

Optimising the use of statins - using statins wisely

Lowering total blood cholesterol and low-density lipoprotein (LDL) cholesterol can reduce coronary events and mortality from coronary heart disease (CHD) in both primary and secondary prevention settings. Clinical trials of statins have shown that the largest reductions in the risk of coronary events occur in patients with established CHD.

The absolute benefits of lowering cholesterol concentrations in people without clinical evidence of CHD are smaller. People at highest risk get greatest benefit; therefore, for primary prevention, formal risk calculation is needed to identify those who have most to gain from intervention.

When assessing patients for CHD prevention it is essential that all risk factors are considered. Research has led to a better understanding of the diseases and therapies that affect vascular risk and the individuals who might benefit from treatment.

This bulletin reviews recent evidence on statins to answer particular questions about their use. It discusses:

- ♦ measuring cholesterol and assessing a person's risk of cardiovascular disease (CVD)
- ♦ current national guidance and targets for using statins in people at risk of CVD
- ♦ study findings that might influence policies on statin use
- ♦ the use of different statins and doses
- ♦ issues surrounding the availability of statins over-the-counter
- ♦ important information regarding monitoring statin therapy and potential interactions with other medications.

Summary

- ♦ There is now evidence that statins are effective in reducing the incidence of CVD events in all patients with atherosclerotic vascular disease, including women, patients up to 80 years of age, those with diabetes, and those with 'normal' and 'low' cholesterol levels.
- ♦ Guidelines recommend statin therapy in patients with established CVD, diabetes, and in people who have a predicted coronary event risk of greater than 30% over 10 years. Whether targeting people who have lower levels of risk is feasible is contentious.
- ♦ Lowering cholesterol concentrations is desirable but when the percentage reduction required is high this must be balanced against the risks associated with the statin doses or lipid-lowering regimens required.
- ♦ Selection of a specific statin should be based on clinical evidence and cost; generic simvastatin is a rational first-line choice for those with significant CVD risk. Atorvastatin is an alternative.
- ♦ Rosuvastatin[▼] and, the new cholesterol-lowering drug, ezetimibe[▼], should not be used routinely in general practice. There is however considerable variation in prescribing of these products across Wales.
- ♦ There is new cautionary advice that prescribers need to be aware of regarding contraindications and drug interactions with statins.
- ♦ Simvastatin 10 mg daily has recently become available over-the-counter. Prescribers should be alert to the possibility that people may be purchasing this treatment and, especially for people at low risk, the potential benefit is unproven and may be limited.

Measuring cholesterol

When managing a person's CVD risk, decisions about lowering cholesterol should be based on the average of at least two measurements. Total cholesterol and high-density lipoprotein (HDL) cholesterol concentrations can be determined from an initial non-fasting sample (the screening test). The ratio of total cholesterol to HDL cholesterol is used in CVD risk calculations as it is a more accurate predictor of risk than total cholesterol concentration alone. The second measurement should, preferably, be made a few weeks later and should be a full fasting lipid profile. This test should be done to confirm a suspicion of high cholesterol and is required for accurate determination of LDL cholesterol and triglyceride concentrations.

Assessing risk

Because simultaneous evaluation of risk factors for CVD (e.g. age, gender, family history, smoking status, blood pressure, cholesterol concentration, glucose tolerance) is difficult, various assessment tools have been developed. To date the most widely used have been tables which estimate CHD risk; however, with clinical evidence that cholesterol-lowering therapy can prevent stroke and other vascular events, new charts that estimate the risk of any vascular event occurring (i.e. CVD risk) are preferred. Updated charts from the British Hypertension Society (BHS) appear in the March 2005 edition of the BNF.¹ The Joint British Societies' 'Cardiac Risk Assessor' computer programme² and the updated European guidelines³ also discuss CVD risk.

CHD risk - risk of a coronary event, such as a myocardial infarction (MI) or revascularisation.

CVD risk - risk of a coronary event, or an ischaemic stroke, or peripheral vascular disease (PVD).

A CHD risk of 15% is roughly equivalent to a CVD risk of 20%.

Some statistics...

It has been estimated that about 5% of adults in the UK have CHD and a further 3% have a 30% risk of suffering a coronary event within 10 years.⁴ If a lower risk threshold is considered, i.e. a 15% risk of a coronary event within 10 years, roughly one-fifth of the adult population can be identified. These figures may be even higher for Wales.⁵

Who should receive a statin?

Joint British Societies' guidelines (1998) state that people at highest risk of CHD (i.e. risk greater than 30% over 10 years) should receive lipid-lowering treatment.⁶ When resources allow, those with a CHD risk greater than 15% over 10 years should be progressively targeted.

Policy in Wales is set by the National Service Framework (NSF) for CHD, which was launched in 2001.⁷ The NSF directs treatment at patients with proven MI or angina, those with type 2 diabetes, and people with a predicted coronary event risk of greater than 30% over 10 years. The cholesterol targets are presented in the table on page 3.

In 2002 the National Institute for Clinical Excellence (NICE) issued specific advice for cholesterol-lowering in patients with type 2 diabetes.⁸ All patients with diabetes who have established CVD should be offered statin therapy, irrespective of their cholesterol concentrations. For diabetic patients who have no history of CVD, the threshold for intervention is a 15% risk of a coronary event over 10 years.⁸ This risk threshold has been lowered from 30% because the calculations used in risk assessment tools tend to underestimate risk in patients with type 2 diabetes. The result is that most people with diabetes aged 40-50 years or older are potential candidates for cholesterol-lowering therapy.

The BHS guidelines published in 2004 (BHS IV) include advice on lowering cholesterol as part of the overall management of CVD risk.⁹ The BHS targets apply to patients with CVD or type 2 diabetes, or for any person "aged up to at least 80 years" with hypertension who has a 10-year CVD risk of 20% or more. Implementation of the BHS recommendations could result in more than one-fifth of adults being considered for treatment to lower both blood pressure and cholesterol. The substantial practical and financial impact on the NHS¹⁰ may not be sustainable and may occur at the expense of other interventions.

Whether BHS IV accurately reflect current evidence has been questioned;¹⁰ no recent statin study has looked solely at primary prevention or set such low cholesterol targets (see the discussion of key studies, pages 3-4). In view of these concerns, it might be prudent to await further guidelines on statin use, which are anticipated later in 2005 from NICE and from the Joint British Societies, before making fundamental changes in practice.

Table: Cholesterol targets

| Guideline | Total cholesterol | LDL cholesterol |
|---|---|--|
| NSF for CHD in Wales ⁷ CHD, type 2 diabetes, or CHD risk >30% over 10 years | <5 mmol/l or reduced by 2 mmol/l | <3 mmol/l |
| NICE – type 2 diabetes ⁸ CVD, or CHD risk >15% over 10 years | <5 mmol/l or reduced by 20-25% , whichever is lower aim for triglycerides <2.3 mmol/l (fibrates may also be required) | <3 mmol/l or reduced by 30%, whichever is lower |
| European guidelines ³ General recommendations | <5 mmol/l | <3 mmol/l |
| CVD, type 2 diabetes, or people at high risk with levels close to those generally recommended | <4.5 mmol/l | <2.5 mmol/l |
| BHS IV ⁹ CVD, type 2 diabetes, or CVD risk >20% over 10 years | <4 mmol/l or reduced by 25%, whichever is lower | <2 mmol/l or reduced by 30%, whichever is lower |

New GP contract targets

With the targets set in the new General Medical Services contract for the Quality and Outcome Framework (QOF), GPs are rewarded according to the proportion of their patients who have established CHD, cerebrovascular disease or diabetes, and who have total cholesterol concentrations below 5 mmol/l.¹¹ Studies have shown that these patients can derive benefit from statin treatment irrespective of their cholesterol concentration (see the section

below). By setting this threshold, many patients requiring treatment for prevention of CVD events may be inadequately managed if their ‘starting’ cholesterol is around or below 5 mmol/l.¹² In people with high cholesterol concentrations, this target may encourage aggressive treatment regimens for which there are insufficient clinical outcome and safety data. It is also important not to neglect patients with PVD, who benefit from statins, although they are not included in the QOF.

Recent evidence for statin use - key studies

The most important recent study of statin use is the UK-based **Heart Protection Study (HPS)**, published in 2002.¹³ This trial looked at the effect of simvastatin 40 mg daily in people aged 40-80 years who had total cholesterol concentrations of at least 3.5 mmol/l, and who were at high risk of a major vascular event occurring with a wide range of conditions: CHD, stroke, PVD, and diabetes. Of approximately 32,000 people who entered a 10-week run-in phase on active treatment, 20,536 were randomised to the placebo-controlled study.

After five years the benefit of simvastatin was significant and similar across all groups. Overall, 19 people would need to be treated (NNT 19) to prevent one major CVD event (i.e. first major coronary event, stroke or revascularisation). All-cause death was significantly reduced. Approximately one-third of subjects were at least 70 years old and one-quarter were women. Simvastatin 40 mg daily was well tolerated, with an average compliance rate of 85%.

This study demonstrated that simvastatin 40 mg daily is effective in reducing the incidence of major

vascular events in a wide population, including women, patients up to 80 years of age, those with diabetes, and in those with ‘normal’ and ‘low’ starting cholesterol levels. It provides evidence that all patients with atherosclerotic vascular disease, including those without evidence of CHD, can benefit from statin therapy. The risk reduction seen with simvastatin was in addition to that of other treatments used by the participants (aspirin, beta-blockers, and angiotensin-converting enzyme inhibitors).

The **PROspective Study of Pravastatin in the Elderly at Risk (PROSPER)** was conducted in 5,804 people (aged 70-82 years) with total cholesterol concentrations of 4-9 mmol/l.¹⁴ Over a mean study period of 3.2 years, pravastatin 40 mg daily reduced the overall incidence of the primary endpoint (a composite of CHD death, MI and stroke) compared with placebo (NNT 48). The secondary endpoint of CHD death and MI was also reduced, but that of stroke alone was not. The risk reduction observed was not significant in women, or in the subgroup of 56% of people who had no history of vascular disease.

Two placebo-controlled studies now provide clinical outcome data for the use of atorvastatin (*Lipitor*[®]). The **Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA)** enrolled 10,305 hypertensive patients with total cholesterol concentrations of 6.5 mmol/l or less and at least three other CVD risk factors; only 14% of patients had a history of CVD.¹⁵ The trial was stopped after a median follow-up of 3.3 years. Atorvastatin 10 mg reduced the incidence of CHD death and MI (NNT 91). Unlike the findings from the HPS, no reduction was seen in the diabetes subgroup, and total mortality was not significantly reduced. It was reported that total serious adverse events “did not differ between patients assigned atorvastatin or placebo”; actual numbers were not given.

The **Collaborative Atorvastatin Diabetes Study (CARDS)** looked at the effectiveness of atorvastatin 10 mg daily for primary CVD prevention in 2,838 people with type 2 diabetes (mean age 62 years).¹⁶ This trial was stopped after a mean follow-up of 3.9 years. Allocation to atorvastatin was associated with a reduction in the incidence of major CVD events (NNT 31). The incidence of acute coronary events and stroke were significantly reduced but not coronary revascularisation or death from any cause. Overall, the frequency of adverse events did not differ between treatments. As in the HPS, the benefit appears to be independent of the initial LDL cholesterol concentration.

Further studies have sought to explore whether higher doses of statins improve outcomes. **PROVE-IT – the Pravastatin or Atorvastatin Evaluation and Infection Therapy** trial was a controlled study involving 4,162 subjects hospitalised with acute coronary syndrome: 30% had unstable angina, 37% had MI without ST elevation, and 33% had MI with ST elevation.¹⁷ Patients were randomised to ‘standard therapy’ with pravastatin 40 mg or ‘intensive therapy’ with atorvastatin 80 mg. The primary endpoint was a composite of death by any cause and serious CVD events. Over the mean follow-up period of two years, the results favoured intensive therapy (NNT 26). A reduction in overall mortality was not statistically significant (P=0.07).

The median LDL cholesterol concentration achieved was significantly lower with atorvastatin (1.6 mmol/l vs 2.5 mmol/l with pravastatin). The rates of discontinuation of treatment were similar for both groups. Study medication was discontinued because of myalgia, muscle aches, or elevations in creatine kinase levels in 2.7% of pravastatin-treated patients and 3.3% of atorvastatin-treated patients (P=0.23): there were no cases of rhabdomyolysis. The percentages of patients who had alanine transaminase (ALT) levels more than three times the upper limit of normal were 1.1% for pravastatin and 3.3% for atorvastatin (P<0.001).

The results of the **Treating to New Targets (TNT)** study were released in March 2005.¹⁸ In this trial, 15,464 people aged 35-75 years who had clinically evident CHD entered an eight-week run-in phase on atorvastatin 10 mg. Subsequently, 10,001 subjects (mean age 61 years) who had LDL cholesterol concentrations below 3.4 mmol/l were randomised to receive either atorvastatin 10 mg or 80 mg daily; 15% had diabetes. Over a median of 4.9 years, the incidence of major CVD events was lower in subjects receiving 80 mg of atorvastatin (NNT 45). There was no difference in overall mortality between the groups. Persistent elevations in ALT levels were seen in this study, occurring in 0.2% of subjects in the 10 mg atorvastatin group vs 1.2% of subjects in the 80 mg group versus (P<0.001; number needed to harm or NNH 100). An accompanying editorial cautions: “We need further reassurance as to the safety of this approach before we can advocate a major shift in our current goals for LDL cholesterol levels in patients with stable CHD”.¹⁹

These studies extend the case for statin therapy, irrespective of cholesterol concentrations, in patients at highest risk of CVD events. However, as the investigators in PROVE-IT caution, patients in clinical practice generally have more co-existing conditions and may not tolerate high-dose statin regimens well.¹⁷ Lowering cholesterol concentrations is desirable but when the percentage reduction required is high this must be balanced against the risks associated with the statin doses or cholesterol-lowering regimens required.

What about rosuvastatin and ezetimibe?

Rosuvastatin ▼ (*Crestor*[®]) became available in 2003. It is marketed as a particularly potent statin having been found in clinical trials to have greater LDL-lowering capabilities than other statins.²⁰ As yet there is no clinical outcome data for rosuvastatin

with respect to morbidity or mortality, and the company have been criticised for marketing it vigorously despite this lack of information.²¹ In Wales, there was a five-fold variation in spending on rosuvastatin across local health boards in the last half of 2004.²²

In 2004 the prescribing advice for rosuvastatin was revised after a Europe-wide review of safety information suggested that the 40 mg dose may be associated with a higher rate of adverse effects, including rhabdomyolysis.²³ Rosuvastatin must be started in *all* patients at 10 mg once daily and it should only be increased to 20 mg, if necessary, after a four week trial.²⁴

The 40 mg dose of rosuvastatin is recommended for use under specialist supervision and should only be necessary for patients with severe hypercholesterolaemia at high risk of CVD. It should also be noted that for all Asian, as for Japanese and Chinese patients, 20 mg is now the maximum recommended dose.

Over-the-counter statins

Zocor Heart-Pro[®] (simvastatin 10 mg) tablets became available for sale over-the-counter (OTC) in September 2004. These can be supplied by pharmacists, in conjunction with necessary lifestyle advice, to reduce the risk of a first coronary event in people who are likely to be at moderate risk (10-15%) over the next 10 years.²⁷ People with this level of risk would not otherwise receive statin treatment according to current NHS policy. The recommended retail price for the product is £12.99 for 28 tablets.

Eligible people will include most men over the age of 55 years, and many women over this age who have risk factors, such as smoking and/or obesity. The absolute benefits of effective statin therapy in people with this low level of risk are likely to be minimal and will be dependent on continued use of the product. One estimate of statin use in higher risk primary prevention cases suggests an NNT of 71 over 3-5 years to prevent a CVD event.²⁸ It should be noted that no primary prevention trials have used simvastatin.

The British Heart Foundation are ambivalent about this development.²⁹ In their view, simvastatin 10 mg daily is potentially useful for primary prevention of CHD (and stroke). They state that the safety of the medicine has been demonstrated and agree that criteria for the change from Prescription-only Medicine to Pharmacy only ('PoM to P') have been met; however, they and the Royal College of General

Ezetimibe[▼] (*Ezetrol*[®]) is a new type of lipid-regulating agent that works by inhibiting absorption of dietary and biliary cholesterol in the intestine. It is licensed for use alone or in combination with a statin.²⁵ The effects of ezetimibe on cardiovascular morbidity and mortality are not known.²⁶

As new drugs, the Committee on Safety of Medicines continues to monitor the use of rosuvastatin and ezetimibe closely. Information on their use in the general population is required to determine comparative levels of safety. In view of the lack of clinical outcome data and safety information, these drugs should not be used routinely in general practice.

Practitioners have reservations:^{29,30}

- ♦ Supply does not require cholesterol to be measured and a proportion of people who obtain OTC simvastatin may not be managed optimally.
- ♦ The GP may be unaware that a patient is taking simvastatin (there are a number of drugs that should not be co-prescribed).
- ♦ People taking the product may think that they are protected against CHD and avoid lifestyle changes, such as taking more exercise, controlling weight, eating a healthy diet, and stopping smoking.

The Royal Pharmaceutical Society of Great Britain has issued guidance for pharmacists on the sale of OTC simvastatin.³¹ This guidance is clear about the need for offering lifestyle advice to all patients. It also sets out standards of good practice with regard to estimating a person's CHD risk before deciding whether or not to provide treatment, or whether to refer to the GP.

A recent *Drug and Therapeutics Bulletin* article is critical of the process that allowed OTC simvastatin to come to market.³² A number of further concerns can be raised:

- ♦ Instead of continuing to purchase simvastatin OTC, people may increase pressure on their GPs to provide it on an NHS prescription.
- ♦ People may buy the product without realising how little individual benefit it may provide, given their low absolute risk.
- ♦ People who purchase OTC treatment may be socio-economically advantaged; this may increase inequity within the population.³⁰

Drug interactions with statins

Care is advised when using simvastatin and atorvastatin in combination with a number of drugs, because of the risk of myopathy and rhabdomyolysis.³³⁻³⁵ Some of the more commonly prescribed drugs include fibrates, amiodarone and verapamil. There is also an increase in risk when diltiazem is used with simvastatin 80 mg daily. Other drugs that are contraindicated with simvastatin include itraconazole, ketoconazole, erythromycin, and clarithromycin. Intake of grapefruit juice and simvastatin should be avoided; with atorvastatin, patients are advised to avoid large quantities of grapefruit juice.

This bulletin is based on work prepared by Dr Martin Duerden, Medical Director of Conwy Local Health Board and university lecturer in therapeutics

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