

DRUG UPDATE

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ADJUNCTS AND ALTERNATIVES TO STATINS

Statins are the agents of choice for lowering LDL-cholesterol in the prevention of heart disease but some patients do not achieve target lipid levels. Compliance should be addressed before assuming the patient is resistant to a statin. Adding a fibrate, nicotinic acid or ezetimibe lowers LDL-C by more than a statin alone but increases cost and the risk of adverse effects. Combination therapy should therefore be reserved for patients with established atheroma or at high cardiovascular disease risk. Adjunctive ezetimibe offers the largest reduction in LDL-C; adding a fibrate or nicotinic acid to a statin may be indicated in patients with low HDL-C or hypertriglyceridaemia. The relative long-term efficacy of these adjunctive therapies is unknown.

Achieving cholesterol targets

The National Service Framework (NSF) for Coronary Heart Disease (CHD) states that a statin should be prescribed for patients with a history of vascular disease and those at high coronary risk to reduce LDL-cholesterol (LDL-C) to below 3 mmol/l (or total cholesterol level to below 5 mmol/l) or by 30%, whichever is greater.¹ Statins - for example, simvastatin 40 mg/day - can reduce LDL-C by 40%.²

The NSF target may not be achieved in some patients despite lifestyle change and treatment with a statin at the maximum tolerated dose; adjunctive treatment may then be necessary. Some patients may not be able to tolerate a statin, in which case an alternative lipid-lowering therapy is indicated.

Fibrates

Overall, fibrates reduce LDL-C by 7 - 11%, increase HDL-C by 10 - 15% and lower triglycerides.³ Low HDL-C is an independent risk factor for CHD but target levels have not been set in the CHD NSF. As secondary prevention, fibrates are not as effective as statins in reducing CHD events.⁴ They do significantly reduce the risk of these events in patients with a low HDL-C (1 mmol/l)⁵ so are appropriate for patients with low levels of HDL-C³ or combined hyperlipidaemia (e.g. associated with diabetes⁶). Adding a fibrate to a statin further lowers LDL-C by about 8% in patients with hypercholesterolaemia.⁷

Nicotinic acid

Nicotinic acid lowers LDL-C by 5 - 25%, raises HDL-C by 15 - 35% and lowers triglyceride levels⁸. Adding nicotinic acid to a statin further lowers LDL-C in hypercholesterolaemia by 13%⁷ and reduces the combined risk of coronary events.⁸ Treatment is limited by a high frequency of adverse effects due to vasodilatation, especially flushing,⁹ this is less of a problem with the modified-release formulation⁸ but the long-term efficacy of this formulation is unknown. Nicotinic acid is associated with a dose-related worsening of glucose intolerance.⁸

Anion exchange resins

Colestyramine and colestipol impair the absorption of vitamins and other drugs and are associated with a high frequency of adverse gastrointestinal effects.⁹ Colestyramine lowers LDL-C by an average of 12%¹⁰ but it may worsen hypertriglyceridaemia.⁹

Ezetimibe

Given alone, ezetimibe reduces LDL-C by approximately 18% and slightly increases HDL-C; in combination with a statin it further lowers LDL-C by 12 - 20%.¹¹ Common adverse events in clinical trials were headache, abdominal pain and diarrhoea. There are no long-term data on the efficacy of ezetimibe in preventing cardiovascular events and the drug is not licensed for this indication.

When should combination therapy be used?

The most likely reason that statin therapy does not achieve the target level for LDL-C is a failure of concordance and this should be remedied before assuming the patient is resistant to a statin. A statin may be ineffective in patients with familial hyperlipidaemia, who should be referred to a specialist.

There is a lack of evidence to guide the choice of adjunctive or alternative treatment after the failure of statin therapy. Fibrate monotherapy is mainly used to treat hypertriglyceridaemia. A combination of a statin with a fibrate may, under specialist supervision, be indicated for the treatment of severe hyperlipidaemia⁹ or in patients with low HDL-C and low LDL-C. NICE recommends this combination for patients with type 2 diabetes who have hyper-triglyceridaemia.¹² Fibrates may be better tolerated than nicotinic acid though their effects on lipids are smaller. The combination of a statin with a fibrate or nicotinic acid is associated with an increased risk of severe muscle toxicity; in particular, gemfibrozil should not be combined with a statin.⁹ Resins are too inconvenient for routine use and more expensive than other options.

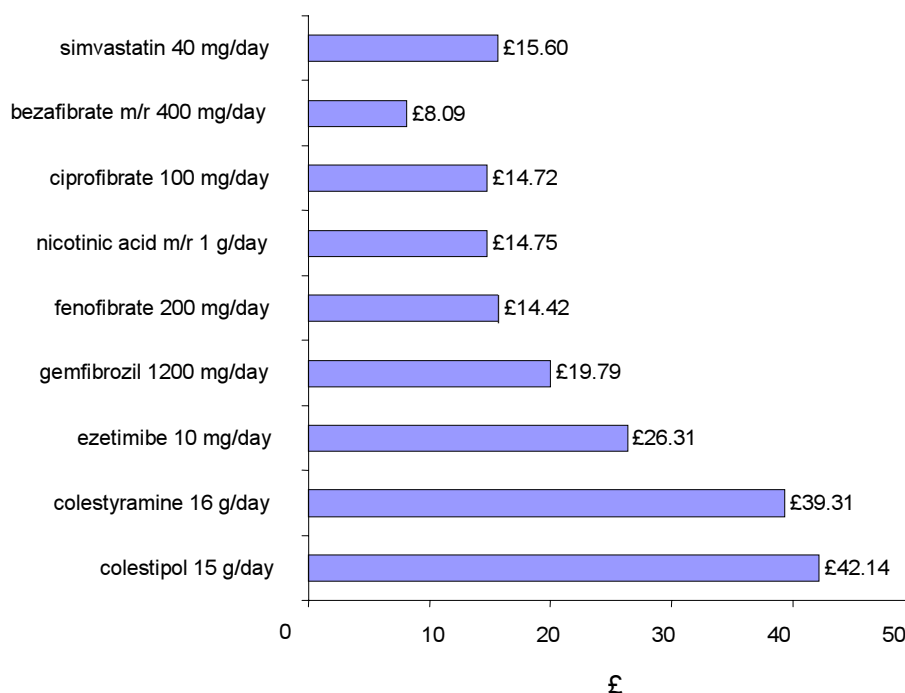
Ezetimibe is licensed as monotherapy when a statin is not suitable or in combination with a statin in patients with hypercholesterolaemia. It is unclear how ezetimibe compares with a fibrate as an adjunct to treatment with a statin but indirect comparisons suggest that it may be associated with a greater reduction in LDL-C. Short-term clinical trials suggest that adding ezetimibe does not increase the risk of muscle

toxicity but the incidence of clinically significant elevation of serum transaminases is increased from 0.4% to 1.3%.¹¹

The risk of adverse effects and cost of combination therapy are greater than monotherapy with a statin. Such therapy should therefore be considered only for patients with established atheroma or at high cardiovascular risk.

How much does it cost?

Cost of 28 days' treatment (prices from MIMS/Drug Tariff February 2005)



N.B. Doses shown are for general comparison only and do not imply therapeutic equivalence.

REFERENCES

- 1 Department of Health. National Service Framework for Coronary Heart Disease. 2000 (G)
- 2 Law MR et al. Quantifying effects of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *BMJ* 2003;326:1423-9 (MA)
- 3 PRODIGY Guidance - Hyperlipidaemia. July 2003 (www.prodigy.nhs.uk) Accessed 30.7.04 (G)
- 4 NHS Centre for Reviews and Dissemination. Cholesterol and coronary heart disease: screening and treatment. *Effective Health Care Bulletin* 1998;4 No. 1 (R)
- 5 Rubins HB et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. *N Engl J Med* 1999;341:410-8 (RCT)
- 6 Athyros VG et al. Atorvastatin and micronized fenofibrate alone and in combination in type 2 diabetes with combined hyperlipidaemia. *Diabetes Care* 2002;25:1198-1202 (RCT)
- 7 Thompson GR. Management of dyslipidaemia. *Heart* 2004;90:949-55 (R)
- 8 UK Medicines information Service. Nicotinic acid (modified release). *New Medicines Profile* 2004 No. 04/01 (R)
- 9 British National Formulary No. 48. September 2004
- 10 The Lipid Research Clinics Coronary Prevention Trial results II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. *J Am Med Assoc* 1984;251:365-74 (RCT)
- 11 Regional Drug & Therapeutics Centre. Ezetimibe. *New Drug Evaluation* No. 60. August 2003 (R)

KEY RCT - randomised controlled trial, CT - controlled trial, O - open study, MA - meta analysis, R - review, U - unpublished, A - abstract, E - editorial, G - guideline

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