\)), a 42% risk reduction in deaths from coronary heart disease (\(P<0.00001\)), a 34% risk reduction in coronary heart disease morbidity (\(P<0.0001\)) and a 37% risk reduction in myocardial revascularization procedures (\(P<0.00001\)). The reduction in risk of major coronary heart disease events was similar in patients with previous myocardial infarction as in those with angina only, was the same in men and women and independent of age up to 70 years.

The mean changes in total cholesterol, low-density lipoprotein cholesterol, triglycerides and high-density lipoprotein cholesterol were −25%, −35%, −15% and +8% respectively.

Primary prevention trials

The first long-term primary prevention trial (the West of Scotland Study\(^\text{[10]}\)) using a statin was conducted in 6595 hypercholesterolaemic 45-65-year-old men over a mean period of 4.9 years. Most men were otherwise healthy, none had previous myocardial infarction and only 5% had self-reported stable angina on admission to the trial. Randomization was made between pravastatin 40 mg daily and placebo. The criteria for entry to the trial comprised low density lipoprotein cholesterol concentrations >4.0 mmol. l\(^{-1}\) (c 155 mg. d.l\(^{-1}\)) at both key screening visits, or >4.5 mmol. l\(^{-1}\) (c 175 mg. d.l\(^{-1}\)) at one of these screening visits, but <6.0 mmol.l\(^{-1}\) (c 230 mg. d.l\(^{-1}\)). Pravastatin reduced total cholesterol by 20%, low density lipoprotein cholesterol by 26%, triglycerides by 12% and high density lipoprotein cholesterol rose by 5%. There were no side-effects or adverse reactions.

In the pravastatin-treated group the risk of coronary heart disease death or non-fatal myocardial infarction, and non-fatal infarction alone, were reduced by 31% (\(P<0.001\)); deaths definitely due to coronary heart disease were reduced by 28% (\(P=0.13\)) and from all causes by 22% (\(P=0.051\)); and the need for coronary angiography was reduced by 31% and PTCA or CABG by 37% (\(P<0.001\)). The clinical benefits of pravastatin treatment were equivalent in the 84% without and the 16% with prior vascular risk.

The West of Scotland primary prevention trial is the fifth long-term randomized study to show benefit from reducing hypercholesterolaemia in healthy men at high risk for coronary heart disease. The results of the Los Angeles Veterans diet trial\(^\text{[11]}\), the WHO clofibrate trial\(^\text{[12]}\), the Lipid Research Clinics cholestyramine trial\(^\text{[13]}\) and the Helsinki Heart trial\(^\text{[14]}\) using gemfibrozil all pointed in the same direction but used measures which reduced low density lipoprotein cholesterol by less than half that of the statins.

When to treat?

There is a degree of artificiality in distinguishing between recommendations for primary and secondary prevention, since an apparently healthy man today may have a myocardial infarct tomorrow. Therefore, advice as to when treatment should be initiated is also somewhat artificial but separating the recommendations for primary prevention from those for secondary prevention serves the purpose of emphasizing two problems: the potential for over-treatment of people without coronary heart disease and that of under-treatment of those with manifest coronary heart disease. Now that safe and effective cholesterol-lowering treatment is available the key issue is when to employ it in these two groups of people. Figure 1 summarises our main recommendations. The role of dietary treatment is always pivotal and will be considered in detail below.
conclusions concerning the benefits of treatment of hypertriglyceridaemia. The ratio is particularly useful and, when over 5, treatment should be considered. Women, as are their total cholesterol and low density levels are usually higher in plasma. Evidence suggests that they should also benefit. Plasma hypercholesterolaemia in women, but circumstantial disease. *Statins for hypercholesterolaemia; fibrates for hypertriglyceridaemia.

**Primary prevention**

Individuals with genetically-determined hyperlipidaemias associated with a high coronary heart disease risk should be treated vigorously with lipid-lowering drugs and strict diets. Those with secondary hyperlipidaemias, related to hypothyroidism, diabetes, renal and liver diseases, require specific management of the primary condition. As emphasized in the recommendations of the Task Force of the European Society of Cardiology, the European Atherosclerosis Society and the European Society of Hypertension, treatment decisions in people without coronary heart disease should be based on an assessment of their total coronary heart disease risk and not only on plasma lipid and lipoprotein concentrations.

Treatment with a statin should be considered for men with additional risk factors and a raised plasma low density lipoproteins level (>4 mmol. l⁻¹ or >155 mg. dl⁻¹). But the question of whether or not men who have plasma cholesterol concentrations of >5.5 mmol. l⁻¹ (or low density lipoproteins cholesterol >4 mmol. l⁻¹ or a total cholesterol/HDL ratio >5) without additional coronary heart disease risk factors should be treated with statins is not settled and will depend on the likely cost–benefit to the individual. Overall, there will be a saving of about eight lives per 1000 over a 5 year period. The cost–benefit of statin therapy is lower in the absence of other risk factors and, in the West of Scotland trial, individuals who had raised levels of low density lipoproteins alone did not reach the threshold required (20% risk over 10 years) to merit lipid-lowering drug therapy, according to the new European guidelines.

At present, there is insufficient data to reach conclusions concerning the benefits of treatment of hypercholesterolaemia in women, but circumstantial evidence suggests that they should also benefit. Plasma high density lipoprotein levels are usually higher in women, as are their total cholesterol and low density lipoproteins levels after the menopause. Therefore, the total cholesterol/high density lipoprotein cholesterol ratio is particularly useful and, when over 5, treatment should be considered.

No clinical trial data are available concerning the benefit of lipid lowering in the elderly without coronary heart disease.

**Secondary prevention**

All patients, men and women, should have their serum cholesterol measured in a standardized laboratory after the development of angina or myocardial infarction. Serum total cholesterol, low density lipoproteins and high density lipoproteins may be as much as 15% below the usual concentrations within 24 h and this decrease may persist for as long as 3 months. But analysis of these lipids within 24 h of the acute event is likely to reflect accurately the preceding concentrations.

The post-infarction dip in plasma cholesterol presents the physician with two practical problems. One is that the impact of advice to the patient to lower his or her cholesterol may be attenuated if high levels cannot be demonstrated. More important is the fact that, by the time the lipid levels have recovered, the patient will usually have left the immediate care of the hospital physician and, by default, may not have adequate follow-up of this key element of coronary risk. For this reason, hospital physicians and their associated primary care physicians should establish an appropriate shared prevention strategem.

Measurements of plasma lipids should be done at least twice before commencing any treatment. One analysis, carried out on a fasting specimen, should include estimation of high density lipoprotein concentration and fasting serum triglycerides. A calculated value for low density lipoproteins cholesterol can then be obtained by the Friedewald equation:

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\text{Low density lipoproteins cholesterol (mmol. l}^{-1}) = \text{total cholesterol} - \text{high density lipoprotein cholesterol} - 0.45 \times \text{triglyceride (mmol. l}^{-1})
\]

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\text{Low density lipoproteins cholesterol (mg. dl}^{-1}) = \text{total cholesterol} - \text{high density lipoprotein cholesterol} - 0.02 \times \text{triglyceride (mg. dl}^{-1})
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All male and female patients below the age of 70 with angina or myocardial infarction and serum cholesterol >5.5 mmol. l⁻¹ (210 mg. dl⁻¹) or low density lipoproteins cholesterol >4 mmol. l⁻¹ (155 mg. dl⁻¹) should be treated indefinitely with a statin. An exception may be those in heart failure, when the prognosis is determined by impaired ventricular function. The number of patients who develop coronary heart disease above the age of 70 is large, particularly in women. For these patients, in the absence of triad evidence, treatment decisions should be made not only on the estimated risk of a recurrent coronary heart disease event but also on their overall cardiac status and the possible presence of other illnesses which may limit prognosis.
How to treat?

**Diet and exercise**

Guidelines on primary and secondary prevention of coronary heart disease recommend that diet should be tried first and those needing lipid-lowering drugs should continue on dietary therapy. Promotion of weight loss in overweight persons by eliminating excess calories and increased physical activity is particularly important. Regular physical activity in normal weight individuals is also recommended in these guidelines. Weight reduction enhances the effect of dietary therapy on low density lipoprotein cholesterol levels, and has other benefits such as reduction of triglycerides and blood pressure, and improvement of glucose tolerance.

The Step 1 diet recommended by the American Heart Association, the U.S. National Cholesterol Education Program and the European expert group aims to reduce the dietary intake of fat to 30% or less of total energy, the intake of saturated fat to no more than one third of total fat intake and the intake of cholesterol to less than 300 mg daily. Reduced saturated fat intake should in part be substituted by an increase in mono- and polyunsaturated fats. The more intensive Step 2 diet aims at further reduction in saturated fat intake to less than 7% of total energy and a dietary intake of less than 200 mg daily.

Plasma cholesterol reductions in response to Step 1 and Step 2 diets have been well documented in metabolic ward studies and, under strictly controlled conditions, they have corresponded with predictions from dietary changes. But long-term compliance with these diets has proved to be a great problem. Thus, Step 1 dietary advice, when given out of metabolic controlled conditions, to persons without coronary heart disease has led to an average reduction of plasma cholesterol of less than 5%\(^2\). Furthermore, a study carried out in an ordinary primary health care setting showed that Step 1 diet advice was no more effective when given by a dietician or nurse than by sending a dietary instruction leaflet by post\(^3\). The more intensive Step 2 diet has been shown to reduce plasma cholesterol by between 6–16% in short-term studies carried out in selected high-risk persons or motivated hospital out-patients or in patients in institutions\(^4\). But the compliance to such an intensive diet regime in those outside strict surveillance is even worse than for the Step 1 diet. The more desirable the diet is, in terms of lowering atherogenic lipoproteins, the less the compliance tends to be. This is a matter of concern. In addition to the problem of non-compliance, the degree of reduction of low density lipoprotein cholesterol levels achieved by dietary means depends on their dietary habits before starting the diet and on inherent biological responsiveness to dietary changes, with some having a greater and others a lower than average response. In general, people with high cholesterol levels tend to have greater absolute reductions in low density lipoprotein cholesterol than people with lower levels, even allowing for the ‘regression to the mean’ phenomenon. The only way to test the individual’s response is a trial of dietary advice.

Since the benefit to be expected in terms of coronary heart disease events appears to be proportional to the degree of cholesterol lowering achieved, and the statin drugs are able to achieve reduction of low density lipoprotein cholesterol in the region of 30%, a real dilemma has now developed with regard to the role of dietary therapy and other lifestyle measures in the clinical practice of coronary heart disease prevention. Due to the small effect of dietary therapy in the majority of people, the use of drugs may become too easily adopted. The results of the recent statin trials should not be extrapolated to such groups of coronary heart disease patients and persons at risk in whom no trial results are yet available, since this might lead to widespread overtreatment with drugs and to a neglect of dietary therapy, weight reduction and increased exercise.

**Drugs**

For hypercholesterolaemia, and elevation of low density lipoprotein cholesterol, the statins are the preferred group of drugs.

The ‘statins’ are inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase step in cholesterol synthesis. By reducing the availability of cholesterol, statins upregulate low density lipoprotein receptors leading to accelerated removal of low density lipoproteins. This results in reduction of plasma low density lipoproteins in the region of 30%. This is a dimension never previously achieved by other drugs or by diet. They are the most powerful and consistent means available of lowering plasma cholesterol and have no adverse effects, at least over 10 years of clinical and trial experience.

The indications for treatment are given in Fig. 1. In those with very high plasma cholesterol concentrations (>8 mmol. l\(^{-1}\)), the possibility of familial hypercholesterolaemia has to be considered. Combination therapy in which the action of statins is complemented with that of an anion-exchange resin may be necessary. This combination represents the most effective cholesterol-lowering pharmacotherapy currently available.

Fibrates are the drugs of choice for the treatment of hypertriglyceridaemia (>5 mmol. l\(^{-1}\)). They promote the catabolism of triglyceride-rich lipoproteins, decrease very low density lipoproteins, increase high density lipoprotein concentrations, and lead also to a modest fall in low density lipoproteins. Some (e.g. bezafibrate) also decrease fibrinogen levels. Where there is combined hypercholesterolaemia and hypertriglyceridaemia and there is no other apparent cause, such as excessive intake of alcohol or diabetes, the possibility of familial combined hyperlipidaemia should be considered. They merit urgent treatment. One of the fibrates or a statin may be tried. Sometimes both are necessary to produce a satisfactory response in both lipids, but such a

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combination may lead to a small increase in the risk of myopathy. There are several fish oil concentrates (n-3 fatty acids) available and these have been shown to reduce elevated plasma triglycerides dramatically. In some cases of combined hyperlipidaemia, their use with a statin should be considered.

Conclusion
The evidence for action in the management of hyperlipidaemias is now clearer than ever for coronary heart disease patients and those at risk for coronary heart disease. Yet in many counties only a minority of patients with manifest coronary heart disease have their plasma lipids analysed and even fewer are adequately treated. Greater awareness of the potential benefits of control of hyperlipidaemia is urgent.

References