

# MANAGEMENT OF DYSLIPIDAEMIA

Coronary disease

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**D**yslipidaemia is a preferable term to hyperlipidaemia because it includes risk factors such as a decreased concentration of high density lipoprotein (HDL) cholesterol as well as qualitative changes in low density lipoprotein (LDL), notably the presence of small, dense LDL particles. Both abnormalities, together with raised triglycerides, are features of the metabolic syndrome, increasingly recognised as a harbinger of coronary heart disease (CHD).

The simplest classification of dyslipidaemia defines the lipid phenotype as hypercholesterolaemia, hypertriglyceridaemia, or mixed hyperlipidaemia (MHL). Each can result from dysfunctional mutations of dominantly expressed genes encoding receptors, enzymes or transfer proteins involved in lipoprotein metabolism, usually indicated by a familial pattern of inheritance. More often, however, dyslipidaemia reflects the interaction between weaker genetic influences and environmental factors such as diet and a sedentary existence. In these situations the adoption of changes in lifestyle is the first line of treatment whereas monogenically determined dyslipidaemias, such as familial hypercholesterolaemia (FH), usually require lipid regulating drug treatment.

## CURRENT GUIDELINES FOR PREVENTING CARDIOVASCULAR DISEASE

Management of dyslipidaemia forms an important part of strategies for preventing cardiovascular disease. Most of the current guidelines reflect the results of the five major statin trials published between 1994 and 1998. Overall, statins reduced the risk of CHD by 31% and total mortality by 21%, benefit being equally evident in men and women below and above the age of 65.<sup>1</sup>

In addition to a decreased incidence of CHD, a significant decrease in the frequency of strokes was apparent in some of the trials. A meta-analysis of those using simvastatin, lovastatin or pravastatin, involving almost 10 000 patients, showed a 27% decrease in the risk of stroke,<sup>2</sup> possibly reflecting a statin induced improvement in cerebrovascular endothelial function.

### UK guidelines

The joint recommendations of the British Cardiac and Hypertension Societies and the British Hyperlipidaemia and Diabetic Associations, published in 1998,<sup>3</sup> advised estimating the absolute risk of CHD using Framingham based criteria, which include HDL cholesterol as a variable. Priority for treatment was given to those with existing CHD or with an estimated risk of  $\geq 15\%$  over the following 10 years, either at current age or if extrapolated to age 60. All individuals in these categories with serum total cholesterol  $\geq 5$  mmol/l or LDL cholesterol  $\geq 3$  mmol/l should receive lifestyle advice designed to reduce the values to  $< 5$  mmol/l and  $< 3$  mmol/l, respectively. Failure to achieve these objectives is regarded as an indication for lipid lowering drug treatment.

More recent guidelines applicable to England and Wales are set out in the National Service Framework for CHD.<sup>4</sup> These recommend that patients with CHD or at high risk (defined as  $\geq 30\%$  per 10 years) should be treated with diet and statins with the object of lowering serum total cholesterol below 5 mmol/l or by 20–25%, whichever would result in the lowest level; equivalent figures for LDL cholesterol are below 3 mmol/l or by 30%. These guidelines are similar to those of the Joint British Societies except that the rate of CHD defining high risk is doubled, presumably in the interests of economy.

### US guidelines

The third report of the National Cholesterol Education Program (NCEP, adult treatment panel III) reiterated the use of the LDL cholesterol value as the criterion for when to initiate treatment and as a therapeutic goal; the greater the risk of CHD, the lower the concentration of LDL cholesterol at which treatment is initiated and the lower is the target value to be achieved.<sup>5</sup> Patients with CHD, diabetes or multiple risk factors, as in the metabolic syndrome, that confer a 10 year risk of CHD of  $> 20\%/10$  years are regarded as being at high risk. The majority will require lipid lowering drug treatment to achieve the LDL cholesterol goal of  $< 2.6$  mmol/l, but therapeutic lifestyle

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**Figure 1** Pie diagrams of total and coronary heart disease (CHD) mortality in England and Wales in 1999 (National Statistics).

changes may achieve the less stringent target values of  $< 4.1$  mmol/l and  $< 3.4$  mmol/l recommended for those at low and moderate risk, respectively.

### European guidelines

The recently published executive summary of the Third Joint Task Force of European and Other Societies' guidelines differs from the others in focusing on the prevention of fatal cardiovascular disease (CVD) rather than CHD events.<sup>6</sup> Assessment of CVD risk is based on the systematic coronary risk evaluation (SCORE) system, high risk being defined as  $\geq 5\%$  chance of fatal CVD within 10 years. High risk subjects should have their total and LDL cholesterol reduced to below 5 mmol/l and 3 mmol/l, respectively, unless they have clinical CVD, diabetes or serum total and LDL cholesterol concentrations which are already below these values, when the goals of treatment become  $< 4.5$  mmol/l and  $< 2.5$  mmol/l, respectively.

Lipid lowering is initially based on lifestyle advice, to which drugs should be added if treatment goals are not achieved within three months. No specific goals are set for triglycerides and HDL cholesterol but a triglyceride value of  $> 1.7$  mmol/l and HDL cholesterol  $< 1.0$  mmol/l (men) or  $< 1.2$  mmol/l (women) are regarded as markers of increased risk. So too is evidence of subclinical atherosclerosis, such as

coronary calcification on computed tomographic (CT) scanning and carotid intima medial thickening on ultrasound.

### MRC/BHF HEART PROTECTION STUDY

All the guidelines, with the exception of the most recent European ones, were formulated before the publication of the results of the Heart Protection Study (HPS).<sup>7</sup> This large, Oxford based trial investigated the effects on mortality and morbidity of cholesterol lowering treatment in subjects with or at high risk of cardiovascular disease. Men and women aged 40–80 years with a total cholesterol of  $> 3.5$  mmol/l were randomised to receive either simvastatin 40 mg daily, anti-oxidant vitamins, the two combined, or placebo.

The results showed an incidence of major coronary events in those on placebo of 11.8% over five years, corresponding to  $> 20\%/10$  years. Patients allocated to simvastatin had a mean difference in LDL cholesterol of  $-1$  mmol/l, with decreases in total and cardiovascular mortality of 12% and 17% and decreases in CHD events and strokes of 26% and 27%, respectively. Benefit from simvastatin occurred irrespective of the value of LDL cholesterol at entry to the study and was not influenced by age, sex, or clinical status.

The results of this study have placed a question mark over the relevance of current UK guidelines for the prevention of CHD, specifically that the prescribing of statins should be

restricted to individuals with LDL cholesterol > 3 mmol/l. One third of the patients in the HPS had a baseline value below this value, which suggests that high risk individuals should be treated with simvastatin 40 mg/day, or its equivalent, irrespective of their LDL cholesterol. Furthermore the HPS showed benefit from statin treatment up to the age of 80 years. Since more than half the deaths from CHD in males and over 75% in females occur after the age of 75 in England and Wales (fig 1), this suggests that restrictions on access to treatment based on age or lipid concentration should be reconsidered.

**USE OF FUNCTIONAL FOODS IN DIETARY MANAGEMENT OF DYSLIPIDAEMIA**

In addition to the well known principles of dietary management involving restriction of total fat intake and substitution of poly- and mono-unsaturated fatty acids for saturated fatty acids, there has been much interest recently in the lipid lowering properties of so called functional foods. Foremost has been the inclusion in the diet of plant sterols and stanols and ω3 fatty acids.

**Plant sterols and stanols**

It has long been known that plant sterols and stanols inhibit the absorption of cholesterol, with which they are closely related structurally. These compounds compete with cholesterol for incorporation into mixed micelles, thereby impairing its absorption from the intestine, but their limited lipid solubility makes it difficult to dissolve them in fat spreads in effective concentrations. This was overcome by esterifying them with long chain fatty acids, which increases their lipid solubility and facilitates their incorporation into foods.

Numerous studies have shown that plant stanol ester intakes in the region of 2 g/day (expressed as free stanol) achieve reductions in serum cholesterol of 5–10%. In the North Karelia study, moderately hypercholesterolaemic subjects were randomised to receive margarine without or with added sitostanol ester 2.6 g daily.<sup>8</sup> In those who remained on this dose for one year, LDL cholesterol decreased by 13% compared with placebo margarine. The accompanying 10% decrease in total cholesterol could be expected to reduce the risk of CHD by 25% if maintained for more than two years.<sup>9</sup>

Plant stanol esters are marketed as Benecol in various food products including margarine, yoghurt, and cereal bars and are virtually unabsorbed. Similar decreases in LDL cholesterol occur with comparable doses of margarine containing plant sterol esters (Flora proactiv); however, plant sterols are absorbed to some extent which raises their plasma concentrations whereas stanol esters lower them. Statins also tend to raise plant sterol values and it remains to be shown

whether this effect is disadvantageous, as has been suggested.<sup>10</sup>

Plant stanol esters have been shown to be an effective and safe means of lowering LDL in several categories of subjects, including children and adults with familial hypercholesterolaemia, diabetics, and post-menopausal women with CHD. Any decrease in LDL cholesterol is additional to that achieved by standard lipid lowering diet and drug treatment. For example, Blair and colleagues<sup>11</sup> showed a further 10% decrease in LDL cholesterol when plant stanol ester was given in conjunction with a statin. This novel dietary approach is advocated as useful in the conventional management of dyslipidaemia.<sup>3</sup>

**ω3 fatty acids**

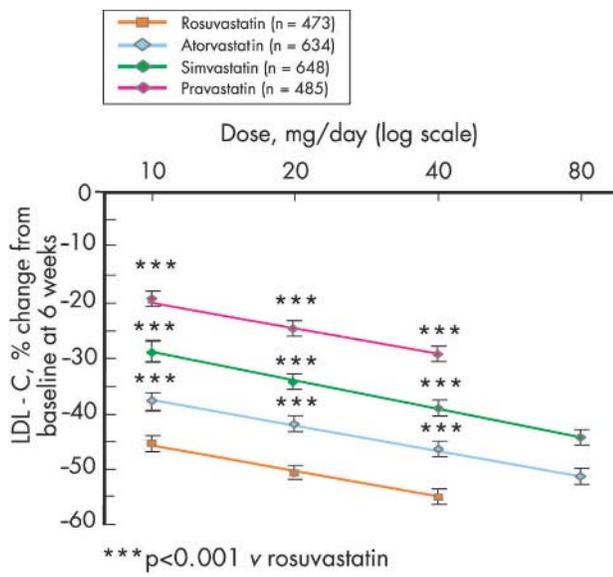
ω3 fatty acids occur in the diet as long chain, polyunsaturated triglycerides derived from plant and marine sources. The three main compounds regarded as functional foods are α-linolenic acid (ALA or 18:3ω3), eicosapentaenoic acid (EPA or 20:5ω3), and docosahexaenoic acid (DHA or 22:6ω3). ALA is mainly derived from certain vegetable oils, EPA and DHA from oily fish. None of these compounds can be synthesised de novo and only a limited amount of interconversion takes place in normal subjects.

In the light of the apparent protection from CHD observed in Inuit (Eskimos) more than 30 years ago several prospective studies have examined the relation between ω3 fatty acid intake or frequency of fish consumption and the incidence of CHD in other populations. The results were inconclusive but showed a possible protective effect of ω3 fatty acids against sudden death from CHD. This emphasised the need for randomised controlled clinical trials and a meta-analysis of the results of 11 such trials was published recently.<sup>12</sup> This showed that the risk of fatal myocardial infarction was reduced by 30% (p < 0.001) and total mortality by 20% (p < 0.001) in those receiving ω3 fatty acids. In five of the trials there was a 30% reduction in sudden death (p < 0.01). Triglycerides decreased by an average of 20% during ω3 fatty

**Table 1** Comparative effects of lipid regulating drugs

Daily dose	Mean change (%)		
	LDL-C	HDL-C	TG
Atorvastatin 40 mg	-51	+5	-32
Nicotinic acid 4 g	-9	+43	-34
Gemfibrozil 1.2 g	-18	+12	-40
Ezetimibe 10 mg	-18.5	+3.5	-4.9
Cholestyramine 24 g	-23	+8	+11

HDL-C, high density lipoprotein; LDL-C, low density lipoprotein cholesterol; TG, triglycerides.



**Figure 2** Comparative LDL lowering efficacy of rosuvastatin, atorvastatin, simvastatin, and pravastatin. Graph based on data of Jones and colleagues.<sup>14</sup>

acid supplementation, but little change was observed in LDL or HDL cholesterol.

Data from various sources suggest that  $\omega$ 3 fatty acids protect against fatal CHD, especially sudden death, rather than non-fatal events. This protective effect is evident within four months and seems to be much greater with EPA and DHA than with ALA. Experimental evidence supports an anti-arrhythmogenic mechanism of action of EPA and DHA.<sup>13</sup>

Data from several studies suggest that the protective effects of  $\omega$ 3 fatty acids in secondary prevention are achieved by consumption of 1 g daily, equivalent to 100 g of oily fish. Higher doses (1–4 g daily) of EPA and DHA are useful in the treatment of severe hypertriglyceridaemia.

### LIPID REGULATING DRUGS

The comparative effects of the major classes of lipid regulating drugs are illustrated in table 1. Statins provide the most effective means of lowering LDL cholesterol, nicotinic acid of raising HDL cholesterol, and fibrates (exemplified by gemfibrozil) of lowering triglyceride. Ezetimibe is relatively ineffective in lowering LDL when given as monotherapy but looks set to displace bile acid sequestrants as an adjunct to statins in the treatment of severe hypercholesterolaemia, being much easier to administer and with fewer side effects.

#### Statins

The introduction into clinical practice of statins has revolutionised the management of dyslipidaemia and the treatment and prevention of CVD. These drugs competitively inhibit HMG-CoA reductase, thereby reducing cholesterol synthesis in the liver, which leads to an increased expression of hepatic LDL receptors and greater uptake of LDL cholesterol from plasma. Production of very low density lipoprotein (VLDL), the precursor of LDL, is decreased, the net effect being dose dependent reductions in LDL cholesterol of 20–60%, accompanied by lesser reductions in plasma triglyceride and a small rise in HDL cholesterol.

Until recently atorvastatin was the most effective statin available for decreasing LDL when given in doses of 10–80 mg daily. Furthermore, the higher dose was shown to decrease serum triglycerides by 45% in individuals with hypertriglyceridaemia. However, rosuvastatin, which was recently launched in the UK, is even more effective than atorvastatin in lowering LDL cholesterol over its licensed dose range of 10–40 mg, although there was no significant difference between rosuvastatin 40 mg and atorvastatin 80 mg in this respect (fig 2).<sup>14</sup>

The extent to which LDL cholesterol should be lowered to obtain maximum benefit has yet to be established. A

**Table 3** Recommendations for drug treatment of dyslipidaemia

Type	First choice	If refractory
Hypercholesterolaemia	Statin	Add cholesterol absorption inhibitor, bile acid sequestrant, or nicotinic acid
Hypertriglyceridaemia	Fibrate	Add nicotinic acid or $\omega$ 3 fatty acids
Mixed hyperlipidaemia	Statin	Substitute or add fibrate (not gemfibrozil + statin)
Low HDL cholesterol	Statin	Substitute or add fibrate or nicotinic acid

Check liver function before and after one month on statin.  
Check renal function before and after one month on fibrate.  
Check serum creatine kinase (CK) only if myalgia occurs during statin or fibrate treatment.

recent analysis which includes the results of HPS showed a strong correlation between the percentage change in serum cholesterol and the logarithmic risk of a CHD event.<sup>15</sup> Extrapolation of the regression line suggests that a decrease in total cholesterol of 45%, equivalent to a decrease in LDL cholesterol of about 60%, would halve the risk of CHD. The recently reported results of the REVERSAL<sup>16</sup> and PROVE IT<sup>17</sup> trials show that decreases in LDL cholesterol of 47–51% on atorvastatin 80 mg/day were of greater benefit in preventing progression of coronary atherosclerosis and reducing cardiovascular events respectively than were decreases of 22–27% on pravastatin 40 mg/day. These findings support “the lower the LDL, the better” concept, but a definitive answer to the question “how low?” will have to await the results of trials not due to be completed until 2005.

The most important adverse effect of statins is myositis, defined as muscle pain plus an increase in creatine phosphokinase (CPK) greater than 10 times the upper limit of normal. Rarely, severe rhabdomyolysis leading to fatal renal damage has occurred and the synthetic HMG-CoA reductase inhibitor, cerivastatin, was recently withdrawn on this account. Other statins have a remarkably good safety record and an analysis of data from over 30 000 patients who had received pravastatin, simvastatin, or lovastatin for a period of five years or more found that the incidence of myositis was only 0.1%, identical to that on placebo. In the HPS the frequency of CK elevations > 10 times the upper limit of normal was 0.09% in patients on simvastatin compared with 0.05% in those on placebo. The likelihood of this complication occurring is dose related and is increased by concomitant treatment with drugs such as cyclosporine, which inhibit the cytochrome P450 3A4 pathway via which most statins are metabolised.

**Table 2** Lipid regulating effects of statin/other drug combination treatment compared with statin monotherapy. Data show mean differences calculated from published studies<sup>19</sup>

Dyslipidaemia phenotype	Statin (mg/day)	Other drug (mg/day)	$\Delta$ Combination v statin		
			LDL-C	HDL-C	TG
Hypercholesterolaemia	P 40, L 20–80 P, F 40	NA 1200–3000 G 1200, B 400	–13%	+9%	–15%
Hypertriglyceridaemia	P 20, A, S, F 5–80	NA 1000–3000	–9.5%	+26%	–25.5%
Mixed hyperlipidaemia	P 20, S 10–20	G 1200, B 400, f 300	+4%	+8%	–34.5%

A, atorvastatin; B, bezafibrate; F, fluvastatin; f, fenofibrate; G, gemfibrozil; L, lovastatin; NA, nicotinic acid; P, pravastatin; S, simvastatin.

### Nicotinic acid

The lipid regulating effect of large doses of nicotinic acid were first described in 1962. Long term follow up of patients who participated in the Coronary Drug Project showed a reduction in total mortality in those taking nicotinic acid during the trial and the drug would be more widely used were it not for its side effects. These include cutaneous flushing, skin rashes, gastrointestinal upsets, hyperuricaemia, hyperglycaemia, and hepatic dysfunction. Sustained release preparations reduce flushing but accentuate the risk of hepatitis.

However, recently an extended release form of nicotinic acid (Niaspan) has been marketed in the UK which seems to be free from this drawback. At the maximum recommended dose of 2 g daily, decreases in LDL cholesterol, triglycerides, and lipoprotein Lp(a) averaged 17%, 35%, and 24%, respectively, whereas HDL cholesterol increased by 26%. Although 30% of those randomised to Niaspan had troublesome side effects, the frequency of abnormal liver function tests was similar to that on placebo.

### Fibrates

The lipid regulating properties of fibrates were first described almost 40 years ago. The five compounds marketed in the UK—clofibrate, bezafibrate, fenofibrate, gemfibrozil, and ciprofibrate—are all effective in controlling hypertriglyceridaemia and in raising HDL cholesterol, but vary in their ability to reduce LDL cholesterol, fenofibrate and ciprofibrate being the most potent. Clofibrate is now obsolete because it increases the risk of developing gall stones. A rare side effect of fibrates is an acute myositic syndrome similar to that seen with statins, patients with renal impairment being particularly vulnerable.

During the Helsinki heart study, reductions in the incidence of primary CHD events by gemfibrozil were attributable both to the decrease in LDL cholesterol and to the increase in HDL cholesterol, being most pronounced in individuals with triglyceride > 2.3 mmol/l and LDL:HDL cholesterol ratio > 5. Additional evidence of the benefits of gemfibrozil came from the Veterans Affairs high density lipoprotein cholesterol intervention trial, which showed that the drug reduced the risk of secondary events in men with a low HDL cholesterol. More recently, the Bezafibrate infarction prevention trial demonstrated the benefits of bezafibrate in secondary prevention of CHD in hypertriglyceridaemic subjects.

### Ezetimibe

Recently, a specific pathway which mediates the uptake of cholesterol from the lumen into the wall of the small intestine was identified. A novel class of compounds, 2-azetidione derivatives, has now been shown to interact with this putative cholesterol transporter in the intestinal brush border membrane, thereby inhibiting cholesterol absorption. The first of these cholesterol absorption inhibitors to be licensed is ezetimibe.

Randomised, placebo controlled trials of ezetimibe in hypercholesterolaemic subjects show dose dependent reductions in LDL cholesterol over the range 0.25–10 mg daily. The mean decrease in LDL cholesterol on 10 mg daily was 18.2% which was accompanied by small but significant increases in HDL cholesterol and decreases in serum triglyceride.<sup>18</sup> The drug was well tolerated and the frequency of adverse events was similar to that in the placebo group.

### Management of dyslipidaemia: key points

- ▶ Effective treatment of dyslipidaemia is an important element of strategies to prevent cardiovascular disease in clinical practice
- ▶ Current guidelines advocate dietary measures as first line management, including functional foods such as plant sterols or stanols and  $\omega$ 3 fatty acids, with addition of lipid regulating drugs in high risk subjects if target values of cholesterol are not achieved
- ▶ The results of the Heart Protection Study suggest that lowering LDL cholesterol reduces risk of CHD and stroke regardless of pre-treatment cholesterol value and age
- ▶ Novel lipid regulating drugs include rosuvastatin, currently the most effective statin in terms of LDL lowering, and ezetimibe, a cholesterol absorption inhibitor
- ▶ The ability of statins given alone in high doses, or combined with ezetimibe, to lower LDL cholesterol by 55–60% should in theory enable the rate of CHD events to be halved

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### COMBINATION DRUG TREATMENT

Monotherapy with one of the statins does not always lower LDL cholesterol and triglycerides or raise HDL cholesterol to the required extent, and it is sometimes necessary to combine their administration with other lipid regulating drugs. For example, in severe FH even maximal doses of statins do not always lower LDL cholesterol sufficiently and an anion exchange resin is often added. Also, in MHL, statin monotherapy may fail to reduce triglycerides and raise HDL cholesterol to the desired levels and it may be necessary to add either nicotinic acid or a fibrate to achieve these objectives.

Mixed hyperlipidaemia is especially common in type II diabetes and is a more important determinant of prognosis than is hyperglycaemia. Subgroup analysis of the statin trials showed that reduction of LDL cholesterol decreased the incidence of coronary and cerebrovascular events to a similar extent in diabetics as in non-diabetics. The American Heart Association advocates a rigorous diet for all diabetics and recourse to lipid lowering drug treatment if LDL cholesterol remains above 3.4 mmol/l, target values being < 3.4 mmol/l for primary prevention and < 2.6 mmol/l for secondary prevention. The ATP III guidelines go further and no longer differentiate between primary and secondary prevention in diabetics.

Statins are recommended as first line drug treatment in diabetics, either alone or combined with a fibrate if fasting triglyceride is > 4.5 mmol/l. The safety of combined statin/fibrate treatment has been questioned because of the perception that this may increase the risk of myositis. However, most of the reported cases developing this complication had received a statin combined with gemfibrozil. Other fibrates do not carry the same risk and the chances of developing myositis with any of the statins combined with bezafibrate or fenofibrate are acceptably low.

Another reason for combination treatment is to improve the response of patients who are refractory to statins. Interindividual variability in response to these drugs is well recognised and it seems that genetic variability in cholesterol absorption is an important determinant of statin responsiveness. This was exemplified by the subgroup analysis conducted on the Finnish cohort of 4S, which showed that those who absorbed cholesterol efficiently and whose basal

### Combined treatment with nicotinic acid or a fibrate and statins

The comparative effects of administering statins alone or in combination with nicotinic acid or a fibrate in patients with different types of dyslipidaemia are illustrated in table 2.<sup>19</sup> Relatively few comparative studies have been published, but they suggest that both nicotinic acid and fibrates are useful adjuncts to statins, the choice of which may depend more on safety and tolerability than on efficacy or, in the case of nicotinic acid, availability of a suitable preparation such as Niaspan. In hypercholesterolaemia, addition of nicotinic acid provides a greater reduction in LDL-C than do fibrates and a similar increase in HDL-C compared with statins alone. The addition of nicotinic acid to a statin notably reduces triglycerides and raises HDL cholesterol in hypertriglyceridaemia, whereas the addition of a fibrate to a statin has similarly beneficial effects on triglycerides and HDL-C in MHL but at the expense of a slight increase in LDL-C.

### Combined treatment with ezetimibe and statins

A study in hypercholesterolaemic patients shows that concomitant administration of ezetimibe 10 mg and simvastatin 10–80 mg daily decreased LDL cholesterol by 14%, triglyceride by 8%, and increased HDL cholesterol by 2% more than did simvastatin alone.<sup>20</sup> These data suggest an additive effect of the two drugs.

Further evidence of an additive effect has come from a study undertaken in 50 patients with homozygous FH, half of whom were undergoing LDL apheresis.<sup>21</sup> The study compared the effects of ezetimibe 10 mg plus atorvastatin or simvastatin 40 or 80 mg daily versus the effects of atorvastatin or simvastatin 80 mg daily, each regimen being tested by its ability to lower LDL cholesterol below baseline values achieved on atorvastatin or simvastatin 40 mg daily. Results on ezetimibe 10 mg plus statin 80 mg daily showed that the combined treatment lowered LDL cholesterol concentrations by an additional 20.5% compared with statin alone.

### CONCLUSIONS

Recommendations for the choice of drugs in high risk individuals whose dyslipidaemia is unresponsive to lifestyle measures are shown in table 3. Statins are the first choice in hypercholesterolaemia, with the addition of ezetimibe, a bile acid sequestrant or nicotinic acid in refractory cases. Fibrates are the first choice in hypertriglyceridaemia, with the addition of nicotinic acid or  $\omega$ 3 fatty acids if necessary. Statins are the first choice in MHL with substitution or addition of a fibrate if raised triglycerides persist or HDL cholesterol remains low. Statins are also the first choice in individuals with low HDL cholesterol, mainly because they lower LDL cholesterol and thus increase the total:HDL cholesterol ratio, but it may be necessary to add or substitute a fibrate or nicotinic acid if the ratio remains above 5.

Children will seldom require drug treatment unless they have FH. A recent study demonstrated the safety of simvastatin in FH heterozygotes aged 10 years or more,<sup>22</sup> and as mentioned previously the combination of simvastatin

or atorvastatin with ezetimibe enables remarkable reductions in LDL cholesterol to be achieved in children with homozygous FH, especially those on LDL apheresis.<sup>21</sup>

It remains to be seen whether ezetimibe/statin combinations will be reserved for the minority of adults with hypercholesterolaemia refractory to statin monotherapy or used to keep statin dosage to a minimum in a much broader range of patients, including those unable or unwilling to take high doses of statins. The trend towards combination drug treatment in the management of dyslipidaemia mirrors that seen with antihypertensive agents and will gain increased momentum if the planned introduction of formulations containing a statin combined with either nicotinic acid or ezetimibe gains regulatory approval.

### REFERENCES

- 1 LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomised controlled trials. *JAMA* 1999;**282**:2340–6.
- 2 Crouse JR III, Bington RP, Hoen HM, et al. Reductase inhibitor monotherapy and stroke prevention. *Arch Int Med* 1997;**157**:1305–10.
- 3 British Cardiac Society, British Hyperlipidaemia Association, British Hypertension Society, endorsed by the British Diabetic Association. Joint British recommendations on prevention of coronary heart disease in clinical practice. *Heart* 1998;**80**(suppl 2):S1–29.
- 4 Department of Health. *The National Service Framework for coronary heart disease*. London: Department of Health, 2000.
- 5 Expert Panel on Detection, Evaluation and Treatment of High Cholesterol in Adults. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation and treatment of high blood cholesterol in adults (adult treatment panel III). *JAMA* 2001;**285**:2486–97.
- 6 De Backer G, Abrosioni E, Borch-Johnsen K, et al. Executive summary: European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and other societies on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2003;**24**:1601–10.
- 7 Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;**360**:7–22.
- 8 Miettinen TA, Puska P, Gylling H, et al. Reduction of serum cholesterol with sitostanol-ester margarine in a mildly hypercholesterolemic population. *N Engl J Med* 1995;**333**:1308–12.
- 9 Law M. Plant sterol and stanol margarines and health. *BMJ* 2000;**320**:861–4.
- 10 Miettinen TA, Strandberg TE, Gylling H. Noncholesterol sterols and cholesterol lowering by long-term simvastatin treatment in coronary patients. *Arterioscler Thromb Vasc Biol* 2000;**20**:1340–6.
- 11 Blair SN, Capuzzi DM, Gottlieb SO, et al. Incremental reduction of serum total cholesterol and low-density lipoprotein cholesterol with the addition of plant stanol ester-containing spread to statin therapy. *Am J Cardiol* 2000;**86**:46–52.
- 12 Bucher HC, Hengstler P, Schindler C, et al. n-3 polyunsaturated fatty acids in coronary heart disease: a meta-analysis of randomised controlled trials. *Am J Med* 2002;**112**:298–304.
- 13 Leaf A, Kang JX. Dietary n-3 fatty acids in the prevention of lethal cardiac arrhythmias. *Curr Op Lipidol* 1997;**8**:4–6.
- 14 Jones PH, Davidson MH, Stein EA, et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin and pravastatin across doses (STELLAR trial). *Am J Cardiol* 2003;**92**:152–60.
- 15 ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomised to pravastatin vs usual care: the antihypertensive and lipid-lowering treatment to prevent heart attack trial. *JAMA* 2002;**288**:2998–3007.

- 16 **Nissen SE**, Tuzcu EM, Schoenhagen P, *et al.* Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomised controlled trial. *JAMA* 2004;**291**:1132–4.
- 17 **Cannon CP**, Braunwald E, McCabe CH, *et al.* Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;**350**:1495–504.
- 18 **Knopp RH**, Dujovne CA, Le Beaut A, *et al.* Evaluation of the efficacy, safety, and tolerability of ezetimibe in primary hypercholesterolaemia: a pooled analysis from two controlled phase III clinical studies. *Int J Clin Pract* 2003;**57**:363–8.
- 19 **Thompson GR**. Combination therapy with statins. In: Gaw A, Packard CJ, Shepherd J, eds. *Statins: the HMG CoA reductase inhibitors in perspective*, 2nd ed. Martin Dunitz. 2004:189–99.
- 20 **Davidson MH**, McGarry T, Bettis R, *et al.* Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. *J Am Coll Cardiol* 2002;**40**:2125–34.  
▶ **Study showing additive effects of ezetimibe 10 mg daily in lowering LDL over a wide range of doses of simvastatin.**
- 21 **Gagne C**, Gaudet D, Bruckert E, *et al.* Efficacy and safety of ezetimibe coadministered with atorvastatin or simvastatin in patients with homozygous familial hypercholesterolemia. *Circulation* 2002;**105**:2469–75.
- 22 **De Jongh S**, Ose L, Szamosi T, *et al.* Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized, double-blind, placebo-controlled trial with simvastatin. *Circulation* 2002;**106**:2231–7.