

DRUG UPDATE

No. 29

April 2004

STATINS

Statins reduce morbidity and mortality in patients at an increased risk of cardiovascular events, regardless of plasma lipid concentrations. Statin therapy should therefore be prescribed for all patients with a history of vascular disease as well as those with a high CHD risk. If a threshold for starting lipid therapy is advocated a baseline total cholesterol of 3.5 mmol/L should be considered but emphasis should be on treating risk rather than cholesterol concentration. There is evidence for benefit in people at least up to the age of 80 years and statin therapy should not be denied on grounds of age alone. Based on current evidence and cost simvastatin at a dose of 40 mg daily is the statin of choice for the primary and secondary prevention of CHD.

Current guidance

The NSF on coronary heart disease (CHD) states that statins should be prescribed for secondary prevention in people with clinical evidence of CHD or other occlusive artery disease, and for primary prevention in people with a 10-year CHD risk greater than 30%.¹ The aim of treatment is to lower total cholesterol (TC) to <5 mmol/L (LDL cholesterol (LDL-C) to <3 mmol/L) or by 30%, whichever is the greater.¹ The Joint British recommendations on prevention of CHD go further, suggesting that if a patient has an absolute risk of 15% or greater of developing CHD over the next 10 years (equivalent to cardiovascular disease (CVD) risk of 20%), this is sufficiently high to justify drug treatment for high blood pressure and/or hyperlipidaemia.² The recently published 2004 British Hypertension Society Guidelines recommend statin therapy for secondary prevention in all hypertensive patients with a baseline TC \geq 3.5 mmol/L, and for primary prevention in hypertensive patients who have a TC \geq 3.5 mmol/L and an estimated 10 year CVD risk of \geq 20%.^{3,4} NICE guidance on the use of statins for the prevention of coronary events is due in April 2005.

Special populations

Elderly

The Heart Protection Study (HPS), the largest cholesterol study to date, was reviewed in a previous Drug Update.^{5,6} This study included 20,536 patients with coronary disease, diabetes or other occlusive arterial disease and a non-fasting TC \geq 3.5 mmol/L, 5,806 patients were at least 70 years old at study entry.⁵ Patients were randomised to simvastatin 40 mg daily or placebo for a mean of 5 years. A prespecified subgroup analysis demonstrated that the reduction in risk of a first major vascular event in elderly patients (65 to 80 years) taking simvastatin was similar to that of the whole cohort.⁵

In the PROSPER trial, 5,804 patients aged 70 to 82 years with a history of, or risk factors for vascular disease were randomised to pravastatin 40 mg daily or placebo for a

mean of 3.2 years.⁷ The primary endpoint was a composite of coronary death, non-fatal myocardial infarction (MI), and fatal or non-fatal stroke. Pravastatin was associated with an absolute risk reduction in the primary endpoint of 2.1% ($p=0.014$, numbers needed to treat of 48 over 3.2 years). However, a post-hoc analysis showed the risk reduction was not statistically significant in the subgroup of patients without prior vascular disease.⁷

Patients who have a reasonable life expectancy and quality of life should not be denied lipid-lowering therapy on the grounds of age alone.

Type 2 diabetics

Current NICE guidance on lipid management in type 2 diabetes recommends monitoring of lipid levels but no lipid lowering drug therapy in patients with a normal lipid profile (LDL-C <3 mmol/L or TC <5 mmol/L and fasting triglycerides <2.3 mmol/L).⁸ However, in a recent sub-analysis of the HPS, simvastatin produced significant reductions in the risk of first major coronary events, stroke or revascularisation in patients \geq 40 years with (mostly) type 2 diabetes, even if they had normal cholesterol levels and/or no manifest CHD.⁹ The authors concluded that statin therapy should be considered routinely for all diabetic patients at sufficiently high risk of major vascular events, irrespective of their baseline cholesterol values.⁹ Two further recent, randomised trials involving large numbers of patients with type 2 diabetes compared statin therapy with either placebo or usual care.^{10,11} In the ALLHAT-LLT trial, treatment with pravastatin 40 mg daily for a mean of 4.8 years was not associated with a significant reduction in all cause mortality or coronary event rates compared with usual care in approximately 10,000 hypertensive patients, of whom 3638 had type 2 diabetes at study entry.¹⁰ However, there was only a modest difference in LDL-C and TC levels between the 2 groups at the end of the study, probably because of the high use of statins in the usual care group (17% of patients at year 4).¹⁰ The ASCOT-LLA trial compared

atorvastatin 10 mg daily with placebo in 10,305 hypertensive patients who were followed up for a median duration of 3.3 years. Atorvastatin was associated with a significant reduction in the incidence of non-fatal MI and fatal CHD compared with placebo. The difference was not significant in patients with diabetes (n=2532), but the study may not have been adequately powered to detect a difference in this subgroup.¹¹

Which statin?

Based on current evidence and cost, generic simvastatin at a dose of 40 mg daily is the statin of choice for the primary and secondary prevention of CHD. Pravastatin 40 mg daily (also licensed for primary and secondary

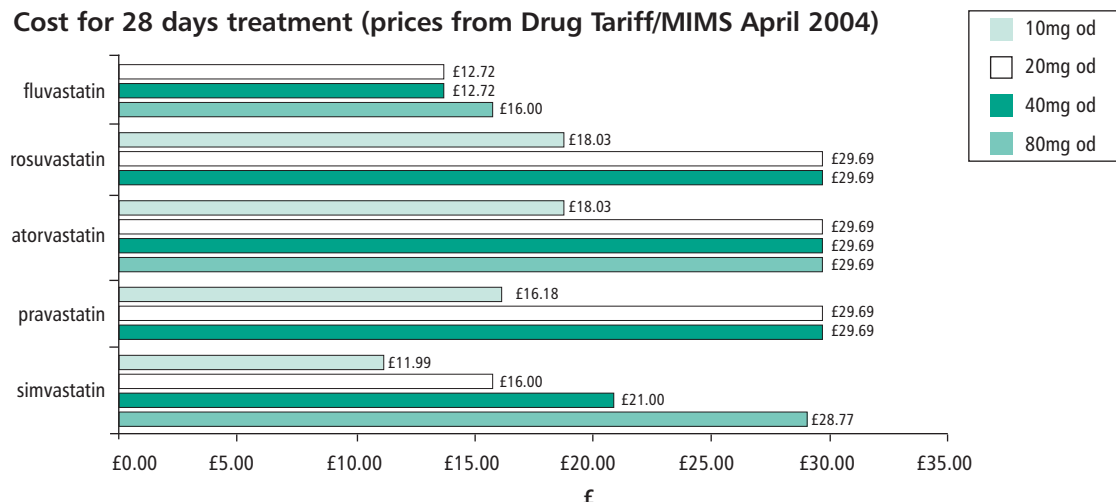
prevention) has an evidence base to support its use first-line but it is less potent at lipid lowering than simvastatin.^{7,12-15} The patent for pravastatin will expire in August 2004 with a likely reduction in costs over time.

Atorvastatin (10-80 mg daily) is a second-line choice for most patients however a recent trial provides preliminary evidence to support the use of atorvastatin 80 mg od for intensive lipid-lowering in certain high risk patients (see Rapid Appraisal No. 1).^{16,17}

The routine use of rosuvastatin cannot be recommended at present. It offers little advantages over existing statins, and there are no published long-term clinical outcome or safety data.¹⁸

How much does it cost?

Cost for 28 days treatment (prices from Drug Tariff/MIMS April 2004)



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

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

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