

DRUG UPDATE

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STATINS

Treatment with a statin reduces morbidity and mortality in people at increased risk of cardiovascular events, regardless of their lipid levels. A statin should therefore be prescribed for all patients with a history of vascular disease as well as those with a 10-year CHD risk greater than 30%. Of the four statins available, only pravastatin and simvastatin are licensed for CHD prevention; simvastatin will soon be available as a generic formulation.

What are they?

Simvastatin, pravastatin, atorvastatin and fluvastatin reduce plasma concentrations of total cholesterol, LDL-cholesterol and triglycerides and increase plasma HDL-cholesterol¹. All are licensed as adjuncts to diet to reduce raised plasma cholesterol levels. All except atorvastatin are also licensed to slow the progression of coronary atherosclerosis in patients with coronary heart disease (CHD). In addition, pravastatin and simvastatin are licensed as primary and secondary prevention of cardiovascular events in patients with CHD whose total cholesterol levels exceed 5.5 mmol/l (simvastatin) or 4.8 mmol/l (pravastatin).

What is the rationale for their use?

Several large placebo-controlled trials published in the 1990s established that long-term (around 5 years) treatment with a statin reduces the risk of major coronary events by approximately one-third as primary and secondary prevention, and reduces overall mortality by approximately a quarter as secondary prevention²⁻⁶. Further analyses of studies involving pravastatin have confirmed that these benefits occur in older (up to 75 years) and younger patients⁷, in men and women, in patients at high or low risk of CHD and with different risk factors⁸. Statins also reduce the risk of non-haemorrhagic stroke by 23 - 29% in patients with CHD^{9,10}.

In 2002, the Heart Protection Study¹¹ showed that a broader range of people in the UK could benefit from treatment with a statin. 20,536 people with CHD, other occlusive arterial disease or diabetes, were randomised to treatment with simvastatin 40 mg/day or placebo for 5 years. Simvastatin produced a 1.8% absolute reduction in all-cause mortality, largely due to an 18% relative reduction in coronary deaths. The statin was also effective as primary prevention, reducing the incidence of first myocardial infarction, stroke or revascularisation by 24%. The risk of major vascular events was reduced in all subgroups of patients, regardless of their history of cardiovascular disease, diabetes or age and were also apparent in people with low cholesterol levels at baseline (LDL-C <3.0 mmol/l or total cholesterol <5.0 mmol/l), with no evidence of a threshold effect. The data indicates that treating 1000 high-risk patients for 5 years would prevent 70 - 100 major vascular events.

When should they be used?

The Coronary Heart Disease National Service Framework specifies that statins should be prescribed for secondary prevention in people with CHD or other occlusive arterial disease, and as primary prevention in people with a 10-year CHD risk greater than 30%. The aim of treatment is to lower LDL-C to <3.0 mmol/l or total cholesterol to <5.0 mmol/l, or by 30%, whichever is greater. Statins are one of several interventions that should form a strategy to reduce cardiovascular risk.

The Heart Protection Study confirms that the decision to offer primary preventative treatment should be determined by an individual's cardiovascular risk, not their lipid levels. Guidance has been published on using risk assessment tools to estimate risk in people who do not have CHD or atherosclerotic disease^{1,12,13}. Factors that should be taken into account include lifetime smoking history, blood pressure and age¹³. The Joint British Societies Coronary Risk Prediction Chart¹³ allows risk to be estimated separately for people with or without diabetes.

These tools are an aid to decision-making; they underestimate risk for patients who are at higher risk due to CHD or inherited dyslipidaemia (who should be prescribed a statin or other lipid-lowering therapy anyway); for British South Asians, people aged 75 or older; women with a confirmed premature menopause and for patients with established hypertension, target organ damage or chronic renal dysfunction^{1,13}.

Statins are contraindicated in patients with active liver disease and during pregnancy and breast-feeding. They should be used with caution in patients with a history of liver disease or high alcohol intake.

How should treatment be initiated and monitored?

The recommended dose for pravastatin is 10 - 40 mg/day and for simvastatin 20 - 80 mg/day; recent major prevention trials used a dose of 40 mg/day for both. The dose should be adjusted at intervals of 4 - 6 weeks depending on LDL-C or total cholesterol levels. Once dose stabilisation is achieved, lipids should be checked annually¹.

What are the adverse effects?

Full details of the adverse effects are listed in the summaries of product characteristics. Cerivastatin was withdrawn by the manufacturer in 2001 following reports of rhabdomyolysis¹⁴. The European Medicines Evaluation Authority is currently reviewing the safety of all statins and is due to report its findings shortly. In the Heart Protection Study, the incidence of myopathy with persistently elevated creatine kinase was 0.07% with simvastatin and 0.01% with placebo ($p < 0.07$); one patient in each group developed myopathy¹¹. Patients should be advised to report unexplained muscle pain or weakness, and treatment should be discontinued if creatine kinase elevation exceeds 10 times the upper limit of normal. Concurrent use of a fibrate, nicotinic acid or ciclosporin increases the risk of muscle damage.

Which statin for primary and secondary prevention?

Simvastatin and pravastatin are currently the only statins licensed for these indications. No long-term studies have directly compared their efficacy in reducing morbidity and mortality. The branded formulations cost the same; simvastatin will shortly be available as a generic formulation.

How much is prescribed?

National surveys of prescribing before the publication of the CHD NSF show that statins were greatly under-used, even in people with high cardiovascular risk^{15,16}.

How much do they cost?

Cost for 28 days treatment (prices from Drug/Tariff/MIMS November 2002)



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KEY RCT - randomised controlled trial, CT-controlled trial, O-open study, MA-meta analysis, R-review, U-unpublished, Abs- abstract, E-editorial, CC-case control study, C-cohort study, L-letter

NHS Northern & Yorkshire
Regional Drug & Therapeutics Centre
Wolfson Unit, Claremont Place, Newcastle Upon Tyne NE2 4HH
Tel: 0191 232 1525 Fax: 0191 261 9359
e-mail: nyrdtc.di@ncl.ac.uk website: www.nyrdtc.nhs.uk