

Cholesterol reduction in the prevention of coronary heart disease: therapeutic rationale and guidelines

Stuart M Cobbe, James Shepherd

Despite the difficulties inherent in conveying hydrophobic lipids through the bloodstream, the biological need for these substances by many cells has led to the evolution of a complex plasma lipoprotein transport system through which gram quantities of cholesterol, triglyceride and phospholipid pass each day. A wide variety of tissues make demands on this pool. The adrenal glands and gonads avidly assimilate lipoprotein cholesterol for the production of steroid hormones and rapidly dividing intestinal villus cells take up the sterol for membrane synthesis. Metabolically active tissues such as skeletal muscle use plasma triglyceride for energy production, while in times of surfeit this lipid is directed into adipocytes for storage. Two organs, the liver and intestine, play a particularly important part in lipid metabolism, and are together responsible for most lipoprotein synthesis and catabolism (figure). Lipid transport in the plasma is regulated by specific apolipoproteins, lipoprotein receptors, lipolytic enzymes, and transfer proteins which act to maintain the balance of cholesterol and triglyceride in tissues and plasma; their malfunction may cause or contribute to the development of dyslipidaemia.

Lipoprotein metabolism

Each day, approximately 120 g of dietary triglyceride and 500 mg of cholesterol are packaged into chylomicron particles in the intestine and secreted into the peripheral blood for transport to their final sites of catabolism. In the circulation they meet and are hydrolysed by the enzyme lipoprotein lipase which is situated on the endothelial surfaces of adipose tissue and skeletal muscle capillary beds.¹ The fatty acids liberated in this hydrolytic process are either stored or used directly as a source of energy by these tissues. More than 95% of chylomicron triglyceride is hydrolysed in this way, leaving behind a relatively cholesterol enriched remnant particle that is rapidly cleared from the circulation by the liver. In the fasting state the focus of lipoprotein metabolism moves from the intestine to the liver. The liver synthesises triglyceride-rich very low density lipoproteins (VLDL) which are substantially smaller and denser than chylomicrons of intestinal origin. Like the chylomicrons, their initial catabolism depends on lipoprotein lipase which converts them to cholesterol enriched particles known as intermediate density lipoproteins (IDL or VLDL remnants). These particles differ from

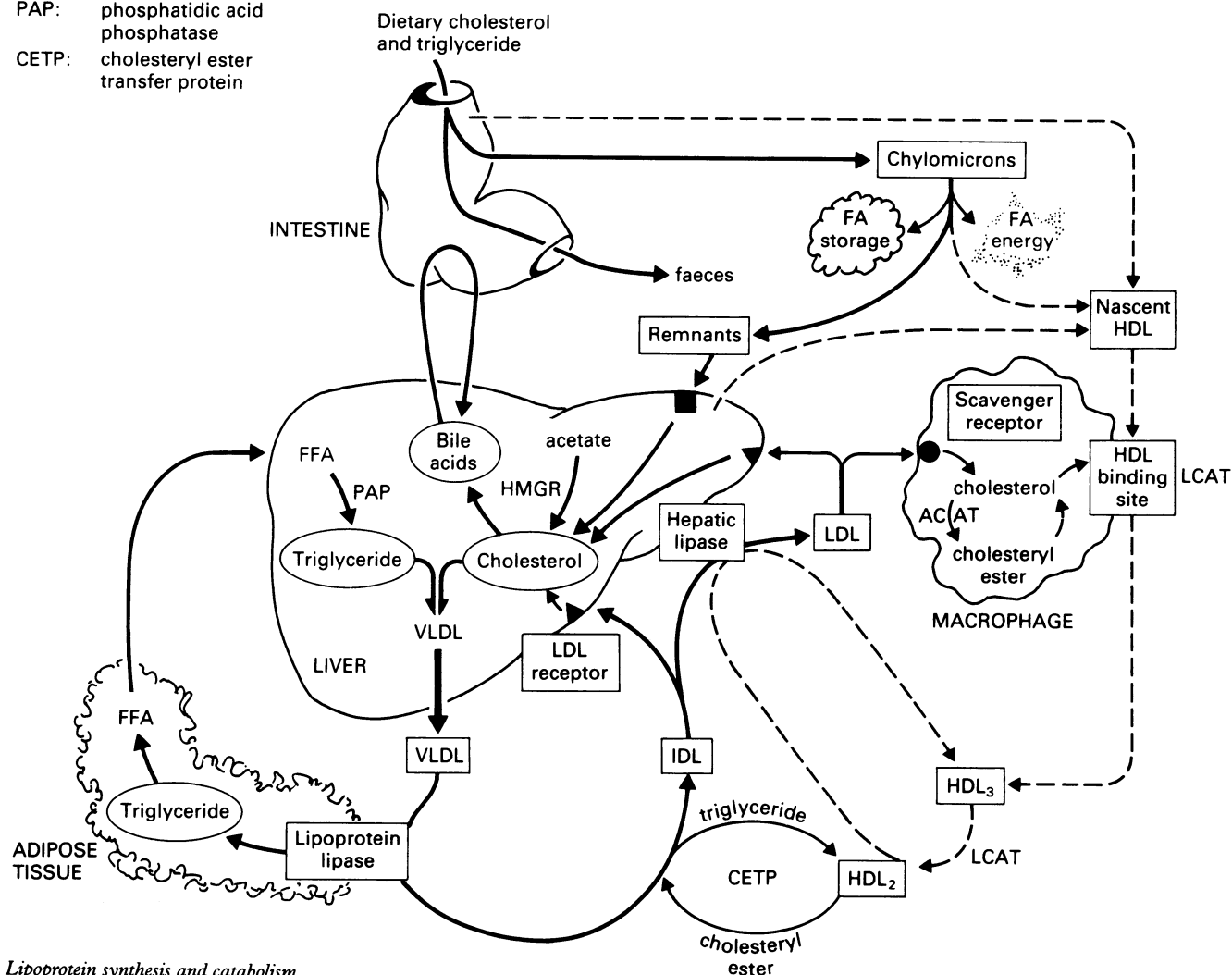
chylomicron remnants in that they are only partially cleared from the bloodstream by the liver. In healthy people most are converted in the circulation to low density lipoproteins (LDL), which persist in the plasma for up to 3 or 4 days. LDL continues to be the focus of intensive research because of its putative involvement in the pathogenesis of atherosclerosis. It transports up to 70% of the cholesterol circulating in the plasma and plays a key part in delivering that sterol to peripheral tissues from the liver. LDL is catabolised by at least two mechanisms. The better understood of these depends on interaction between the lipoprotein and cell membrane associated LDL receptors.² This process is responsible for the regulated delivery of cholesterol to tissues in response to their structural and metabolic requirements. When the demand for sterol is high, LDL receptors are activated to accelerate uptake of the lipoprotein. Conversely, when the intracellular sterol pool is replete, the receptor mechanism is down-regulated, protecting the cell from the toxic effects of cholesterol accumulation. This process has a primary role in regulating intracellular and extracellular cholesterol concentrations. Ineffective operation of the receptor, the hallmark of familial hypercholesterolaemia, results in severe and premature atherosclerosis. Under these circumstances, the burden of sterol elimination falls upon less well understood receptor independent mechanisms which apparently lead to accumulation of cholesterol esters in the scavenger cells of the monocyte-macrophage system, resulting in lipid deposition in arterial walls. A similar effect may also be seen in individuals who overindulge in dietary fat and cholesterol. Saturated fat and cholesterol down-regulate LDL receptor activity and increase the amount of sterol directed into receptor independent catabolic mechanisms.

Because cholesterol cannot be degraded *in vivo*, but must be excreted intact into the bile by the liver, sterol transport from peripheral tissues to the liver is a prerequisite for cholesterol metabolism overall. This process of reverse cholesterol transport seems to be mediated by another lipoprotein fraction—high density lipoprotein (HDL). In contrast to LDL, which is associated with an increased risk of atherosclerosis, HDL seems to protect against it, thanks to the activities of its major protein component, apolipoprotein A-I. This protein, which makes up 70% of the mass of total HDL polypeptides, is a co-factor for the plasma enzyme lecithin: cholesterol acyltrans-

Department of
Medical Cardiology
and Institute of
Biochemistry, Royal
Infirmary, Glasgow
S M Cobbe
J Shepherd

Correspondence to
Professor James Shepherd,
Institute of Biochemistry,
Royal Infirmary, Glasgow
G4 0SF.

ACAT: acyl CoA:cholesterol acyltransferase
 LCAT: lecithin:cholesterol acyltransferase
 HMGR: HMG CoA reductase
 PAP: phosphatidic acid phosphatase
 CETP: cholesteryl ester transfer protein



Lipoprotein synthesis and catabolism.

ferase (LCAT) which, by esterifying free cholesterol on the surface of HDL, increases hydrophobicity and promotes its transfer to the lipid filled core of the particle. The vacated sites on the HDL surface are thereby free to accept more cholesterol from the nearby tissues. The operation of this sterol acceptor mechanism is naturally limited by the capacity of HDL for esterified cholesterol. In humans this can be expanded many-fold because of the existence in the plasma of a protein (cholesteryl ester transfer protein) which is able to shuttle esterified sterol from HDL into VLDL and thereby ultimately transfer the cholesterol to the liver.

Definition of hyperlipoproteinaemia

Unlike most biochemical variables, circulating cholesterol and triglyceride values vary widely both within and between populations. For example, the mean total cholesterol in middle-aged men is 6.7 mmol/l in Britain³ but only 4.2 mmol/l in China.⁴ The standard practice of adopting the mean $\pm$ 2 standard deviations as the reference range is therefore

not applicable since such an approach would define as "normal" many individuals who are at substantially increased risk of ischaemic heart disease. Consensus guidelines have been drawn up both within Europe and elsewhere to permit the identification and appropriate management of patients with hyperlipoproteinaemia. Application of these guidelines to the British population would bring up to 50% of all adults into the hyperlipoproteinaemic category. Current opinion suggests that for most individuals the problem derives from dietary indiscretion and can be reversed by modification in food intake. For that reason, dietary modification is always the first line of action in the treatment of hyperlipoproteinaemia. Some patients will not respond adequately to this approach and will therefore require drug treatment, (see below). Table 1 shows the clinical and molecular features of the major hyperlipoproteinaemias.

Guidelines for the management of hyperlipidaemia

The published guidelines of the British

Table 1 The hyperlipoproteinaemias

Genotypic classification	Molecular defect	Phenotypic classification	Clinical and laboratory findings
Hyperchylomicronaemia syndrome	(1) Lipoprotein lipase deficiency	Type I and type V hyperlipoproteinaemia	Severe hypertriglyceridaemia, lipaemia retinalis, papular rash, pancreatitis
Familial hypertriglyceridaemia	(2) Apo CII deficiency	Type IV hyperlipoproteinaemia	Premature atherosclerosis, hypertriglyceridaemia, hyperuricaemia
Familial dysbetalipoproteinaemia	(1) VLDL oversynthesis (2) Defective VLDL catabolism	Type III hyperlipoproteinaemia	Planar palmar xanthomata, tuberous and tendinous xanthomata, premature atherosclerosis, hypercholesterolaemia, hypertriglyceridaemia
Familial hypercholesterolaemia	Primary sequence defect in apo E plus other unknown genetic/ environmental factors	Type II hyperlipoproteinaemia	Hypercholesterolaemia, tendinous xanthomata, premature vascular disease
Familial combined hyperlipidaemia	LDL receptor defect	Type II and type IV hyperlipoproteinaemia	Hypercholesterolaemia and/or hypertriglyceridaemia, premature vascular disease

Hyperlipidaemia Association,⁵ the British Cardiac Society,⁶ US National Cholesterol Education Program Treatment Panel,⁷ and the European Atherosclerosis Society⁸ are remarkably concordant both with regard to dietary intervention and action limits for drug therapy. Their recommendations on diet are outlined below and the Appendix contains a synopsis of their overall proposals.

There is general agreement on cholesterol lowering diets (table 2): Stage 1 is recommended for the general population and/or individuals with mild hypercholesterolaemia; Stage 2 is regarded as the therapeutic approach for individuals with moderate to severe hyperlipidaemia. A period of 2-3 months is required for the assessment of the effectiveness of the Stage 1 diet, whereas up to 6 months of dietary monitoring might be necessary to achieve maximal effects of the Stage 2 diet. Drug treatment can be introduced earlier in patients with severe hyperlipidaemia.

Despite the publication of guidelines by expert committees, the issue of hyperlipidaemia and its management continues to attract controversy.⁹ Disquiet about implementation of guidelines arises from uncertainty about the impact of cholesterol reduction on all cause mortality and from the logistic and financial problems in implementation.

Cholesterol reduction and all cause mortality

The evidence from 22 randomised clinical trials of dietary and drug therapy of hyperlipidaemia is reviewed elsewhere in this supplement by Holme.¹⁰ The overall impact on coronary mortality was a reduction in the

odds ratio of 9% (95% CI 4.5 to 13.4%), while the effect on all cause mortality was a non-significant increase of 2% (95% CI - 2.6 to + 6.8%). The implication is that while cholesterol reduction reduces the risk of myocardial infarction and coronary death, there is a parallel increase in non-coronary mortality that offsets the beneficial effect on coronary mortality. The increase in non-cardiac deaths is not attributable to any single cause. An excess of cancer deaths was reported in the WHO clofibrate trial.¹¹ However, no evidence of an increased risk from cancer was identified in the Lipid Research Clinics (LRC) trial^{12,13} or its follow up.¹⁴ Although these results have cast suspicion on fibrates and their possible association with cancer, meta-analysis of the trials does not suggest that cholesterol lowering itself increases the risk of cancer.¹⁵

The possibility of an excess of deaths from accidents, suicide, and violence has been widely discussed after analysis of the causes of death in the LRC and Helsinki Heart Study, and a recent epidemiological study has found an association between low cholesterol and short-term excess risk of suicide in men.¹⁶ Behavioural changes have been reported in animals on low-cholesterol diets. It has been argued that cholesterol reduction alters cell membrane composition which may alter behaviour. However, detailed examination of the deaths in the LRC and Helsinki trials has shown that many of the suicides and accidental deaths were associated with prior histories of alcohol abuse or psychiatric disease, or occurred after withdrawal from active therapy.¹⁷ The association between low cholesterol and a short-term but not long-term increase in suicide risk¹⁶ argues against a defect in cellular function predisposing to sui-

Table 2 Recommended cholesterol and fat content of diet

	BHA	BCS	EAS	NCEP
Stage 1 diet:				
Total fat (% energy)	< 30	< 35	< 30	< 30
Saturated fat (% energy)	< 10	< 15	< 10	< 10
Polyunsaturated fat (% energy)	*	*	< 10	up to 10
Monounsaturated fat (% energy)	*	*	< 10	10-15
Cholesterol (mg/day)	*	*	< 300	< 300
Stage 2 diet:				
Total fat (% energy)	*	< 30	20-25	< 30
Saturated fat (% energy)	*	*	*	< 7
Cholesterol (mg/day)	*	*	< 150	< 200

*Guidelines not provided. BHA, British Hyperlipidaemia Association; BCS, British Cardiac Society; EAS, European Atherosclerosis Society; NCEP, National Cholesterol Education Program.

Table 3 Mortality in control groups of primary and secondary prevention trials

Type	Trial No	Subject No	Mean follow up (yr)	Patient-yr	Deaths	Deaths/1000 patient-yr
Primary	9	56 935	6.5	369 529	2973	8.1
Secondary	13	6402	5.7	36 251	1264	34.9

See article by Holme for details of studies.

Table 4 Theoretical impact of cholesterol reduction on total mortality (deaths/1000 patients treated over 5 year period)

	CHD death	Non-CHD death	Total	Reduction (%)
Primary prevention:				
Control	20	20	40	0
Treatment	18	22	40	
Secondary prevention:				
Control	128	32	160	6.25
Treatment	115	35	150	

cide and more in favour of an alteration in dietary behaviour and cholesterol concentrations in those already psychiatrically ill or predisposed to suicide.

Primary versus secondary prevention

How can the failure of plasma cholesterol reduction to reduce all cause mortality be reconciled with the published guidelines on management of hyperlipidaemia? To do so, we must consider a more selective approach to coronary prevention. This does not preclude general dietary advice to the whole population.

Evidence for a reduction in all cause mortality is most likely to be obtained in trials of secondary rather than primary prevention. Table 3 shows that the mortality rates in secondary prevention trials are up to four times greater than in primary prevention trials. Furthermore, coronary mortality in secondary prevention studies represents 80% of all deaths as compared to only 50% in the primary prevention trials. Evidence reviewed by Brown *et al*¹⁸ in this supplement supports the hypothesis that the percentage reduction in coronary events for a given reduction in cholesterol concentration is likely to be at least as great in secondary as in primary prevention. Thus it is possible to calculate the theoretical numbers of deaths prevented per 1000 patient-years of treatment, assuming that a 10% reduction in cholesterol concentration is achieved and that each 1% reduction in cholesterol produces a 1% reduction in coronary mortality. We have allowed an excess of 10% in non-coronary mortality, although this may prove in the future to have been a statistical quirk (table 4). It can be seen that the benefit of cholesterol reduction on coronary mortality in primary prevention is quantitatively small and the impact on total mortality is highly sensitive to a slight adverse trend in non-coronary mortality. If, as has been suggested, the excess in non-coronary deaths in the published trials is due to the play of chance, its impact will be diluted in the results of current primary prevention trials of reductase inhibitors which can achieve a

greater fall in cholesterol and projected cardiac event rate. In contrast to primary prevention, the small percentage lipid reduction in secondary prevention will produce a similar relative but a much greater absolute reduction in coronary mortality. Since 80% of deaths in a secondary prevention population will be cardiac, the effect of a slight adverse trend on non-coronary mortality is greatly diluted, and is no longer sufficient to offset the favourable effect of cholesterol reduction on coronary mortality.

These observations lead to the conclusion that the cost-effectiveness in terms of deaths prevented/patient year of treatment is far greater in secondary prevention. The previous view that it was too late to consider risk factor intervention after the development of clinically overt coronary artery disease is not tenable in view of the evidence on atheroma regression and delay of progression reviewed by Brown *et al*¹⁸ in this supplement.

The feasibility of population-wide interventions with hypolipidaemic drugs in primary prevention has been questioned.¹⁹ The requirements for intensive dietary management and possible drug therapy for individuals with cholesterol values above 6.5 mmol/l as recommended by the British Hyperlipidaemia Association⁵ and European Atherosclerosis Society⁸ could result in 34% and 37% respectively of all men and women in Scotland being eligible for therapy. A problem of such magnitude can realistically only be tackled using an approach adapted to the available resources. Where these are limited, attention should focus first on individuals at particular risk because they exhibit clinical or electrocardiographic evidence of coronary artery disease, are diabetic or genetically hyperlipidaemic, or display multiple risk factors in their lifestyle.

Mechanisms of action of lipid lowering drugs

The mounting evidence from lipid lowering clinical trials has given physicians a new confidence in treating hyperlipidaemia, and the resulting interest in this therapeutic area has

led to a plethora of novel compounds and revitalisation of older drugs. These agents are being used singly and in combination, the latter being an increasingly attractive option where monotherapy has failed to achieve treatment goals. Awareness is also increasing of the effects of other drugs on plasma lipoprotein concentrations. Commonly used antihypertensive agents such as thiazides and β blockers can adversely affect the plasma lipid profile to an extent that the benefit of blood pressure lowering might be offset by increases in triglyceride and LDL cholesterol and a reduction of HDL cholesterol levels. Steroidal preparations whether for use in men (for example stanozolol (Stromba, Sterling Winthrop)) or women (oral contraceptives or hormone replacement therapy) can also produce significant changes in blood lipids.

In deciding between the treatments on offer, the prescriber should be aware of the mechanism of action of the agent and its expected efficacy in the subject under treatment. Some drugs are of use only in certain well defined situations. In the following discussion an outline is given of each class of drug together with some indication of its appropriate use.

FIBRATES

The fibrates currently available in the UK are bezafibrate (Bezalip, MCP Pharmaceuticals), gemfibrozil (Lopid, Parke-Davis), fenofibrate (Lipantil, Fournier Pharmaceuticals), and clofibrate (Atromid, ICI Pharmaceuticals). These are convenient to take (Bezalip Mono is efficacious in a single dose at night) and have good patient acceptability and compliance. They are used when a lipid lowering diet has failed to produce satisfactory control in hypertriglyceridaemic patients and may be considered as a first-line option for type IV hyperlipidaemia. Opinion varies as to their place in the treatment of moderate to severe hypercholesterolaemia. Some argue that their palatability makes them a first option in subjects with raised LDL but others would favour an HMG CoA reductase inhibitor or a bile acid sequestrant in this instance and would reserve a fibrate for those unable to take prolonged resin therapy. The safety record of new fibrate analogues is good and we have a substantial amount of information on gemfibrozil from the Helsinki Heart Study.²⁰ Serious side effects are limited and there seems to be no increase incidence of cancer in the long term. Fenofibrate is unique in significantly reducing plasma uric acid concentrations; hyperuricaemia is regarded as a risk factor for coronary artery disease.

NICOTINIC ACID AND ITS ANALOGUES

This vitamin, given in gram quantities, will produce substantial lowering of triglyceride and cholesterol in many hyperlipidaemic patients. Although not popular in the United Kingdom, it is frequently used in the United States because it is inexpensive and of all the drugs tested it is the only one to produce a reduction in total mortality in a clinical trial.²¹

However, the use of nicotinic-acid-like compounds in Britain may be stimulated by the recent launch of acipimox (Olbetam, Farmitalia Carlo Erba) which is a derivative with reportedly fewer unpleasant side effects than the original vitamin.

Flushing, nausea, and vomiting can often be overcome by administration of low dose aspirin before the drug is given. The agent does have a good safety record, and though liver enzymes may be transiently raised in new patients they return to baseline in a few weeks. It is usually used as a second line choice in hypertriglyceridaemia and hypercholesterolaemia and is a viable alternative to fibrate therapy.

BILE ACID SEQUESTRANT RESINS

The bile acid sequestrants are polymers of either styrene and divinylbenzene (cholestyramine, Questran, Bristol-Myers) or tetraethylenepentamine and epichlorohydrin (colestipol, Colestid, Upjohn), which bind large quantities of bile acids irreversibly, preventing their uptake by mucosal cells. By mechanisms which are only now being understood, these events in the intestinal lumen are accompanied by changes in plasma triglyceride, cholesterol, and lipoprotein metabolism. Most significantly, bile acid sequestrants have a considerable hypocholesterolaemic action, lowering the plasma concentration of LDL by 20–30% in individuals with type II hyperlipoproteinaemia. Their safety is well established and they have been used for decades as efficacious cholesterol lowering agents. The resins are quoted as first choice in the treatment of moderate and severe hypercholesterolaemia. They should be used with caution or in combination with other drugs when triglyceride concentrations are also high because they aggravate hypertriglyceridaemia. Patient acceptability and compliance can be optimised by carefully building up to the full recommended dose over a period of 10–14 days. Recently, reduced doses (5–15 g colestipol per day) have been used with reasonable efficacy to treat moderately raised LDL concentrations.²² These smaller doses are also used successfully when a resin is combined with one of the other classes of agent (fibrate, nicotinic acid, or reductase inhibitor).

HMG COA REDUCTASE INHIBITORS

The synthesis of cholesterol is subject to feedback control at several key steps including that involving the conversion of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) to mevalonic acid. This is catalysed by an enzyme whose activity is controlled by cholesterol, the end point of the pathway. In the late 1970s fungal products (including compactin from *Penicillium citrinum* and mevino- lin (now called lovastatin) from *Aspergillus terreus*) were discovered that potently inhibited the action of this enzyme. When given to humans in milligram quantities they effectively suppress cholesterol synthesis leading to a 30–40% reduction in LDL cholesterol and

concomitant changes in triglyceride and HDL. These compounds hold great promise for controlling plasma lipid concentrations. Two compounds—simvastatin and pravastatin—are now available in the United Kingdom. They offer the means of regulating plasma cholesterol in high risk patients. It would be prudent to use these new agents first in those individuals at greatest risk because of raised LDL (that is, those with familial hypercholesterolaemia). Evaluation of short and medium term safety studies will then allow their wider application. To date the reported side effects of reductase inhibitors are mild. Some subjects show increases in liver enzymes, and a few complain of muscle pain. One area of early concern was the possibility that the new cholesterol synthesis inhibitors might induce cataract formation in the same way as the older agent triparanol. However, careful ophthalmological follow up over several thousand patient-years of treatment has indicated that this is unlikely to be a problem.

OTHER AGENTS

Two other pharmaceutical compounds, Maxepa (Duncan Flockhart) and probucol (Lurselle, Merrell), are used sporadically as lipid lowering agents. Maxepa is a concentrate of eicosapentaenoic acid derived from fish oil. At doses of 10 ml/day the oil effectively reduces VLDL concentrations by about 40% with little effect on HDL cholesterol. Its primary mode of action is to reduce hepatic triglyceride synthesis and hence limit VLDL secretion. In recent studies a rise in LDL cholesterol was reported in many subjects taking Maxepa, and this effect has reduced its potential. It does have a place as a seemingly safe triglyceride lowering drug in individuals with primary hypertriglyceridaemia (type IV and type V hyperlipidaemia).

Probucol, a bis-phenol structure, is given in a dose of 1 g/day. It produces a highly variable reduction in plasma cholesterol usually in the range 10–25%. Both LDL and HDL cholesterol are reduced while plasma triglyceride concentrations are unaffected by the drug. There is no clear mechanism for its hypocholesterolaemic effect. LDL turnover studies showed slight changes in both synthesis and catabolism but these are not uniformly observed. The pattern of the drug's effect on HDL is more consistent. The cholesterol content per particle decreases and there is also a reduction in the number of HDL particles in the circulation, apparently owing to reduced synthesis of the major protein constituent apo A-I. The effect of probucol on HDL has dampened enthusiasm for the drug, and currently it is used only occasionally in patients in whom hypocholesterolaemia is refractory to other agents. However, recent developments suggesting that it may operate by inhibiting LDL oxidation and prevent its assimilation by macrophages have revived interest in the anti-atherogenic potential of this agent. More extensive studies are required to establish the validity and clinical relevance of these findings.

COMBINED USE OF HYPOLIPIDAEMIC AGENTS

Because the drugs described above differ in their modes of action when given together they may produce additive or even synergistic reductions in plasma cholesterol and triglyceride. Combinations of a resin with a fibrate, nicotinic acid, or a reductase inhibitor have been successful. The combination of a resin with a reductase inhibitor was particularly effective, producing 50–70% reductions in LDL even in patients severely affected by familial hypercholesterolaemia. This approach may be adopted increasingly as therapeutic goals become more ambitious.

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Appendix: Management guidelines for hyperlipidaemia

- (1A) RECOMMENDATIONS OF THE BRITISH HYPERLIPIDAEMIA ASSOCIATION
- (1) Optimal cholesterol concentration for general population: 5.2 mmol/l
 - (2) Individuals with cholesterol concentration of 5.2–6.5 mmol/l should receive general dietary counselling and advice on risk factors.
 - (3) Individuals with cholesterol concentrations above 6.5 mmol/l require clinical care—that is, diet and combined diet and drug therapy, except for those with HDL cholesterol concentration above 2.0 mmol/l.
 - (4) Drug therapy is rarely required if cholesterol concentration is below 6.5 mmol/l and only in a few patients with concentrations between 6.5–7.8 mmol/l and would be most common in patients with cholesterol above 7.8 mmol/l. The most obvious candidates for drug therapy should be individuals below 30 years of age, and/or with other risk factors for coronary heart disease.

- (1B) BRITISH CARDIAC SOCIETY GUIDELINES
- (1) Dietary advice is required if cholesterol concentration is above 6.5 mmol/l.
 - (2) Diet/drug treatment should be considered in individuals with cholesterol concentration above 7.8 mmol/l.
 - (3) Treatment goals: lowering towards 5.2 mmol/l.

(1C) CURRENT POLICY OF THE EUROPEAN ATHEROSCLEROSIS SOCIETY		
Cholesterol (mmol/l)	Triglyceride (mmol/l)	Recommended action
(1) 5.2–6.5	Below 2.3	Diet, rarely drugs
(2) 6.5–7.8	Below 2.3	Drugs if no response to diet
(3) Below 5.2	2.3–5.6	Correct underlying causes (alcohol, obesity). Diet. Consider drugs if other risk factors for coronary heart disease are present
(4) 5.2–7.8	2.3–5.6	Suspect familial combined hyperlipidaemia. Use drugs if diet is ineffective.
(5) Above 7.8	Above 5.6	Diet and drugs.

(1D) NATIONAL CHOLESTEROL EDUCATION PROGRAM		
(i) Risk status		
Total serum cholesterol (mmol/l)	Interpretation	Recommended action
< 5.18	Desirable	Repeat in 5 years
5.18–6.20	Borderline	If no CHD or other risk factors repeat in one year. If CHD or two other risk factors—lipoprotein analysis and appropriate treatment based on LDL cholesterol.
Above 6.21	High	Lipoprotein analysis. Further action based
(ii) Treatment goals		
	Initiation of therapy: LDL cholesterol concentration (mmol/l)	Minimal treatment goal (mmol/l)
(a) Individuals without CHD or two other risk factors	Diet 4.15 Drugs > 4.92	< 4.15 < 3.37
(b) Individuals with CHD or two other risk factors	Diet > 3.37 Drugs > 4.15	< 3.37 < 3.37