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Statins for the prevention of cardiovascular events

Technology Appraisal 94 Statins for the prevention of cardiovascular events

Ordering information

You can download the following documents from www.nice.org.uk/TA094

- The full guidance for this technology appraisal (this document).
- A quick reference guide, which has been distributed to healthcare professionals working in the NHS in England.
- Information for people who have or are at increased risk of cardiovascular disease, their families and carers, and the public.
- The assessment report – details of all the studies that were looked at.

For printed copies of the quick reference guide or information for the public, phone the NHS Response Line on 0870 1555 455 and quote:

- N0971 (quick reference guide)
- N0972 (information for the public).

This guidance is written in the following context

This guidance represents the view of the Institute, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. The guidance does not, however, override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

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1 Guidance

This guidance relates only to the initiation of statin therapy in adults with clinical evidence of cardiovascular disease (CVD) and in adults considered to be at risk of CVD. It assumes that other strategies for managing CVD risk are being appropriately considered when initiating statin therapy. The guidance does not include specific advice for genetic dyslipidaemias (for example, familial hypercholesterolaemia). The guidance relates only to the use of statins within their licensed indications.

A clinical guideline on cardiovascular risk assessment is currently in development (expected date of publication: September 2007). This guidance should be read in the context of the clinical guideline when it is available.

- 1.1 Statin therapy is recommended for adults with clinical evidence of CVD.
- 1.2 Statin therapy is recommended as part of the management strategy for the primary prevention of CVD for adults who have a 20% or greater 10-year risk of developing CVD. This level of CVD risk should be estimated using an appropriate risk calculator, or by clinical assessment for people for whom an appropriate risk calculator is not available (for example, older people, people with diabetes or people in high-risk ethnic groups).
- 1.3 Within the recommendations outlined in Section 1.1 and Section 1.2, the decision whether to initiate statin therapy should be made after an informed discussion between the responsible clinician and the individual about the risks and benefits of statin treatment, and taking into account additional factors such as comorbidities and life expectancy.
- 1.4 When the decision has been made to prescribe a statin, it is recommended that therapy should usually be initiated with a drug with a low acquisition cost (taking into account required daily dose and product price per dose).

2 Clinical need and practice

- 2.1 Cardiovascular disease (CVD) is defined as disease of the heart and blood vessels. The most common manifestation of CVD is coronary heart disease (CHD), also known as coronary artery disease and ischaemic heart disease. CHD is caused by the narrowing of the arteries that supply the heart and is due to a gradual build-up of fatty material called atheroma. The narrowing can cause myocardial infarction (MI [heart attack]), angina (pain or discomfort in the chest or neighbouring parts of the body due to insufficient oxygen reaching the heart) and other forms of chronic heart disease. Angina is usually classified as stable or unstable disease. Other forms of CVD include stroke, transient ischaemic attack (TIA) and peripheral arterial disease (PAD).
- 2.2 CVD is the single most common cause of death in the UK, accounting for nearly 238,000 in 2002. Approximately 50% of these deaths were from CHD and 25% from stroke. Almost 30% (67,000) of the deaths in 2002 were classified as premature (that is, they occurred before the age of 75 years), equating to 35% and 27% of all premature deaths in men and women, respectively. CVD is also a significant cause of morbidity and can have a major impact on quality of life. CHD has been estimated to be the leading cause of disability in Europe, accounting for 9.7% of total disability-adjusted life years.
- 2.3 Mortality and morbidity rates associated with CVD vary by socio-economic group (higher in manual social classes), geographic area (CHD rates are highest in Wales, the North West and Northern and Yorkshire regions and lowest in the North and South Thames regions; stroke rates are highest in the Yorkshire region and lowest in the Oxford region) and ethnic group (for example, CHD rates are high among people from the Indian subcontinent, and stroke rates are particularly high in people of black Caribbean origin). The prevalence of CVD also increases with age and is higher among males than females. Blood cholesterol levels (including high total cholesterol [TC], high low-density lipoprotein cholesterol [LDL-C] and low high-density lipoprotein

cholesterol [HDL-C]) also influence a person's risk of developing CHD, as do smoking, high blood pressure, type 1 and type 2 diabetes mellitus, physical inactivity and obesity; these risk factors can be modified, treated or controlled.

- 2.4 The term primary CVD prevention refers to interventions that aim to prevent cardiovascular events in people who have no clinical evidence of CVD. In secondary CVD prevention, the aim is to prevent further events in people who already have clinical evidence of CVD. Interventions used in both primary and secondary CVD prevention include lifestyle measures such as smoking cessation, increased physical activity and diet modification. Drug treatments, such as lipid-lowering drugs, beta-blockers for people who have had an MI, antihypertensives to control blood pressure, and aspirin, are also commonly prescribed. In primary CVD prevention, an appropriate risk calculator designed to estimate a person's 10-year cardiovascular event risk is used as an aid to making clinical decisions about how intensively to intervene with lifestyle measures and drug treatments.
- 2.5 People who have clinical evidence of CVD may also require revascularisation (the restoration of blood supply, either pharmacologically or surgically, to a particular part of the body), such as a coronary artery bypass graft (CABG) operation or a percutaneous transluminal coronary angioplasty (PTCA) procedure.

3 The technology

- 3.1 Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, an enzyme involved in cholesterol synthesis. Inhibition of HMG CoA reductase lowers LDL-C levels by slowing down the production of cholesterol in the liver and increasing the liver's ability to remove the LDL-C already in the blood.
- 3.2 Five statins currently have a UK marketing authorisation: atorvastatin, fluvastatin, pravastatin, rosuvastatin and simvastatin.

- 3.3 Adverse events associated with statins include headache, altered liver function, paraesthesia and gastrointestinal effects (including abdominal pain, flatulence, diarrhoea, nausea and vomiting). Rash and hypersensitivity reactions have been reported but are rare. Muscle effects (myalgia, myositis and myopathy) have also been reported with the use of statins. Severe muscle damage (rhabdomyolysis) is a very rare but significant side effect. Further adverse events are associated with individual statins. For full details of adverse effects, contraindications and interactions, see the Summaries of Product Characteristics.
- 3.4 In clinical practice, statins are used in conjunction with lifestyle measures (for example, smoking cessation, increased physical activity and diet modification) to control CVD risk and other appropriate interventions (for example, drugs to control chronic conditions such as high blood pressure and diabetes mellitus).

Atorvastatin

- 3.5 Atorvastatin (Pfizer Ltd) is a synthetic statin. It is licensed as an adjunct to diet for the treatment of people with primary hypercholesterolaemia, homozygous familial hypercholesterolaemia, heterozygous familial hypercholesterolaemia or combined (mixed) hyperlipidaemia, when response to diet and other non-pharmacological measures is inadequate.
- 3.6 Atorvastatin is available as 10-mg, 20-mg, 40-mg and 80-mg tablets. The usual starting dosage is 10 mg/day, which may be increased at intervals of at least 4 weeks. The maximum dosage is 80 mg/day.
- 3.7 The acquisition cost of atorvastatin under the brand name Lipitor (Pfizer Ltd) is £18.03 for 28 x 10-mg tablets, £24.64 for 28 x 20-mg tablets, £28.21 for 28 x 40-mg tablets, and £28.21 for 28 x 80-mg tablets (excluding VAT; *British National Formulary [BNF]* 49th edition, March 2005). Costs may vary in different settings because of negotiated procurement discounts.

Fluvastatin

3.8 Fluvastatin (Novartis Pharmaceuticals UK Ltd) is a synthetic statin and is available in two formulations: an immediate-release (IR) formulation available as 20-mg and 40-mg capsules, and an extended-release (XL) formulation available as 80-mg tablets.

3.9 Fluvastatin is licensed:

- as an adjunct to diet in people with primary hypercholesterolaemia or mixed dyslipidaemia
- to slow the progression of coronary atherosclerosis in people with primary hypercholesterolaemia and CHD who do not adequately respond to dietary control
- for the secondary prevention of coronary events after percutaneous coronary intervention in people with CHD
- for the increase of HDL-C in people with primary hypercholesterolaemia and mixed dyslipidaemia (XL formulation only).

3.10 The recommended starting dosage is 40 mg/day, although a dosage of 20 mg/day may be adequate in mild cases. Dose adjustment to 80 mg/day may be made at intervals of at least 4 weeks. In people with CHD after percutaneous coronary intervention, the dosage is 80 mg/day.

3.11 The acquisition cost of fluvastatin under the brand names Lescol and Lescol XL (Novartis Pharmaceuticals UK Ltd) is £12.72 for 28 x 20-mg IR capsules, £12.72 for 28 x 40-mg IR capsules, and £16.00 for 28 x 80-mg XL tablets (excluding VAT; *BNF* 49th edition, March 2005). Costs may vary in different settings because of negotiated procurement discounts.

Pravastatin

3.12 Pravastatin (Bristol-Myers Squibb Pharmaceuticals Ltd) is a natural statin found in fungi. It became available in generic form in the UK in 2004.

Pravastatin is licensed for:

- the treatment of people with primary hypercholesterolaemia or mixed dyslipidaemia, as an adjunct to diet, when response to diet and other non-pharmacological treatments is inadequate
- the reduction of cardiovascular mortality and morbidity in people with moderate or severe hypercholesterolaemia and at high risk of a first cardiovascular event, as an adjunct to diet
- the reduction of cardiovascular mortality and morbidity in people with a history of MI or unstable angina and with either normal or increased cholesterol levels, as an adjunct to correction of other risk factors
- the reduction of post-transplantation hyperlipidaemia in people receiving immunosuppressive therapy following solid organ transplantation.

3.13 Pravastatin is available as 10-mg, 20-mg and 40-mg tablets. The recommended dosage for hypercholesterolaemia is 10 to 40 mg/day, which can be adjusted at intervals of not less than 4 weeks.

3.14 The acquisition cost of pravastatin under the brand name Lipostat (Bristol-Myers Squibb Pharmaceuticals Ltd) listed in the *BNF* is £15.05 for 28 x 10-mg tablets, and £27.61 for 28 x 20-mg tablets and for 28 x 40-mg tablets; for non-proprietary pravastatin, the acquisition cost listed in the *BNF* is £15.83 for 28 x 10-mg tablets, £29.05 for 28 x 20-mg tablets, and £29.26 for 28 x 40-mg tablets (excluding VAT; *BNF* 49th edition, March 2005). Prices for pravastatin have recently decreased, and the acquisition cost of pravastatin listed in the NHS Drug Tariff (July 2005) is £3.41 for 28 x 10-mg tablets, £4.22 for 28 x 20-mg tablets, and £4.59 for 28 x 40-mg tablets. Costs may vary in different settings because of negotiated procurement discounts.

Rosuvastatin

- 3.15 Rosuvastatin (AstraZeneca UK Ltd) is a synthetic statin. It is licensed for the treatment of people with primary hypercholesterolaemia or mixed dyslipidaemia, as an adjunct to diet, when response to diet and other non-pharmacological treatments is inadequate. It is also indicated for the treatment of homozygous familial hypercholesterolaemia as an adjunct to diet and other lipid-lowering treatments or if such treatments are not appropriate.
- 3.16 Rosuvastatin is available as 5-mg, 10-mg, 20-mg and 40-mg tablets. The recommended starting dosage is 5 or 10 mg/day and should take account of the individual patient's characteristics and the recommendations in the Summary of Product Characteristics. A dose adjustment to the next dose level can be made after 4 weeks if necessary. An increase to 40 mg/day (after at least a further 4 weeks) should only be considered in people with severe hypercholesterolaemia who are at high cardiovascular risk and in whom routine follow-up will be performed. Specialist supervision is recommended when the 40-mg dose is initiated. The 40-mg dose is contraindicated in patients of Asian origin.
- 3.17 The acquisition cost of rosuvastatin under the brand name Crestor (AstraZeneca UK Ltd) is £18.03 for 28 x 5-mg tablets, £18.03 for 28 x 10-mg tablets, £29.69 for 28 x 20-mg tablets, and £29.69 for 28 x 40-mg tablets (excluding VAT; *BNF* 49th edition, March 2005). Costs may vary in different settings because of negotiated procurement discounts.

Simvastatin

3.18 Simvastatin (Merck Sharp & Dohme Ltd) is a semi-synthetic statin based on lovastatin. It became available in generic form in the UK in 2003. Simvastatin is licensed for:

- the treatment of people with primary hypercholesterolaemia or mixed dyslipidaemia, as an adjunct to diet, when response to diet and other non-pharmacological treatments is inadequate
- the treatment of people with homozygous familial hypercholesterolaemia, as an adjunct to diet and other lipid-lowering treatments or if such treatments are not appropriate
- the reduction of cardiovascular mortality and morbidity in people with manifest atherosclerotic CVD or diabetes mellitus (with either normal or increased cholesterol levels), as an adjunct to correction of other risk factors and other cardioprotective therapy.

3.19 Simvastatin is available as 10-mg, 20-mg, 40-mg and 80-mg tablets. The recommended starting dosages are based on the indication and, if required, dose titrations should be made at intervals of not less than 4 weeks. The 80-mg/day dosage is only recommended in people with severe hypercholesterolaemia and at high risk of cardiovascular complications.

3.20 The acquisition cost of simvastatin under the brand name Zocor (Merck Sharp & Dohme Ltd) listed in the *BNF* is £18.03 for 28 x 10-mg tablets, and £29.69 for 28 x 20-mg tablets, 28 x 40-mg tablets and 28 x 80-mg tablets; for non-proprietary simvastatin, the acquisition cost listed in the *BNF* is £5.78 for 28 x 10-mg tablets, £7.80 for 28 x 20-mg tablets, £15.60 for 28 x 40-mg tablets, and £28.77 for 28 x 80-mg tablets (excluding VAT; *BNF* 49th edition, March 2005). Prices for simvastatin have recently decreased, and the acquisition cost of simvastatin listed in the NHS Drug Tariff (July 2005) is £1.65 for 28 x 10-mg tablets, £1.48 for 28 x 20-mg tablets, £3.57 for

28 x 40-mg tablets, and £20.29 for 28 x 80-mg tablets. Costs may vary in different settings because of negotiated procurement discounts.

- 3.21 In July 2004, simvastatin became available as an over-the-counter medicine at a dosage of 10 mg/day (McNeil Ltd). It is licensed to reduce the risk of a first major coronary event in people at moderate (10 to 15%) 10-year risk of CHD.

4 Evidence and interpretation

The Appraisal Committee (Appendix A) considered evidence from a number of sources (see Appendix B).

4.1 Clinical effectiveness

Placebo-controlled trials

- 4.1.1 Twenty-eight randomised controlled trials (RCTs) were identified that: were of at least 6 months' duration; were in adults with or at risk of CVD; compared a statin with placebo; and reported clinical events as outcomes. The statin investigated was pravastatin in eleven studies, simvastatin in eight studies, atorvastatin in five studies and fluvastatin in four studies; no studies of rosuvastatin that reported clinical events as outcomes were identified.
- 4.1.2 A meta-analysis of all placebo-controlled trials (primary and secondary prevention studies) that published data in a usable form indicated that therapy with a statin was associated with a statistically significant reduction in risk of all-cause mortality (relative risk [RR] 0.83, 95% confidence interval [CI] 0.78 to 0.90), cardiovascular mortality (RR 0.79, 95% CI 0.74 to 0.85), CHD mortality (RR 0.77, 95% CI 0.72 to 0.83) and fatal MI (RR 0.54, 95% CI 0.44 to 0.67), but not of stroke mortality (RR 0.92, 95% CI 0.74 to 1.14).
- 4.1.3 For non-fatal outcomes, the meta-analysis of all placebo-controlled trials indicated that statin therapy was associated with a statistically significant reduction in the risk of non-fatal stroke (RR 0.75, 95% CI 0.63 to 0.90), TIA

(RR 0.79, 95% CI 0.68 to 0.91), non-fatal MI (RR 0.68, 95% CI 0.62 to 0.76), unstable angina (RR 0.82, 95% CI 0.74 to 0.90) and hospitalisations for unstable angina (RR 0.88, 95% CI 0.84 to 0.94). Statin treatment was also associated with a statistically significant reduction in risk of requiring CABG and PTCA (CABG or PTCA: RR 0.75, 95% CI 0.70 to 0.81). Few studies reported the effect of statins on PAD and the results were not statistically significant.

Primary CVD and primary CHD prevention

- 4.1.4 Two of the placebo-controlled trials identified were conducted in patients without clinical evidence of CVD at study entry, and three studies conducted a subgroup analysis in this population. Four placebo-controlled trials were conducted in patients without clinical evidence of CHD at study entry, but with possible other CVD, and three studies conducted a subgroup analysis. The studies did not generally include people at very low risk of a CHD event.
- 4.1.5 For patients without clinical evidence of CVD at study entry, a meta-analysis indicated that statin therapy was associated with a statistically significant reduction in the risk of fatal MI (RR 0.41, 95% CI 0.19 to 0.88) and non-fatal MI (RR 0.60, 95% CI 0.37 to 0.97). Statistically significant effects were not, however, demonstrated for all-cause mortality, cardiovascular mortality, CHD mortality, stroke mortality, non-fatal stroke, unstable angina and revascularisation.
- 4.1.6 For patients without clinical evidence of CHD at study entry, a meta-analysis indicated that statin therapy was associated with a statistically significant reduction in the risk of all-cause mortality (RR 0.83, 95% CI 0.70 to 0.98), fatal MI (RR 0.41, 95% CI 0.19 to 0.88), non-fatal MI (RR 0.58, 95% CI 0.36 to 0.94) and stable angina (RR 0.59, 95% CI 0.38 to 0.90). No statistically significant differences were found for cardiovascular mortality, CHD mortality, stroke mortality, non-fatal stroke, PAD, unstable angina and revascularisation.

- 4.1.7 Results from the largest primary prevention study (n = 10,305), which compared atorvastatin with placebo over approximately 3 years, suggested that the number needed to treat (NNT) to avoid either a death from CHD or a non-fatal MI, in people without existing CHD, was 95 (95% CI 60 to 216).

Secondary CVD and secondary CHD prevention

- 4.1.8 Fourteen placebo-controlled studies, in which all participants had CHD at study entry, were identified for inclusion in a meta-analysis. The meta-analysis indicated that statin therapy was associated with a statistically significantly reduced risk of all-cause mortality (RR 0.79, 95% CI 0.70 to 0.90), CVD mortality (RR 0.75, 95% CI 0.68 to 0.83), CHD mortality (RR 0.72, 95% CI 0.64 to 0.80), fatal MI (RR 0.57, 95% CI 0.45 to 0.72), non-fatal MI (RR 0.69, 95% CI 0.59 to 0.79), unstable angina (RR 0.82, 95% CI 0.72 to 0.94), hospitalisation for unstable angina (RR 0.90, 95% CI 0.84 to 0.97), non-fatal stroke (RR 0.75, 95% CI 0.59 to 0.95), new or worsening intermittent claudication (RR 0.64, 95% CI 0.46 to 0.91) and coronary revascularisation (RR 0.77, 95% CI 0.69 to 0.85). Statin therapy was not, however, associated with a statistically significant reduction in stroke mortality (RR 1.07, 95% CI 0.67 to 1.71) or TIA (RR 0.66, 95% CI 0.37 to 1.17).
- 4.1.9 Results from the three largest trials of people with CHD (n = 9014 [pravastatin], n = 4444 [simvastatin] and n = 4159 [pravastatin]), with follow-up of approximately 5 to 6 years, suggested that the NNT to avoid either a death from CHD or a non-fatal MI, in people with CHD, was 29 (95% CI 20 to 48), 12 (95% CI 9 to 16) and 34 (95% CI 20 to 96), respectively.
- 4.1.10 A meta-analysis of RCTs in which all patients had CHD or other CVD at study entry was also conducted. This comprised the 14 placebo-controlled studies of patients with CHD at study entry, as discussed in Section 4.1.8, and three smaller studies of patients with intermittent claudication. The

results of this meta-analysis closely resembled those relating to the meta-analysis of patients who had CHD at study entry (see Section 4.1.8).

Subgroups

4.1.11 The Assessment Group stated that the evidence from placebo-controlled trials does not suggest that statins differ in their relative effectiveness in a number of subgroups: in women compared with men at a similar level of cardiovascular risk; in people with diabetes compared with people without diabetes; or in people aged over 65 years compared with people aged under 65 years. No placebo-controlled trials were identified that provided information relating to people from different ethnic groups.

Studies comparing two or more statins

4.1.12 Three RCTs of at least 6 months' duration were identified that compared two or more statins and reported clinical events in secondary prevention populations.

4.1.13 Two of the studies compared atorvastatin with pravastatin. The first (n = 4162) compared intensive therapy with atorvastatin (80 mg/day) with moderate therapy with pravastatin (40 mg/day) in patients recently hospitalised with acute coronary syndrome. High-dose atorvastatin was associated with a statistically significant reduction in two composite endpoints compared with pravastatin: CHD death, non-fatal MI or coronary revascularisation (14% risk reduction, p = 0.029); and all-cause mortality, MI, hospitalisation for unstable angina or coronary revascularisation (16% risk reduction, p = 0.005). There was no statistically significant difference between the two statins for all-cause mortality, stroke, MI or the composite endpoint of CHD death or non-fatal MI.

4.1.14 The second trial (n = 657) compared intensive therapy with atorvastatin (80 mg/day) with moderate therapy with pravastatin (40 mg/day) in patients with CHD. The trial was not designed to examine clinical events. The

investigators did, however, report that, in the pravastatin arm, 0.3% of participants died, 2.1% experienced an MI and 0.3% experienced a stroke. In the atorvastatin arm, 0.3% of participants died, 1.2% experienced an MI and 0.3% experienced a stroke.

- 4.1.15 The third RCT (n = 1093) compared atorvastatin (20 mg/day) with simvastatin (20 mg/day) in patients with CVD and dyslipidaemia. The trial was not designed to examine clinical events, and it found no significant differences between groups in clinical events.
- 4.1.16 A further two RCTs of at least 6 months' duration were identified that compared two or more statins but did not report clinical events. Both studies were in people with hypercholesterolaemia. One trial (n = 412) compared the lipid-lowering effects of rosuvastatin (5 to 80 mg/day or 10 to 80 mg/day) with atorvastatin (10 to 80 mg/day), and the other (n = 477) compared rosuvastatin (5 to 80 mg/day or 10 to 80 mg/day) with pravastatin (20 to 40 mg/day) and simvastatin (20 to 80 mg/day). Treatment in both trials was initiated at the lowest dose for 12 weeks and titrated upwards, as required, at specified time intervals. Some patients in both trials received rosuvastatin 80 mg/day, a dose that is not licensed for use in the UK. Both studies found that rosuvastatin was the most effective drug for reducing TC and LDL-C.
- 4.1.17 One further RCT of at least 6 months' duration (n = 10,006) was identified after the completion of the Assessment Report. This compared 80 mg/day atorvastatin with 10 mg/day atorvastatin in people with stable CHD. The mean LDL cholesterol levels were 2.0 mmol/l during treatment with 80 mg/day atorvastatin and 2.6 mmol/l during treatment with 10 mg/day atorvastatin. Treatment with 80 mg/day atorvastatin was associated with a 22% relative reduction in the primary composite endpoint of death from CHD, non-fatal non-procedure-related MI, resuscitation after cardiac arrest, or fatal or non-fatal stroke (hazard ratio 0.78, 95% CI 0.69 to 0.89). No statistically significant difference in overall mortality between the two groups was detected.

Adverse events

4.1.18 Aggregation of the trial data included in the review of clinical effectiveness revealed that there were six non-fatal cases of rhabdomyolysis among the 47,637 people randomised to statin therapy, and three cases among the 47,180 people randomised to a control. In the trials that reported myositis, there were 22 cases among the 43,125 people randomised to statin therapy and 25 cases among the 42,678 people randomised to placebo. Not all studies reported the number of participants who experienced myalgia. However, in the largest study (n = 20,536), similar numbers of participants in the statin and placebo treatment groups experienced unexplained muscle pain or weakness.

Continuation and compliance

4.1.19 Rates of continuation with statin therapy were approximately 87%, after 3 years of treatment in the primary prevention trials, and approximately 75%, after 4 years of treatment in the secondary prevention trials. Compliance with treatment was over 95% in the only primary prevention study (the duration of which was less than a year) that reported this outcome and between approximately 85% and 95% after 3 to 4 years of treatment in secondary prevention studies. The Assessment Group identified three non-trial-based UK studies that estimated compliance. The studies reported that between 64% and 86% of patients were compliant with therapy (defined as taking more than 70% or 80% of therapy).

4.2 Cost effectiveness

4.2.1 The Assessment Group identified five published economic evaluations that assessed the cost effectiveness of statin therapy in a UK setting and expressed outcomes in terms of life years gained (LYG) or quality-adjusted life years (QALYs). In addition, five manufacturers submitted economic evidence (four developed economic models), and the Assessment Group also developed its own economic model.

Published studies

- 4.2.2 One study published in 1992 assessed the cost effectiveness of various cholesterol-lowering strategies, including simvastatin, based on an economic model that used cholesterol reduction as an indicator of clinical events. The cost per LYG ranged from £10,000 to £23,000 for a 50-year-old man with a baseline cholesterol level of 7.5 mmol/l and additional risk factors.
- 4.2.3 Another economic evaluation published in 1992 estimated the cost effectiveness of statins (based on simvastatin and pravastatin) using a lifetable approach. The average cost per LYG was £136,000 for primary prevention in men aged between 45 and 64 years with a cholesterol level greater than 6.5 mmol/l, and £32,000 for people with CHD and a cholesterol level greater than 5.4 mmol/l. There was, however, wide variation in the estimates for different levels of baseline cholesterol level and age.
- 4.2.4 A third study published in 1997 used a model-based approach to estimate the cost per LYG of pravastatin in men with hypercholesterolaemia. The additional cost of pravastatin was £20,000 per LYG.
- 4.2.5 Two studies published in 1999 estimated the cost effectiveness of simvastatin and pravastatin for the prevention of CHD in men using a lifetable approach. One study reported that, for annual risks of CHD ranging from 4.5% to 1.5%, the cost per LYG ranged from £5000 to £13,000 for simvastatin, and from £7000 to £18,000 for pravastatin. The second study reported that the cost per LYG for both drugs combined ranged from £5000 to £13,000 for annual mortality rates of 6% to 0.5%, respectively.

Manufacturers' analyses

- 4.2.6 Pfizer Ltd (the manufacturer of atorvastatin) submitted an economic model designed to estimate the cost effectiveness of atorvastatin compared with placebo and simvastatin using changes in cholesterol levels to predict clinical events. Costs (2004 prices) and health-related utilities were

estimated from published sources and discounted at 6% and 1.5%, respectively, and a lifetime horizon was used. The incremental cost per QALY of atorvastatin compared with placebo ranged from £1000 to £7000 for primary prevention (varying by gender and baseline risk), and from £3000 to £6000 for secondary prevention in people without diabetes. Pfizer Ltd also submitted details of an economic evaluation conducted alongside an RCT (subsequently published in 2005). This economic analysis was based on data from a large multinational primary prevention RCT that compared atorvastatin with placebo (n = 10,305). The average incremental cost per event avoided was £7000.

- 4.2.7 Novartis Pharmaceuticals Ltd (the manufacturer of fluvastatin) submitted a probabilistic secondary prevention economic model. This estimated the cost effectiveness of fluvastatin based on an RCT of people who had undergone a successful percutaneous coronary intervention. Estimates of health-related utility came from published sources and costs of events were based on NHS reference costs. Costs and QALYs were discounted at 3.5% and were measured over a 10-year period. The results showed that the incremental cost per QALY was £3000. A separate analysis in a subgroup of people with diabetes found that the incremental cost per QALY gained was £2000.
- 4.2.8 Bristol-Myers Squibb Pharmaceuticals Ltd (a manufacturer of pravastatin) submitted an economic model that compared the cost per LYG of pravastatin therapy combined with diet and exercise, with diet and exercise alone. Costs and benefits were discounted at 3.5% and the time horizon was a maximum of 5 years. For primary prevention, the cost per LYG ranged from less than £1000 to £121,000 and varied according to gender and baseline risk. For secondary prevention, the analysis showed that pravastatin was less costly and more effective than diet and exercise alone for both men and women.
- 4.2.9 AstraZeneca UK Ltd (the manufacturer of rosuvastatin) submitted two economic models. The short-term (1-year) probabilistic model estimated the cost effectiveness of each statin in bringing newly diagnosed people with

hypercholesterolaemia to the cholesterol target levels included in the National Service Framework (NSF) for CHD. The results of the short-term model suggested that more people achieve target cholesterol levels on lower doses of rosuvastatin compared with other statins. The long-term (21-year) model used cholesterol lowering as an indicator of clinical events. Cost, resource use and utility data were taken from published studies where available, and discount rates of 3.5% were used. The incremental costs per QALY of rosuvastatin compared with no treatment varied according to gender and baseline risk and ranged from £2000 to £5000 for primary prevention, and from £13,000 to £31,000 for secondary prevention.

- 4.2.10 Merck Sharp & Dohme Ltd (a manufacturer of simvastatin) submitted reports of two economic evaluations. One was an update of a published economic evaluation of a large RCT that compared simvastatin with placebo in people with CHD. Costs were based on the number of CVD events reported in the trial. The cost of simvastatin was based on the 2004 drug tariff. The investigators found that the incremental cost per LYG was just over £2000. The second economic evaluation (subsequently published in 2005) was based on 5-year data from a large trial that compared simvastatin with placebo in people with vascular disease or diabetes (n = 20,536). Costs (2001 prices) included the cost of simvastatin and hospitalisations for vascular events observed during the trial. There was substantial variation in cost effectiveness between risk groups. The cost of avoiding a major vascular event ranged from £5000 in the highest risk group (95% CI £2000 to £7000) to £31,000 in the lowest risk group (95% CI £23,000 to £43,000).

Assessment Group's model

- 4.2.11 The Assessment Group developed a probabilistic Markov model designed to estimate the cost effectiveness of statin therapy compared with no treatment in people at different ages and levels of risk in three different scenarios.

- The base case scenario: the prevention of coronary events (that is, stable angina, unstable angina, non-fatal MI or death from CHD-related causes) in adults who have experienced, or who are at risk of, a coronary event.
- Scenario 1: the prevention of cardiovascular events (that is, coronary events, stroke and TIA) in adults who have experienced, or who are at risk of, a coronary event.
- Scenario 2: the prevention of cardiovascular events in adults who have experienced, or who are at risk of, a cardiovascular event.

4.2.12 Data from UK epidemiological studies were used to estimate event rates. The model was run separately for specified risk levels, age groups and gender. The effect of statins on the reduction of events was based on relative risks of coronary and cardiovascular outcomes estimated by a Bayesian meta-analysis, which incorporated data from the RCTs reported in Section 4.1.1.

4.2.13 The Assessment Group's main analysis did not include estimates of the cost effectiveness of rosuvastatin because trials of rosuvastatin to date have not reported clinical events (see Section 4.1.1). The Assessment Group modified its model to assess the cost effectiveness of rosuvastatin based on changes in cholesterol. Owing to the absence of data on clinical events for rosuvastatin, the Assessment Group stated that the cost-effectiveness results for rosuvastatin would be subject to significant uncertainty over and above that incorporated within the main economic analysis. The effect of rosuvastatin on lowering cholesterol was estimated from the combined results of the two RCTs described in Section 4.1.16.

4.2.14 Health-related utility estimates included in the economic model were derived from published and unpublished studies. Health-related utilities were assumed to vary by age based on data from a large UK population-based survey using the EQ-5D questionnaire. Disutility associated with statin treatment was not included in the model.

4.2.15 The costs associated with treating cardiovascular events were taken from published UK sources, supplemented by expert opinion where data from published sources were unavailable. Expert opinion was also used to provide information on monitoring costs (that is, the costs associated with liver function tests, cholesterol tests and creatinine kinase tests). The costs of managing adverse events were excluded from the analysis. The cost of each statin was based on 2004 prices (*BNF* 48th edition, September 2004) and weighted by the dose and number of people included in the trials. Costs and benefits were estimated over a lifetime horizon and discounted at 6% and 1.5%, respectively.

Results of the base case scenario (see Section 4.2.11)

4.2.16 For secondary CHD prevention, the incremental cost per QALY ranged from £10,000 to £16,000 for all age groups (45 to 85 years), with little difference in the results for men and women. For people with diabetes and a history of CHD, the cost per QALY was estimated to be below £9000 for all age groups.

4.2.17 The base case secondary prevention results outlined in Section 4.2.16 were most sensitive to a reduction in the cost of statins, the discount rates used and the timeframe of the model. The estimates for all ages ranged from £6000 to £10,000 based on a 40% reduction in the weighted statin cost, and from £16,000 to £24,000 using discount rates of 3.5% for costs and QALYs (instead of 6% for costs and 1.5% for QALYs). Shortening the time horizon to 10 years instead of lifetime suggested that it is less cost effective to treat younger people than older people, the incremental cost per QALY ranging from £19,000 at age 85 years to £125,000 at age 45 years.

4.2.18 Probabilistic sensitivity analysis produced results that were consistent with the secondary prevention base case results outlined in Section 4.2.16 and, for values between £20,000 and £30,000 per QALY, showed a high probability (greater than 85%) that statin therapy is cost effective for all people with a history of CHD.

- 4.2.19 The Assessment Group's modified secondary prevention analysis of rosuvastatin (see Section 4.2.13) generated lower cost per QALY estimates compared with the base case results discussed in Section 4.2.16. The estimates for rosuvastatin ranged from £6000 to £8000 between the ages of 45 and 65 years (the modified analysis was restricted to people in these age groups).
- 4.2.20 For primary CHD prevention, the estimated cost per QALY varied substantially according to risk level and age of treatment initiation, being lower at higher levels of risk and in younger age cohorts. The lower costs per QALY associated with commencing treatment at a younger age reflect the greater potential to prevent events, and thus the higher utility and cost benefits accrued from remaining in the event-free health state. At an annual risk of a CHD event ranging from 3% to 0.5%, the ranges of cost per QALY gained were £10,000 to £31,000 at age 45 years, £13,000 to £40,000 at age 55 years, £17,000 to £59,000 at age 65 years, £26,000 to £99,000 at age 75 years and £37,000 to £111,000 at age 85 years. The costs per QALY were lower for people with diabetes, and, at an annual risk of CHD ranging from 3% to 0.5%, the cost per QALY gained ranged from £6000 to £22,000 at age 45 years to £27,000 to £96,000 at age 85 years.
- 4.2.21 The base case primary prevention results outlined in Section 4.2.20 were most sensitive to a reduction in the cost of statins, the discount rates used and the timeframe of the model. With a 40% reduction in the weighted statin cost, and based on annual CHD risk ranging from 3% to 0.5%, the incremental costs per QALY ranged from £6000 to £20,000 at age 45 years to £24,000 to £72,000 at age 85 years. Applying 3.5% discount rates to costs and QALYs increased the incremental costs per QALY to £19,000 to £72,000 at age 45 years and to £46,000 to £149,000 at age 85 years. Using a shorter time horizon of 10 years, the incremental costs per QALY ranged from £36,000 to £286,000 at age 45 years to £53,000 to £367,000 at age 85 years.

- 4.2.22 Probabilistic sensitivity analysis produced results that were consistent with the primary prevention base case results outlined in Section 4.2.20. This showed that, for people aged 45 years at a 1.5% annual risk of a CHD event (this risk level was chosen by the Assessment Group for illustrative purposes), there is a high probability that statin therapy is cost effective for values between £20,000 and £30,000 per QALY. However, the probability that statins are cost effective at these levels decreases as age increases.
- 4.2.23 The Assessment Group's surrogate endpoint analysis, used to assess the cost effectiveness of rosuvastatin in primary CHD prevention, generated lower cost per QALY estimates compared with the base case results outlined in Section 4.2.20. At an annual risk of a CHD event ranging from 3% to 0.5%, the ranges of cost per QALY gained were £5000 to £15,000 at age 45 years, £7000 to £20,000 at age 55 years and £9000 to £29,000 at age 65 years.

Results of Scenario 1 (see Section 4.2.11)

- 4.2.24 In Scenario 1, the estimated costs per QALY for primary and secondary prevention closely resembled the base case results discussed in Sections 4.2.16 and 4.2.20. For secondary prevention, the incremental cost per QALY ranged from £9000 to £14,000 for all age groups, with little difference in the results for men and women.
- 4.2.25 For primary CHD prevention, at an annual risk of CHD ranging from 3% to 0.5%, the ranges of the incremental costs per QALY in Scenario 1 were £9000 to £30,000 at age 45 years, £13,000 to £40,000 at age 55 years, £17,000 to £59,000 at age 65 years, £26,000 to £98,000 at age 75 years and £36,000 to £110,000 at age 85 years.
- 4.2.26 The Assessment Group performed an additional series of analyses for Scenario 1, exploring a broader range of time horizons in primary prevention. This showed that, as the time horizon over which the costs and benefits associated with statin treatment are accrued increases from 5 years to

lifetime, the incremental costs per QALY decrease. At an annual risk of CHD ranging from 3% to 1.5% (the additional analysis was restricted to people with at least a 1.5% annual CHD risk), and using a 20-year time horizon instead of a lifetime horizon, the ranges of the incremental cost per QALY were £17,000 to £45,000 at age 45 years, £20,000 to £42,000 at age 55 years, £21,000 to £41,000 at age 65 years, £28,000 to £56,000 at age 75 years and £36,000 to £69,000 at age 85 years.

4.2.27 The Assessment Group also performed an additional primary prevention analysis for Scenario 1, examining the cost effectiveness of lowering risk thresholds for treatment (for example, from a threshold of 3% annual risk to a threshold of 2% annual risk) and taking into account the increased number of people eligible for treatment who would incur costs and receive benefits. This estimated that the incremental cost per QALY of lowering the risk threshold for treatment from 3% to 2% was £16,000 for males and £21,000 for females, from 2% to 1.5% was £18,000 for males and £24,000 for females, and from 1.5% to 1% was £18,000 for males and £29,000 for females. The impact on these results of using 3.5% discount rates for costs and benefits was also assessed. Using these rates, the incremental cost per QALY of lowering the threshold from 3% to 2% was £28,000 for males and £37,000 for females, from 2% to 1.5% was £32,000 for males and £43,000 for females, and from 1.5% to 1% was £35,000 for males and £55,000 for females.

Results of Scenario 2 (see Section 4.2.11)

4.2.28 In Scenario 2, the incremental costs per QALY were lower than the estimates for both the base case (discussed in Sections 4.2.16 and 4.2.20) and Scenario 1 (discussed in Sections 4.2.24 and 4.2.25), particularly for primary prevention. For secondary CVD prevention, the incremental cost per QALY ranged from £8000 to £13,000 for all age groups, with little difference in the results for men and women. In primary CVD prevention, at an annual risk of a CVD event ranging from 3% to 0.5%, the ranges of the incremental

cost per QALY were £5000 to £12,000 at age 45 years, £6000 to £14,000 at age 55 years, £6000 to £20,000 at age 65 years, £9000 to £32,000 at age 75 years and £15,000 to £50,000 at age 85 years.

4.3 Consideration of the evidence

- 4.3.1 The Committee reviewed the data available on the clinical and cost effectiveness of statins for the prevention of cardiovascular events, having considered evidence on the nature of the condition and the value placed on the benefits of statins by people with or at risk of CVD, those who represent them, and clinical experts. It was also mindful of the need to take account of the effective use of NHS resources.
- 4.3.2 The Committee took into account the responses received during consultation on the preliminary recommendations. It agreed that the guidance should focus on the appropriate initiation of statin therapy in adults with clinical evidence of CVD and in adults considered to be at risk of CVD.
- 4.3.3 The Committee first considered the evidence on the clinical and cost effectiveness of statin therapy for the secondary prevention of CVD. The Committee concluded that, on the basis of this evidence, statin therapy is clinically effective and cost effective for people with clinical evidence of CVD.
- 4.3.4 The Committee then considered the use of statins for the primary prevention of CVD. To ensure compatibility with the risk calculators currently used in clinical practice, the Committee acknowledged that its recommendations should be based on 10-year CVD risk. It considered that a 1.5% annual CHD risk, as reported in the Assessment Report, was approximately equivalent to a 15% 10-year CHD risk and a 20% 10-year CVD risk.
- 4.3.5 The Committee noted that CVD risk can be calculated on the basis of the presence of a variety of risk factors including total and sub-fractions of cholesterol measured in the blood. It was mindful that its remit did not extend to the evaluation of specific risk factor algorithms, which would be considered in the NICE clinical guideline on cardiovascular risk assessment

currently under development. It was aware that this clinical guideline would also consider the use of cholesterol target levels and the associated pathways of care for people with dyslipidaemia.

- 4.3.6 The Committee discussed in detail the results of the economic analyses from the manufacturers' models and the Assessment Group's model. It concluded that the Assessment Group's model, which estimated cost effectiveness for statins as a class, represented the most appropriate analysis on which to base its decision regarding the initiation of statin treatment. This was because the model used clinical events to measure effectiveness rather than the surrogate endpoint of cholesterol lowering, and it presented health outcomes in terms of QALYs. The Committee noted that this analysis excluded evidence on rosuvastatin because data on clinical events were not available. Of the three scenarios presented as part of the Assessment Group's model (see Section 4.2.11), the Committee agreed that Scenario 2, the analysis of people at risk of CVD, taking into account CVD outcomes, was the most appropriate. It noted that the sensitivity analyses related to the base case analysis (see Section 4.2.11) but concluded that the same general patterns of uncertainty would also apply to Scenario 2.
- 4.3.7 The Committee acknowledged the uncertainties around the results of the Assessment Group's primary prevention model. It was aware of substantial recent reductions in the prices of some statins, in particular simvastatin and pravastatin, and noted that this would significantly reduce the incremental costs per QALY estimated by the Assessment Group. The Committee considered that a time horizon based on the costs and health outcomes associated with a lifetime of statin therapy was the most appropriate for the economic analysis, given that statin therapy is a lifelong treatment and benefits occur well into the future. It acknowledged, however, that this extrapolation of the available data introduced additional uncertainty into the results, and that shortening the time horizon, to 20 years or less, markedly increased the incremental costs per QALY estimates. The Committee also noted the marked effect that discount rates had on the results, and that

applying rates of 3.5% to both costs and QALYs (instead of 6% for costs and 1.5% for QALYs) substantially increased the incremental costs per QALY. It accepted that the discount rates for this appraisal require the use of 6% for costs and 1.5% for QALYs, but it considered that the alternative rates were important for a check on the sensitivity of the results to change.

- 4.3.8 The Committee also carefully considered the Assessment Group's re-analysis of the cost effectiveness of statin therapy on the basis of decreasing risk in a stepwise manner (for example, from a threshold of 3% annual risk to 2% annual risk – see Section 4.2.27). It concluded that, although this analysis related to Scenario 1 of the Assessment Group's model (see Section 4.2.11), it gave an important insight into the true incremental cost effectiveness of treating decreasing levels of absolute risk and usefully supplemented the analysis based upon individual single point estimates of risk.
- 4.3.9 The Committee considered the nature of the population who would be treated with statins for primary prevention. It acknowledged that this group was essentially asymptomatic or free of CVD but at measurable risk of future events. The Committee noted that the Assessment Group's additional analysis suggested that it might be cost effective to initiate statin therapy in people with an annual risk of a CHD event lower than 1.5% (approximately equivalent to a 10-year risk of a CVD event lower than 20%). However, it was concerned by the uncertainty associated with the cost-effectiveness results, particularly at lower levels of CVD risk, because most of the clinical trials included in the review did not include people at very low risk of a CHD event. Additionally, the Committee took into consideration the risks of adverse events associated with the use of statins and that these should be taken into account when initiating lifelong treatment in a large population at a low risk of CVD. The Committee was also aware of the possibility that further adverse events might become apparent with extended use in wider populations and over time. Taking account of these factors and those outlined in Section 4.3.7, and the need to consider the effective use of NHS

resources given the large eligible population, the Committee concluded that initiation of statin therapy for primary prevention would be most appropriate in people at a 20% or greater 10-year CVD risk.

- 4.3.10 The Committee noted the increase in the incremental costs per QALY at all levels of risk in people over the age of 75 years in the economic model. It acknowledged that this change reflected the fact that older people have a higher risk of death from other causes, a higher prevalence of comorbidities and a shorter life expectancy, and hence have a lower capacity to benefit overall from statin therapy. However, taking into consideration the recent reductions in the prices of some statins, the Committee noted that statin therapy would be cost effective for all age groups at a 20% or greater 10-year risk of CVD. It was also aware that current risk calculators are not validated for individuals over the age of 70 years, and concluded that CVD risk should be estimated on the basis of a clinical assessment.
- 4.3.11 Consideration was given to the use of statins in people with diabetes. The Committee accepted that generally people with diabetes have a higher absolute risk of CVD compared with people without diabetes. It was aware that the review of clinical and cost effectiveness included evidence relating to the use of statins in type 2 diabetes only, and that statin therapy was cost effective in this group of people. The Committee was also aware that the absolute risk of CVD in people with diabetes varied according to the type of diabetes (type 1 or type 2) present. The Committee further noted the limitations of assessing risk in people with diabetes using standard risk calculators. The Committee concluded that the decision whether to initiate statin therapy in people with diabetes should be made where a clinical assessment has estimated the CVD risk to be likely to be equivalent to at least 20% over 10 years.
- 4.3.12 The Committee was also aware that people from some ethnic groups have a particularly high prevalence of CVD, although there are no validated risk assessment tools for such groups. The Committee agreed that the decision

whether to initiate statin therapy in such groups should therefore be made where a clinical assessment has estimated the CVD risk to be likely to be equivalent to at least 20% over 10 years.

- 4.3.13 The Committee was mindful that the initiation of statin therapy may not be an appropriate recommendation in all people. It considered that, when initiating statin therapy, clinicians should take into account all factors that relate to the individual's life expectancy and capacity to benefit from the reduction in cardiovascular events associated with statin usage. The Committee concluded that the decision whether to initiate statin therapy in any one individual, regardless of age, should be made after informed discussion between the responsible clinician and the patient about the risks and benefits of statin treatment and taking into account factors such as comorbidities and life expectancy.
- 4.3.14 The Committee noted from the evidence available that, for the purposes of initiating therapy, there were no data on clinical events to suggest the superiority of any one statin over all the others in reducing cardiovascular events. It was mindful that data on clinical events were not currently available for rosuvastatin. It was also aware of the substantial differences in price between the different statins, resulting partly from the recent large reductions in the price of some statins, and of the potential for future price changes. The Committee concluded that, when the decision has been made to initiate a statin, therapy should usually be initiated with a drug with a low acquisition cost (taking into account required daily dose and product price per dose).
- 4.3.15 Finally, the Committee discussed the importance of other strategies for managing CVD risk over and above statin therapy, such as lifestyle measures and other drug therapies. It concluded that, although making recommendations on other management strategies was outside the remit of the current appraisal, the guidance should be issued on the assumption that

such strategies are being appropriately considered when initiating statin therapy.

5 Recommendations for further research

- 5.1 Research should be conducted to compare the clinical and cost effectiveness of different statins in preventing cardiovascular events. This should also include, where such data do not exist, comparison of the use of statins with, or in combination with, other lipid-modifying drugs.
- 5.2 Research should be undertaken to determine the clinical effectiveness of statin therapy in populations at very low risk of a CVD event, and the impact of such therapy in terms of adverse events and quality of life.
- 5.3 Research is needed on the attitudes of people at low risk of CVD to taking medication over a lifetime, and the optimal methods of explaining risks and benefits of treatment to people so that they can make informed choices. Research is also needed on compliance and continuance with statin therapy in low-risk populations.
- 5.4 Research should be conducted into the clinical effectiveness of statin therapy in different ethnic groups.
- 5.5 The Institute notes that four studies of rosuvastatin that will report clinical event outcomes are currently ongoing: two in patients with heart failure, one in patients requiring ongoing renal dialysis, and one in primary prevention in people at low risk.

6 Implications for the NHS

- 6.1 Since the final appraisal determination was issued, NICE has carried out more detailed costing analysis to support implementation of the guidance. The following costing tools are available from the NICE website (www.nice.org.uk/TA094).

- A national costing report, which estimates the overall resource impact associated with implementation.
- A local costing template: a simple spreadsheet that can be used to estimate the local cost of implementation.

7 Implementation and audit

7.1 NHS organisations and all clinicians who care for people who have CVD or who are at risk of CVD should review their current practice and policies to take account of the guidance set out in Section 1.

7.2 Local guidelines or care pathways for people with CVD or people who are at risk of CVD should incorporate the guidance.

7.3 To measure compliance locally with the guidance, the following criteria could be used. Further details on suggestions for audit are presented in Appendix C. The criteria relate only to the initiation of statin therapy in adults.

7.3.1 Statin therapy is prescribed for adults with clinical evidence of CVD.

7.3.2 Statin therapy is prescribed as part of the management strategy for the primary prevention of CVD for adults who are at risk, defined as having a 20% or greater 10-year risk of developing CVD as estimated by an appropriate risk calculator or after a clinical assessment for people for whom an appropriate risk calculator is not available.

7.3.3 The decision whether to initiate statin therapy for adults with clinical evidence of CVD or as part of the management strategy for the primary prevention of CVD for adults who are at risk (see Sections 7.3.1 and 7.3.2) is made on an individual basis after informed discussion between the responsible clinician and the individual about the risks and benefits of statin treatment, and taking into account other factors.

7.3.4 When the decision has been made to prescribe a statin, therapy is usually initiated with a drug with a low acquisition cost.

7.4 Local clinical audits on the care of patients with CVD could also include criteria for the management of CVD based on the national standards, including standards in the NSF.

8 Related guidance

8.1 Published technology appraisals:

- Guidance on the use of drugs for early thrombolysis in the treatment of acute myocardial infarction. *NICE technology appraisal no. 52* (2002). Available from: www.nice.org.uk/TA052
- Guidance on the use of coronary artery stents. *NICE technology appraisal no. 71* (2003). Available from: www.nice.org.uk/TA071
- Myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction. *NICE technology appraisal no. 73* (2003). Available from: www.nice.org.uk/TA073
- Clopidogrel and modified-release dipyridamole in the prevention of occlusive vascular events. *NICE technology appraisal no. 90* (2005). Available from: www.nice.org.uk/TA090

8.2 Technology appraisals in development:

- Ezetimibe for the treatment of hypercholesterolaemia (publication expected July 2007).

8.3 Published clinical guidelines:

- Myocardial infarction: prophylaxis for patients who have experienced a myocardial infarction. *NICE inherited clinical guideline A* (2001). Available from: www.nice.org.uk *Currently being reviewed*
- Management of type 2 diabetes: management of blood pressure and blood lipids. *NICE inherited clinical guideline H* (2002). Available from: www.nice.org.uk
- Hypertension: management of hypertension in adults in primary care. *NICE clinical guideline no. 18* (2004). Available from: www.nice.org.uk/CG018

8.4 Clinical guidelines in development:

- Cardiovascular risk assessment: the modification of blood lipids for the primary and secondary prevention of cardiovascular disease (publication expected September 2007).
- Familial hypercholesterolaemia: identification and management (publication expected November 2008).

9 Review of guidance

9.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider whether the technology should be reviewed. This decision will be taken in the light of information gathered by the Institute, and in consultation with consultees and commentators.

9.2 The guidance on this technology will be considered for review in November 2008.

Andrew Dillon
Chief Executive
January 2006

Appendix A. Appraisal Committee members and NICE project team

A. Appraisal Committee members

NOTE The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets three times a month except in December, when there are no meetings. The committee is split into three branches. In order to ensure consistency, the chair of each branch is also a member of a branch of which he is not chair. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Jane Adam

Radiologist, St George's Hospital, London

Professor Ron Akehurst

Dean of School of Health and Related Research, University of Sheffield

Dr Sunil Angris

General Practitioner, Waterhouses Medical Practice, Staffordshire

Professor David Barnett (Chair)

Professor of Clinical Pharmacology, University of Leicester

Professor Stirling Bryan

Professor of Health Economics, Health Economics Facility, Health Services Management Centre, University of Birmingham

Professor John Cairns

Professor of Health Economics, Public Health and Policy, London School of Hygiene and Tropical Medicine, London

Professor David Chadwick

Professor of Neurology, Department of Neurological Science, Walton Centre for Neurology & Neurosurgery, Liverpool

Dr Lorna Duggan

Consultant Forensic Psychiatrist in Developmental Disabilities, St Andrew's Hospital, Northampton

Mrs Fiona Duncan

Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital, Blackpool

Dr Paul Ewings

Statistician, Taunton & Somerset NHS Trust, Taunton

Dr Trevor Gibbs

Head, Global Clinical Safety & Pharmacovigilance, GlaxoSmithKline, Greenford

Mr Sanjay Gupta

Stroke Services Manager, Basildon & Thurrock University Hospitals NHS Trust

Professor Philip Home (Acting Chair)

Professor of Diabetes Medicine, Department of Medicine, University of Newcastle upon Tyne

Dr Peter Jackson

Clinical Pharmacologist, Molecular & Clinical Pharmacology, University of Sheffield

Dr Terry John

General Practitioner, The Firs, London

Dr Mike Laker

Medical Director, Newcastle Hospitals NHS Trust, Royal Victoria Infirmary,
Newcastle-upon-Tyne

Dr George Levvy

Chief Executive, Motor Neurone Disease Association, Northampton

Mr Terence Lewis

Mental Health Consultant, National Institute for Mental Health in England, Solihull,
West Midlands

Professor Richard Lilford

Professor of Clinical Epidemiology, Department of Public Health and Epidemiology,
University of Birmingham

Professor John Lumley

Honorary Consultant, The Ernest Cooke Clinic Microvascular Unit, Great Ormond
Street, Bart's and the Royal London NHS Trust, Barbican, London

Dr Simon Mitchell

Consultant Neonatal Paediatrician, St Mary's Hospital, Manchester

Dr Christa Roberts

UK Manager Vascular Intervention, Guidant Ltd.

Dr Stephen Saltissi

Consultant Cardiologist, Royal Liverpool University Hospital

Dr Lindsay Smith

General Practitioner, Westlake Surgery, Somerset

Mr Mike Spencer

General Manager, Clinical Support Services, Cardiff and Vale NHS Trust

Dr Rod Taylor

Senior Lecturer, Department of Public Health & Epidemiology, University of Birmingham

Professor Mary Watkins

Professor of Nursing, University of Plymouth

Professor Norman Waugh

Department of Public Health, University of Aberdeen

B. NICE project team

Each appraisal of a technology is assigned to one or more Health Technology Analysts and a Technology Appraisal Project Manager within the Institute.

Louise Longworth

Technical Lead

Zoe Charles

Technical Lead

Emily Marschke

Project Manager

Appendix B. Sources of evidence considered by the Committee

A The assessment report for this appraisal was prepared by the School of Health and Related Research, University of Sheffield.

Ward S, Lloyd Jones M, Pandor A et al. *Statins for the prevention of coronary events*, January 2005.

B The following organisations accepted the invitation to participate in this appraisal. They were invited to make submissions and comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD). Consultee organisations are provided with the opportunity to appeal against the Final Appraisal Determination.

I Manufacturers/sponsors:

- AstraZeneca UK Ltd
- Bristol-Myers Squibb Pharmaceuticals Ltd
- Merck Sharp & Dohme Ltd
- Novartis Pharmaceuticals UK Ltd
- Pfizer Ltd (Parke-Davis)

II Professional/specialist and patient/carer groups:

- Association of British Clinical Diabetologists
- Blood Pressure Association
- Diabetes UK
- Heart UK
- Cochrane Heart Group
- National Screening Committee for CHD/Diabetes/Stroke
- Primary Care Cardiovascular Society
- Royal College of Nursing
- Royal College of Physicians

III Commentator organisations (without the right of appeal):

- British National Formulary
- British Regional Heart Study
- Cholesterol Treatment Trialists' Collaboration
- Cochrane Heart Group
- National Collaborating Centre for Primary Care
- National Public Health Service for Wales
- National Screening Committee for CHD/Diabetes/Stroke
- NHS Confederation
- NHS Purchasing and Supplies Agency
- NHS Quality Improvement Scotland

C The following individuals were selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on statins for the prevention of cardiovascular events by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Professor John Betteridge – nominated by Royal College of Physicians
- Dr Rubin Minhas – nominated by Primary Care Cardiovascular Society
- Dr John Reckless – nominated by Heart UK
- Ms Yvonne Dumsday – nominated by Heart UK
- Mr Ian Powell – nominated by Diabetes UK
- Professor Alistair Hall – nominated by British Cardiac Society

Appendix C. Detail on criteria for audit of the use of statins for the prevention of cardiovascular events

Possible objectives for an audit

An audit could be carried out on the appropriateness of use of statin therapy.

Possible patients to be included in the audit

The audit design relates only to the initiation of statin therapy in adults with clinical evidence of cardiovascular disease (CVD) and in adults considered to be at risk of CVD. The audit design assumes that other strategies for managing CVD are being appropriately considered when initiating statin therapy. The audit design does not include prescribing statin therapy for genetic dyslipidaemias, such as familial hypercholesterolaemia. The audit measures relate only to the use of statins within their licensed indications.

In a primary care setting, as a starting point, the audit could include all adults who are on a practice's coronary heart disease (CHD) register. It is recognised that such registers may be specific to CHD and not CVD. In addition, the audit could include adults who have been identified as having a 20% or greater 10-year risk of developing CVD, if these adults are not on the register.

In an acute care setting, the audit could include all adults being referred for clinical evidence of CVD or who have been identified as having a 20% or greater 10-year risk of developing CVD and adults admitted or treated on an emergency basis for CVD. The audit could include all adults identified in either of these groups over a reasonable period for audit, for example, 3 to 6 months.

Measures that could be used as a basis for an audit

The measures that could be used in an audit of the use of statins for the prevention of cardiovascular events are as follows.

Criterion	Standard	Exception	Definition of terms
1. Statin therapy is prescribed for an adult with clinical evidence of CVD	100% of adults with clinical evidence of CVD	A. Statin therapy is contraindicated B. The person declines the prescription following informed discussion with the responsible clinician (see 3 below)	Statins include: atorvastatin, fluvastatin, pravastatin, rosuvastatin and simvastatin. Clinicians will need to agree locally on what constitutes clinical evidence of CVD, for example, myocardial infarction (MI), angina, stroke, transient ischaemic attack and peripheral arterial disease. For contraindications, see the Summaries of Product Characteristics.
2. Statin therapy is prescribed as part of the management strategy for the primary prevention of CVD for adults who are at risk	100% of adults who are at risk of developing CVD	A. Statin therapy is contraindicated B. Statin therapy is not considered clinically appropriate following clinical assessment C. The person declines the prescription following informed discussion with the responsible clinician (see 3 below)	'At risk of developing CVD' means people who have a 20% or greater 10-year risk of developing CVD as estimated by an appropriate risk calculator, agreed by local clinicians, or after a clinical assessment to estimate CVD risk when an appropriate risk calculator is not available, for example, in older people, people with diabetes and people in high-risk ethnic groups. Clinicians will need to agree locally on when statin therapy would not be considered clinically appropriate following clinical assessment (exception B) and interventions that are included in the management strategy for the primary prevention of CVD, for

			audit purposes. These may include lifestyle measures such as smoking cessation, increased physical activity, diet modification, and drug treatments such as lipid-lowering drugs, beta-blockers for people who have had an MI, antihypertensives to control blood pressure, and aspirin.
3. The decision whether to initiate statin therapy for an adult with clinical evidence of CVD or as part of the management strategy for the primary prevention of CVD for adults who are at risk (see 1 and 2 above) is made on an individual basis after informed discussion between the responsible clinician and the patient	100% of people for whom statin therapy is initiated for clinical evidence of CVD or part of the management strategy for the primary prevention of CVD for adults who are at risk	None	'Informed discussion' includes discussing the risks and benefits of statin treatment. 'Individual basis' means taking into account factors such as comorbidities and life expectancy. Clinicians will need to agree locally on how the decision is documented, for audit purposes, including the informed discussion with the patient.
4. When the decision has been made to prescribe a statin, therapy is initiated with a drug with a low acquisition cost	100% of initial prescriptions for statin therapy	A. There is a clinical justification for selecting another drug	Clinicians will need to agree locally on how acquisition costs should be calculated and on clinical justifications for selecting another drug. The calculation should take into account required daily dose and product price per dose.

Calculation of compliance

Compliance (%) with each measure described in the table above is calculated as follows.

$$\frac{\text{Number of patients whose care is consistent with the **criteria** **plus** number of patients who meet any **exception** listed}{\text{Number of patients to whom the **measure** applies}} \times 100$$

Clinicians should review the findings of measurement, identify whether practice can be improved, agree on a plan to achieve any desired improvement and repeat the measurement of actual practice to confirm that the desired improvement is being achieved.