Dyslipidaemia

— drug treatment

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Fish such as salmon can be used to derive omega-3 fatty acids which are effective in treating hypertriglyceridaemia

Lifestyle modifications are important in reducing cholesterol, but many people also require cholesterol-lowering drugs to reduce their risk of cardiovascular disease. This article outlines the different types of drug available and highlights some of the most important clinical trials to demonstrate efficacy

Epidemiological data give a clear indication of the scale of the problem of raised lipids within the UK population, particularly in view of our high levels of cardiovascular disease and the associated mortality. While other countries have had some success in lowering cardiovascular risk with clear health promotion messages which have resulted in changes in dietary habits, the UK has failed to make major advances using this approach.

While diet alone can be a useful tool to reduce cardiovascular risk within the population, in most individuals at risk, pharmacological strategies are also required to achieve target cholesterol levels. In addition, there are patients with genetic disorders resulting in higher serum cholesterol levels who require more aggressive management strategies. Specifically targeted drug therapy is usually required in this instance, depending on the underlying lipid abnormality. This article discusses the currently available drug classes used to treat dyslipidaemia.

Evidence for statins

Over the past 10 years, inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase — more commonly referred to as statins — have become the most commonly prescribed lipid lowering agents worldwide. These agents partially block the conversion of 3-hydroxy-3-methylglutaryl coenzmye A to mevalonic acid. This is an important regulatory step occurring early in the process of intracellular cholesterol biosynthesis within the liver. As a result, cholesterol levels fall rapidly on initiation and remain suppressed as long as the patient continues to take the medicine, although there is some evidence of tachyphylaxis over time. Statins have favourable effects across the full lipid profile, lowering low-density lipoprotein (LDL), which is most clearly associated with cardiovascular risk, as well as triglycerides and total serum cholesterol levels. In addition, statins increase levels of high-density lipoprotein (HDL) which has cardiovascular protective effects (see Panel 1, p178).

The popularity of statins stems from the wealth of clinical trial data confirming that the reduction in lipid levels in treated populations translates into a reduction in overall risk of cardiovascular events, in particular cardiac and total mortality, rates of myocardial infarction and the need for revascularisation procedures. For example, the landmark Scandinavian Simvastatin Survival Study (4S) published in 1994 treated 4,444 patients with established coronary disease and total cholesterol levels of 5.5–8.0mmol/L with simvastatin 20–40mg, or matched placebo, each evening.[2] The trial reported a 30 per cent reduction in all-cause mortality over the course of the five year study (absolute risk reduction [ARR] 4 per cent; P=0.0003) with a 34 per cent reduction in coronary events (ARR 9 per cent; P<0.00001).

The results of 4S have been repeated over the past decade with benefits demonstrated in a broad range of different patient groups with lower average cholesterol levels at enrolment. In secondary prevention, the Cholesterol and Recurrent Events (CARE) study (pravastatin 40mg vs placebo) treated patients with cholesterol levels <6.2mmol/L;[3] the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) study (pravastatin 40mg vs placebo) recruited coronary heart disease patients with cholesterol levels of 4–7mmol/L and with a wider range of co-morbidities;[4] and the Heart Protection Study (HPS) (simvastatin 40mg vs placebo) treated patients with established vascular disease or diabetes plus one cardiovascular risk factor and cholesterol levels above 3.5mmol/L.[5] All these studies demonstrated reductions in cardiovascular mortality and coronary events and overall these studies add to the evidence base to support the use of statins in women, the elderly and people with diabetes in particular. Similarly, evidence from studies such as West of Scotland Coronary Prevention study (WOSCOPS) and Air Force/Texas Coronary Atherosclerosis Prevention Studies (AfCAPS/TexCAPS) support the use of statins for primary prevention in patients at

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risk of cardiovascular events.[6,7] The Collaborative Atorvastatin Diabetes Study (CARDS) study focused on primary prevention of cardiovascular events by treatment of type II diabetes with low-dose atorvastatin and reported a 37 per cent reduction in the composite endpoint of acute coronary events, revascularisation procedures or stroke (P=0.001).[8]

More recently, a potential role in the early management of acute coronary syndromes has been established, even in patients with normal cholesterol levels. The Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction (PROVE-IT) study demonstrated that intensive lipid lowering with atorvastatin 80mg improves outcomes more than moderate lipid lowering with pravastatin 40mg in patients with acute coronary syndromes and cholesterol levels less than 6.2mmol/L.[9]

Adverse effects of statins

There has long been concern that statin therapy may precipitate liver failure. Minor transient elevations in liver enzymes are frequently seen during the first few months of statin therapy but usually resolve without progression. Significant liver elevations occur in a dose-dependent manner in up to 2 per cent of patients initiated on statin therapy. Reversal is frequently seen on withdrawal of the statin or following dose reduction and rarely recurs with rechallenge. Routine liver enzyme monitoring is recommended throughout statin therapy, particularly at baseline, one month, three months and six months after initiation and annually thereafter. Despite licensing restrictions, there is little evidence that statin therapy is harmful in patients with chronic liver disease such as hepatitis B or C, or cholestasis (an arrest in the flow of bile).

Myopathy (disease of the muscle) is a well-recognised adverse effect of statins, occurring in up to 5 per cent of patients. Most commonly this presents as non-specific muscle aches or joint pain without any change in creatine kinase (CK) levels. It is likely that statin therapy is a relevant factor in some, but not all, of these cases. Severe myopathy occurs much less frequently, probably in less than 0.2 per cent of patients on statins. There is a high risk of developing potentially fatal rhabdomyolysis where muscle pain, soreness or weakness is associated with elevations in CK levels in the order of 10 times the upper limit of normal (ULN) (normal range is 10–150IU/L). Immediate drug discontinuation is therefore essential. In patients reporting pain, but with lower CK levels (3–10 times the ULN), weekly monitoring is advised until the situation resolves or worsens (at which point the drug should be discontinued). Dose reduction may aid early symptom resolution and an earlier fall in CK levels. Muscle toxicity occurs more frequently in patients on combination drug therapy to lower lipids, such as statin plus fibrate or nicotinic acid. Patients must be advised to report any unexplained muscle pain or weakness which occurs during statin therapy, in order that CK levels can be checked. Other more commonly occurring adverse effects include gastrointestinal disturbance, rash and insomnia.

Recommended use of statins

The use of statins has been discussed in many clinical guidelines. A summary of the advice includes the following:

- Statins should be prescribed for all patients with known coronary disease (angina, previous myocardial infarction, surgical revascularisation or percutaneous coronary intervention) and in those patients at high risk of developing it (multiple risk factors, diabetics, strong family history of premature coronary events, etc). High risk is currently defined by the government as a cumulative risk of cardiac events of 30 per cent or more over the next 10 years, although more recent clinical guidelines have indicated that this threshold may be lowered to include risks of 20 per cent or more over 10 years.
- The absolute threshold for initiation is still controversial, but there is evidence that statin therapy is beneficial in cardiac patients or those at high risk with total cholesterol levels as low as 3.5mmol/L, before initiation. As a minimum, in line with current government guidelines, statins should be prescribed in cardiac patients with cholesterol >5mmol/L or LDL >3.0mmol/L, although more aggressive therapy will give further mortality and morbidity benefits.
- In terms of general lipid lowering for cardiovascular risk reduction, the majority of trial data support the use of simvastatin at a dose of 20–40mg daily or pravastatin at a dose of 40mg daily. More recent data to support cardiovascular outcome benefits in patients treated with high-dose atorvastatin have become available, but there remain concerns over safety and there are costs implications of taking such an approach across the general population.[10]
- The absolute benefits of statin therapy are greater in those at highest risk of cardiac events, ie, patients with higher baseline lipid levels, established coronary disease and multiple co-morbidities or risk factors.
- The summaries of product characteristics for the shorter acting statins (especially fluvastatin, pravastatin and simvastatin) recommend that the statin dose is taken at night to maximise levels during the time when the liver is most active in producing cholesterol. This is not essential with longer acting agents such as atorvastatin or rosuvastatin.
- Statin therapies are generally well-tolerated, but care should be taken to discuss any adverse effects with the patients and tailor drug and dose to minimise side effects where possible, with the aim of improving long-term concordance.
- Total serum cholesterol and liver function should be checked at least annually once the patient is stable on statin therapy.
- Statins are associated with a number of common drug interactions as a result of inhibitory effects on the cytochrome P450 system.

Fibrates

Fibric acid derivatives (fibrates) were widely prescribed in the 1980s and 90s but their use has gradually fallen as evidence to support the role of statins has grown. The primary effect of fibrates is a marked reduction in triglyceride levels but, in addition, moderate reductions in LDL cholesterol may be seen in individuals with raised levels at initiation alongside an increase in HDL cholesterol (see Panel 1). Four key mechanisms are responsible for the effects of fibrates:

- Increased lipolysis
- Increased hepatic fatty acid uptake and reduced hepatic triglyceride production
- Increased LDL uptake by LDL receptors
- Stimulation of reverse cholesterol transport resulting in increased HDL

Fibrates are primarily employed to lower triglyceride levels in patients with isolated hypertriglyceridaemia but can be also be useful in the treatment of mixed hyperlipidaemia, especially where HDL levels are low.

Panel 1: Effect of drug therapy on cholesterol subtypes[1]

Cholesterol subtype	Approximate effect of drug therapy: Statin	Fibrate	Niacin
Total cholesterol	↓ 15–40%		
Low-density lipoprotein	↓ 20–60%	↓ 10–15%	↓ 20–30%
High-density lipoprotein	↑ 5–15%	↑ 5–20%	↑ 15–35%
Triglycerides	↓ 10–40%	↓ 20–50%	↓ 20–50%

They may be added to statin therapy where target levels have not been achieved on monotherapy, and can be used as an alternative where patients fail to tolerate statin therapy. It must be noted that co-prescribing statins with fibrates markedly increases the risk of myopathy, and newer agents (such as ezetimibe) may be a more appropriate choice.

Evidence of cardiovascular benefits from cholesterol lowering using fibrate therapy is less compelling than for the statins. The Veteran Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) was designed to look at the benefits of raising HDL levels in a group of coronary heart disease patients with low HDL levels at baseline (HDL<1mmol/L, LDL<3.6mmol/L, triglycerides<3mmol/L). Over the course of the study LDL levels remained constant, while triglycerides fell 31 per cent and HDL levels increased 6 per cent. These changes were associated with a 22 per cent reduction in the risk of coronary events (composite endpoint of coronary heart disease death and non-fatal myocardial infactions) over the five year study (ARR 4 per cent, *P*=0.006).[11] The Bezafibrate Infarction Prevention (BIP) study was similarly designed, but failed to show a reduction in the risk of cardiovascular events across the whole population despite a 17.9 per cent increase in HDL. A post-hoc analysis of the sub-group recruited with raised triglycerides alongside a low HDL identified an impressive 39.5 per cent reduction in risk of death or myocardial infarction (ARR 7.7 per cent; *P*=0.02),[12] which warrants further prospective investigation.

In primary prevention studies, treatment with fibrates has similarly been shown to reduce the frequency of coronary events. All studies have used composite endpoints to demonstrate cardiovascular outcome benefits — there remains no evidence of mortality benefits alone for fibrates in either primary or secondary prevention studies.

Adverse effects of fibrates

Fibrates are generally well-tolerated, with the most frequent adverse effect being gastrointestinal disturbance (reported in up to 5 per cent of patients). As with statins, changes in liver enzyme levels can occur, particularly on initiation of therapy, but there is no evidence of progression to liver failure or hepatitis. Myopathy is rarely reported when fibrates are prescribed alone. A risk/benefit assessment must be undertaken before prescribing combination therapy.

Bile acid sequestrants

Bile acid sequestrants have been employed to lower cholesterol levels for at least 30 years. They act by a dual mechanism involving increased clearance of cholesterol and reduced recirculation of bile acids. Firstly, they bind bile acids in the intestine, thus preventing their entero-hepatic recirculation. As a result bile acid excretion is increased up to 10-fold and, as the bile acid pool falls, the liver responds by increasing bile acid production via cholesterol breakdown. In addition, LDL receptors are upregulated to increase the binding of LDL cholesterol, resulting in a further fall in circulating cholesterol levels.

Bile acid sequestrants primarily reduce LDL cholesterol by 15–30 per cent, but can also increase HDL levels by up to 5 per cent. Unfortunately, in some patients, bile acid sequestrants can increase triglyceride levels, and they must therefore be avoided in patients with hypertriglyceridaemia or mixed hyperlipidaemia with significantly raised triglycerides. In terms of cardiovascular risk reduction, early lipid lowering trials conducted in the 1980s, such as the Lipid Research Clinics Coronary Primary Prevention study, demonstrated that bile acid sequestrants can reduce cardiac events and atherosclerotic progression.[13] They are particularly useful in treating patients with isolated raised LDL cholesterol levels or as an add-on to other drug classes which have failed to achieve therapeutic targets when prescribed alone.

The primary problem with bile acid sequestrants is that many patients find them unpalatable. They are usually taken, up to four times daily, in the form of a powder mixed in a relatively large volume of water. At maximum doses they frequently cause bloating, abdominal discomfort, gastro-oesophageal reflux and constipation. In addition to binding bile acids, these agents can also bind drug therapy, such as digoxin, levothyroxine or warfarin. As a result, it is important to pay attention to the times these drugs are administered in relation to the bile acid sequestrants. The dosing interval should be at least one hour before or 4–6 hours after the bile acid sequestrants.

Ezetimibe

Launched in 2003, ezetimibe is the first in a new class of lipid lowering therapies. It acts by blocking the intestinal absorption of cholesterol by selective inhibition of transport mechanisms within the brush-border surface of the intestinal epithelial cells. As cholesterol delivery from the intestine falls, the liver increases uptake from the circulation to compensate, hence serum cholesterol levels fall. As a monotherapy, the primary effect of ezetimibe is to reduce LDL cholesterol levels by up to 18 per cent, with little impact on triglycerides and HDL cholesterol levels. When combined with statin therapy, it can produce an additional 20 per cent reduction in serum LDL cholesterol concentrations over and above that of statin monotherapy, with a reduction in triglyceride levels (approximately 9 per cent), and a small increase in HDL cholesterol (approximately 3 per cent). Ezetimibe, at a dose of 10mg daily, is licensed for the treatment of primary hypercholesterolaemia.

At present its main use is for patients who fail to reach therapeutic targets on statin therapy alone, or as a monotherapy in patients unable to tolerate statins. In short-term studies, ezetimibe has been found to have a similar side effect profile to placebo and is therefore generally well-tolerated. The most commonly reported adverse effects include headache, abdominal pain and diarrhoea. Long-term data are needed to confirm safety before widespread use can be recommended, particularly as no cardiovascular outcomes data are available at this time, although studies are ongoing. A recent *Drug and Therapeutics Bulletin* concluded that, based on current evidence, ezetimibe "offers no advantage over, and should not replace, a statin alone in the routine management of patients at increased risk of developing complications of atherosclerotic disease" and further commented on the addition of ezetimibe to statin therapy "such a strategy is no safer and is much more expensive than maximising the dose of statin".[14] Co-administration of ezetimibe and a fibrate is not currently recommended. A combination statin-ezetimibe product is due to be launched in the UK imminently.

Nicotinic acid derivatives

Nicotinic acid, or niacin, and related compounds are known to reduce cholesterol levels substantially (Panel 1, p178), although the exact mechanism of this reduction is not fully understood. It is postulated that their primary action is by inhibiting the release of free fatty acids from adipose tissue, reducing the amount available to the liver for the production of triglycerides, very-low-density lipoprotein (VLDL) and hence LDL. As a result plasma triglyceride and LDL-cholesterol levels fall, and HDL levels increase. The dose of nicotinic acid required to lower cholesterol is much higher than those used to correct vitamin deficiency in the diet. Levels of circulating HDL can be increased with a dose of 1g per day, but 2–6g daily is required to have the maximum effect on other lipid subtypes.

The cardiac benefits of nicotinic acid were established as early as the 1970s. The Coronary Drug Project showed a reduction in recurrent myocardial infarction in patients treated with nicotinic acid.[15] A further 15-year follow-up study showed a reduction in total mortality in the group originally randomised to receive niacin treatment.[16] Despite the clinical evidence, nicotinic acid derivatives have never achieved widespread use in the UK due to a poor side effect profile, with high rates of prostaglandin-mediated flushing of the face and neck, dizziness and palpitations. Tolerance to these effects does develop with continued therapy, but their frequency and severity can be reduced by a slow dose-titration programme at initiation, avoidance of compounds known to exacerbate flushing (such as caffeine- and alcohol-containing drinks) and suppression of prostaglandins using low doses of aspirin and ibuprofen. Other common problems reported during therapy include gastrointestinal upset, loss of glycaemic control in diabetic patients and gout due to increased urate levels.

More recently, a slow release formulation of nicotinic acid has been launched, which is generally better tolerated, as peak drug levels are lower. Preliminary data from the small Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER-2) study were recently announced. This angiographic study compared the effect of nicotinic acid in combination with a statin, with a statin alone, and demonstrated a slower progression of atherosclerosis over a year.[17]

The trial also reported a non-significant reduction in cardiac events, but further trial work is required to fully establish the impact of nicotinic acid on cardiovascular outcomes. The primary effect of nicotinic aicd in this study was to raise circulating HDL cholesterol levels. Further data from the American Heart Association (AHA) support the view that increasing HDL levels can have a more powerful effect on cardiovascular event reduction than LDL lowering.[18] Nicotinic acid is particularly useful in patients with a mixed hyperlipidaemia, raised LDL, raised triglycerides, and low HDL (sometimes referred to as the "lipid triad"). Nicotinic acid may also be added to statin or fibrate therapy if the response to monotherapy is inadequate.

Fish oil supplements

Epidemiological evidence has long suggested that diets rich in omega-3 fatty acids derived from fish oils reduce the risk of cardiovascular events. Omega-3 fatty acids, particularly eicosapentanoic acid and docosahexanoic acid, have a number of effects on lipids and lipid metabolism, but the cardiovascular protective effects may be linked to other non-lipid actions, including changes in blood pressure, arterial compliance, platelet activity, endothelial function and vascular reactivity.

In terms of lipid lowering, omega-3 fatty acids suppress hepatic triglyceride and VLDL production and increase the conversion of VLDL to LDL. As a result triglyceride levels fall by up to 30 per cent, with a small increase in HDL levels. An associated rise in LDL cholesterol levels can exacerbate hypercholesterolaemia if present. Omega-3 fatty acid supplementation, at doses of 4–6g daily, is primarily used to treat hypertriglyceridaemia. In addition, they may be added to other drug classes such as statins or fibrates for greater lipid lowering efficiacy. Lower doses (1g daily) may be used to reduce cardiovascular risk in high-risk patients following the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardio (GISSI-Prevenzione study), an open label post-myocardial infarction trial investigating the effects of low-dose omega-3 fatty acid supplementation. A 10 per cent reduction in the composite end point of death, myocardial infarction and stroke was reported, with most of the benefit attributed to an unexpected 44 per cent reduction in the rates of sudden cardiac death in the group treated with omega-3 fatty acids.[19] The main adverse effects of these drugs are gastrointestinal, with diarrhoea commonly reported.

Summary

Statin therapy remains the mainstay of therapy for the majority of patients, but in many cases, a combination of two (or occasionally more) agents may be required to reach the ever more aggressive lipid management goals. It is important to remember that lipid lowering is one of a number of treatment strategies which should be employed to lower the cardiovascular risk in individual patients.

References

1. Gotto AM, editor. Contemporary diagnosis and management of lipid disorders. Pennsylvania, USA: Handbooks in Healthcare Company; 2001.
2. Randomised trial of cholesterol lowering in 4,444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383–9.
3. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, et al. The effect of pravastatin on coronary events after MI in patients with average cholesterol levels. New England Journal of Medicine 1996;335:1001–9.
4. The LIPID Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. New England Journal of Medicine 1998:339:1349–57.
5. Heart Protection Study Collaborative Group. Heart protection study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomized placebo-controlled trial. Lancet 2002:360:7–22.
6. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. New England Journal of Medicine 1995;333:1301–7.
7. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: Results of AFCAPS/TexCAPS. JAMA 1998;279:1615–22.
8. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 2004;364:685–96.
9. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. New England Journal of Medicine 2004;350:1495–504.
10. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart J-C, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. New England Journal of Medicine 2005;352:1425–35.
11. Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, et al, for the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Study Group. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. New England Journal of Medicine 1999;341:410–18.
12. BIP Study Group. Secondary prevention by raising HDL cholesterol and reducing triglyceride levels in patients with coronary heart disease: the Bezafibrate Infarction (BIP) Study. Circulation 2000;102:21–7.
13. Lipid Research Clinics Program. The Lipid Research Clinics coronary prevention trial results II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. JAMA 1984:251;365–74.
14. Ezetimibe — a new cholesterol-lowering drug. Drugs and Therapeutics Bulletin 2004:42;65–7.
15. Coronary Drug Project Research Group. Clofibrate and niacin in coronary heart disease. JAMA 1975:231:360–81.
16. Coronary Drug Project Research Group. Fifteen year mortality in coronary drug project patients: long-term benefit with niacin. Journal of the American College of Cardiology 1986;8:1245–55.
17. Taylor AJ, Sullenberger LE, Lee HJ, Lee JK, Grace KA. Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2: a double-blind, placebo-controlled study of extended-release niacin on atherosclerosis progression in secondary prevention patients treated with statins. Circulation 2004;110:3512–7.
18. Alsheikh-Ali AA, Abjourjaily HM, Stanek E. Increases in HDL-cholesterol are the strongest predictors of risk reduction in lipid intervention trials. Circulation 2004;110(Suppl III):813.
19. Marchioli R, Barzi F, Bomba E, Chieffo C, Di Gregorio D, Di Mascio R, et al. Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione. Circulation 2002;105:1897–903.