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Abstract

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Objectives: To evaluate the clinical effectiveness and cost-effectiveness of statins for the primary and secondary prevention of cardiovascular events in adults with, or at risk of, coronary heart disease (CHD).

Data sources: Electronic databases were searched between November 2003 and April 2004.

Review methods: A review was undertaken to identify and evaluate all literature relating to the clinical and cost effectiveness of statins in the primary and secondary prevention of CHD and cardiovascular disease (CVD) in the UK. A Markov model was developed to explore the costs and health outcomes associated with a lifetime of statin treatment using a UK NHS perspective.

Results: Thirty-one randomised studies were identified that compared a statin with placebo or with another statin, and reported clinical outcomes. Meta-analysis of the available data from the placebo-controlled studies indicates that, in patients with, or at risk of, CVD, statin therapy is associated with a reduced relative risk of all cause mortality, cardiovascular mortality, CHD mortality and fatal myocardial infarction (MI), but not of fatal stroke. It is also associated with a reduced relative risk of morbidity [non-fatal stroke, non-fatal MI, transient ischaemic attack (TIA), unstable angina] and of coronary revascularisation. It is hardly possible, on the evidence available from the placebo-controlled trials, to differentiate between the clinical efficacy of atorvastatin, fluvastatin, pravastatin and simvastatin. However, there is some evidence from direct comparisons between statins to suggest that atorvastatin may be more effective than pravastatin in patients with symptomatic CHD. There is limited evidence for the effectiveness of statins in different subgroups. Statins are generally considered to be well tolerated and to have a good safety profile. This view is generally supported both by the evidence of the trials

included in this review and by postmarketing surveillance data. Increases in creatine kinase and myopathy have been reported, but rhabdomyolysis and hepatotoxicity are rare. However, some patients may receive lipid-lowering therapy for as long as 50 years, and long-term safety over such a timespan remains unknown. In secondary prevention of CHD, the incremental cost-effectiveness ratios (ICERs) increase with age varying between £10,000 and £17,000 per quality adjusted life year (QALY) for ages 45 and 85 respectively. Sensitivity analyses show these results are robust. In primary prevention of CHD there is substantial variation in ICERs by age and risk. The average ICERs weighted by risk range from £20,000 to £27,500 for men and from £21,000 to £57,000 for women. The results are sensitive to the cost of statins, discount rates and the modelling time frame. In the CVD analyses, which take into account the benefits of statins on reductions in stroke and TIA events, the average ICER weighted by risk level remains below £20,000 at CHD risk levels down to 0.5%. Limitations of the analyses include the requirement to extrapolate well beyond the timeframe of the trial period, and to extrapolate effectiveness results from higher risk primary prevention populations to the treatment of populations at much lower risk. Consequently, the results for the lower age bands and lower risks are subject to greater uncertainty and need to be treated with caution.

Conclusions: There is evidence to suggest that statin therapy is associated with a statistically significant reduction in the risk of primary and secondary cardiovascular events. As the confidence intervals for each outcome in each prevention category overlap, it is not possible to differentiate, in terms of relative risk, between the effectiveness of statins in primary and secondary prevention. However, the absolute risk of CHD death/non-fatal MI is higher, and the number

needed to treat to avoid such an event is consequently lower, in secondary than in primary prevention. The generalisability of these results is limited by the exclusion, in some studies, of patients who were hypersensitive to, intolerant of, or known to be unresponsive to, statins, or who were not adequately compliant with study medication during a placebo run-in phase. Consequently, the treatment effect may be reduced when statins are used in an unselected population. The results of the economic modelling show that statin therapy in secondary prevention is likely to be considered cost-effective. In primary prevention, the cost-effectiveness ratios are dependent on the level of CHD risk and age, but the results for the CVD analyses offer support for the more aggressive treatment recommendation issued by recent guidelines in UK. Evidence on clinical endpoints for rosuvastatin is awaited from on-going trials. The potential targeting of statins at low-risk populations is however associated with major uncertainties, particularly the likely uptake and long-term compliance to lifelong medication by asymptomatic younger patients. The targeting, assessment and monitoring of low-risk patients in primary care would be a major resource implication for the NHS. These areas require further research.

Contents

Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary

Acute coronary syndrome   Symptoms compatible with acute myocardial ischaemia (primarily unstable angina or MI).

Alopecia   Hair loss.

Anaphylaxis   A sudden, severe, potentially fatal allergic reaction.

Angina pectoris   Discomfort or pain resulting from a reduction in the oxygen supply to the heart muscle, most commonly caused by atherosclerosis.

Angiodema   Temporary, potentially life-threatening, swelling, often due to allergy.

Anorexia   Abnormal loss of appetite for food.

Aphasia   Total or partial loss of the ability to use or understand language.

Asthenia   Weakness or loss of energy.

Atherosclerosis   A condition in which fatty deposits (atheromas) develop in the arteries; these narrow the blood vessels and can rupture to form a complete blockage resulting in heart attack or stroke (depending on location).

Body mass index   A measure of relative weight, calculated by dividing an individual's weight in kilograms by their height in metres squared (kg/m^2).

Cardiovascular   Pertaining to the heart and blood vessels.

Cardiovascular disease   A term generally used to refer to all vascular disease caused by atherosclerosis.

Cerebrovascular   Pertaining to the blood vessels of the brain.

Coronary arteries   The arteries that supply the heart muscle with blood.

Coronary heart disease   Narrowing or blockage of the coronary arteries that reduces the blood supply to the heart, and potentially causes angina or myocardial infarction. Also known as coronary artery disease or ischaemic heart disease.

Diabetes mellitus   A disorder caused by insufficient production of insulin by the pancreas (type 1 diabetes) or by insensitivity to the effects of insulin (type 2 diabetes).

Dysaesthesia   Impairment of sense of touch.

Heterozygous   Possessing two different forms of a particular gene.

Homozygous   Possessing two identical forms of the same gene.

Hypercholesterolaemia   High blood cholesterol.

Hyperglycaemia   High blood glucose.

Hyperlipidaemia   High blood lipids.

Hypoaesthesia   Impairment of sense of touch.

Hypoglycaemia   Low blood glucose.

Hypothyroidism   A condition in which the body lacks sufficient thyroid hormone.

Infarction   Death of tissue following interruption of the blood supply.

Intermittent claudication   Pain in the calf or buttock which is brought on by exercise and relieved by rest.

Ischaemic heart disease   Coronary heart disease.

Glossary *continued*

Minimisation   A method of randomly allocating study subjects to treatment groups which can take account of a greater number of prognostic factors than is possible by stratification.

Myalgia   Diffuse muscle pain, tenderness and weakness.

Myocardial infarction   Permanent damage to an area of heart muscle as a result of interruption of the blood supply to the area caused by narrowed or blocked blood vessels ('heart attack').

Myopathy   Muscle pain, tenderness or weakness associated with abnormal elevations in creatinine kinase levels (more than ten times the upper limit of normal).

Myositis   Inflammation of the muscles.

Paraesthesia   An abnormal burning or prickling sensation that is generally felt in the hands, arms, legs or feet, but which may occur in any part of the body.

Peripheral arterial disease   Obstruction of the arteries carrying blood to the arms or, more commonly, the legs, usually caused by atherosclerosis.

Peripheral neuropathy   Damage to the peripheral nerves resulting in muscle weakness and atrophy, pain and weakness.

Pleiotrophic   Of a drug: acting in the body in more than one way, which combine to result in its clinical effects.

Polyneuropathy   Generalised disorder of the peripheral nerves.

Porphyria   Disorder of porphyrin metabolism.

Premature death   Death before the age of 75 years.

Primary cardiac arrest   Cardiac arrest that results from heart disease, and is not secondary to trauma, respiratory failure, renal failure or other non-cardiac causes.

Primary prevention   Activity intended to delay or prevent the onset of a disease.

Pruritus   Itching skin.

Revascularisation   The restoration of blood supply, either pharmacologically or surgically.

Rhabdomyolysis   A syndrome resulting from destruction of skeletal muscle resulting in myoglobinuria, muscle weakness, pain, swelling and cramps. Serious complications of rhabdomyolysis include acute renal failure, ischaemia, disseminated intravascular coagulation and respiratory failure.

Rose Angina Questionnaire   A questionnaire developed to identify, in a standard way, the characteristic symptom complex known as angina, and which has been validated by comparison with clinical diagnosis.

Secondary prevention   Activity intended to delay the recurrence of, or prevent mortality from, a disease.

Stable angina   Angina that occurs during exercise or emotional stress, and which is relieved by medication with nitrates.

Stratification   A method of randomly allocating study subjects to treatment groups which achieves balance for one or two prognostic variables (such as disease status) by randomising each prognostic subgroup separately.

Stroke   The sudden death of some brain cells when the blood supply to the brain is impaired by the blockage or rupture of an artery.

Thrombocytopenia   Decrease in the number of platelets in the blood, which may result in easy bruising and excessive bleeding.

Transient ischaemic attack   Temporary disturbance of the blood supply to a restricted area of the brain, causing neurological dysfunctions lasting for less than 24 hours.

Unstable angina   A spectrum of clinical states including angina that occurs at rest, new-onset angina (within 2 months of onset), increasing angina (e.g. angina that occurs with increasing frequency, for longer duration or at lower thresholds), variant angina (ST-segment elevation) and angina occurring more than 24 hours post-myocardial infarction. Unstable angina typically, although not always, indicates significant coronary artery disease.

List of abbreviations

4S	Scandinavian Simvastatin Survival Study		HSE	Health Survey for England
ACE	angiotensin-converting enzyme		ICER	incremental cost-effectiveness ratio
ACS	acute coronary syndrome		ITT	intention-to-treat
AE	adverse event		LDL-C	low-density lipoprotein cholesterol
AHA	American Heart Association		LIPID	Long-Term Intervention with Pravastatin in Ischaemic Disease
AMI	acute myocardial infarction			
BCHDR	Bromley Coronary Heart Disease Register		LYG	life-year gained
BMI	body mass index		LYS	life-years saved
BNF	British National Formulary		MI	myocardial infarction
CABG	coronary artery bypass graft		MINAP	Myocardial Infarction National Audit Project
CAD	coronary artery disease		NA	not applicable
CCTR	Cochrane Central Register of Controlled Trials		NCEP	National Cholesterol Education Program
CDSR	Cochrane Database of Systematic Reviews		NHAR	Nottingham Heart Attack Register
CEAC	cost-effectiveness acceptability curve		NHS EED	NHS Economic Evaluation Database
CHD	coronary heart disease		NICE	National Institute for Health and Clinical Excellence
CI	confidence interval			
CK	creatine kinase		NNT	number needed to treat
CRP	C-reactive protein		NR	not reported
CSM	Committee on Safety of Medicines		NSF	National Service Framework
CVD	cardiovascular disease		ONS	Office for National Statistics
DARE	Database of Abstracts of Reviews of Effectiveness		OTC	over-the-counter
			PAD	peripheral arterial disease
EQ-5D	EuroQol 5 Dimensions		PCI	percutaneous coronary intervention
FDA	Food and Drug Administration			
GPRD	General Practitioner Research Database		PCT	primary care trust
			PTCA	percutaneous transluminal coronary angioplasty
HDL-C	high-density lipoprotein cholesterol			
HMG CoA	3-hydroxy-3-methylglutaryl coenzyme A		PSA	probabilistic sensitivity analysis
			QALY	quality-adjusted life-year
HPS	Heart Protection Study		RCT	randomised controlled trial
HRQoL	health-related quality of life		RR	relative risk
			SAE	serious adverse event

continued

List of abbreviations *continued*

ScHARR	School of Health and Related Research		TC	total cholesterol
SD	standard deviation		TIA	transient ischaemic attack
SE	standard error		WOSCOPS	West of Scotland Coronary Prevention Study
SLSR	South London Stroke Register			

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Objective

This study evaluated the use of a group of statins, atorvastatin, fluvastatin, pravastatin, rosuvastatin and simvastatin, for the prevention of cardiovascular events.

Epidemiology and background

Cardiovascular disease (CVD) is one of the major causes of premature death in the UK, accounting for 35% of premature deaths in men and 27% in women. It is also a significant cause of morbidity.

The three major manifestations of CVD are:

- coronary heart disease (CHD), including myocardial infarction (MI, heart attack) and angina
- cerebrovascular disease [transient ischaemic attack (TIA) and stroke]
- peripheral arterial disease (obstruction of the arteries carrying blood to the legs or, less commonly, the arms).

Several risk factors for CHD have been identified; these include hyperlipidaemia. Some of these risk factors (e.g. smoking, obesity and hypertension) can be modified, treated or controlled. Others (e.g. age, gender and ethnicity) cannot. CHD risk can be reduced by cholesterol lowering, changes in lifestyle, such as smoking cessation, exercise and the use of cholesterol-lowering diets, along with non-cholesterol drug treatments, including aspirin and antihypertensives. The cost-effectiveness of statins must be seen in the context of these other interventions.

Methods

A review was undertaken to identify all literature relating to the clinical effectiveness of statins for the prevention of coronary events, as well as to identify and evaluate studies exploring the cost-effectiveness of statins in primary and secondary prevention of CHD and CVD in the UK. Electronic literature searches were conducted between November 2003 and April 2004.

A Markov model was developed to explore the costs and health outcomes associated with a lifetime of statin treatment using a UK NHS perspective. Data from UK epidemiological studies were used to inform event rates, and were combined with results from the meta-analysis of RCT evidence on the effectiveness of statins to model the relative risk reductions of event rates for patients on statin therapy. Costs of health states (first-year costs and subsequent year) were based on a review of published evidence to obtain the most recent and appropriate costs. The annual cost of statins is a weighted average cost for statins (weighted by the trial evidence), for different statins at different dosage. Given that statins have a good safety profile, and adverse events are rare, costs of managing adverse events are not modelled. Utility estimates for health states within the model were identified by a literature review. The utility of the general population is assumed to vary by age. Input parameters were assigned probability distributions to reflect their imprecision, and Monte Carlo simulations were performed to reproduce this uncertainty in the results. Results were presented in terms of quality-adjusted life years (QALYs) for both primary and secondary prevention of CHD/CVD events. Costs were at 2004 prices and discount rates of 6% and 1.5% applied to costs and health benefits, respectively.

The basecase analysis considered the cost-effectiveness of statins for a population with CHD or at risk of CHD, taking into account CHD outcomes only. This complied with the scope specifically requested by the Department of Health to consider only coronary heart disease. Two further scenarios were explored to take into account the growing evidence on the impact of statins on reducing stroke events. Scenario 1 was as the basecase but also took into account the potential of statins to reduce stroke events in patients with a history of CHD. Scenario 2 explored the costs and benefits associated with statin treatment in reducing CVD events for patients with or at risk of CVD, with all patients entering the treatment arm of the model assumed to receive benefits associated with statin treatment.

Given that current trials of rosuvastatin report only on the intermediate end-point of cholesterol

lowering and there is currently no direct trial evidence of the effect of rosuvastatin on morbidity and mortality, the ScHARR model was also adapted to calculate the risk of CHD (morbidity and mortality) using a Framingham risk equation. There were, however, several issues concerning the robustness of estimation of cost-effectiveness when using Framingham equations to model the link between cholesterol lowering and CHD risk, which are discussed in detail within the report.

Results

Number and quality of studies, and direction of evidence

Thirty-one randomised studies were identified that compared a statin with placebo or with another statin, and that reported clinical outcomes. Meta-analysis of the available data from the placebo-controlled studies indicates that, in patients with, or at risk of, CVD, statin therapy is associated with a reduced relative risk of all-cause mortality, cardiovascular mortality, CHD mortality and fatal MI, but not of fatal stroke. It is also associated with a reduced relative risk of morbidity (non-fatal stroke, non-fatal MI, TIA, unstable angina) and of coronary revascularisation. It is hardly possible, on the evidence available from the placebo-controlled trials, to differentiate between the clinical efficacy of atorvastatin, fluvastatin, pravastatin and simvastatin. However, there is some evidence from direct comparisons between statins to suggest that atorvastatin may be more effective than pravastatin in patients with symptomatic CHD.

There is no evidence from randomised controlled trials (RCTs) for the effectiveness of the 10-mg over-the-counter dose of simvastatin in preventing clinical events.

No relevant studies of rosuvastatin were identified that reported clinical outcomes. Thus, although there is RCT evidence to suggest that rosuvastatin is more effective than atorvastatin, pravastatin and simvastatin in reducing both total and low-density lipoprotein cholesterol, it is not possible to prove that these reductions translate into comparable reductions in clinical events.

There is limited evidence for the effectiveness of statins in different subgroups. There is no evidence that statins differ in their effectiveness, measured in terms of relative risk reduction, in primary compared with secondary prevention, in women compared with men at a similar level of cardiovascular risk, in people with diabetes compared with those without, or in people aged 65 and over compared with those younger than 65. In renal transplant patients, statin therapy is associated with a reduced risk of CHD death or non-fatal MI. However, no benefit has been demonstrated in cardiac transplant patients. For ethical reasons, no placebo-controlled trials have been carried out in patients with familial hypercholesterolaemia. The only randomised trial in this group compared two statins, and found no significant difference between them. People from the Indian subcontinent are known to be at increased risk of CVD. However, no placebo-controlled studies were found that studied the clinical effectiveness of statins in this population.

Safety

Although concerns have been raised about rosuvastatin, statins are generally considered to be well tolerated and to have a good safety profile. This view is generally supported both by the evidence of the trials included in this review and by postmarketing surveillance data. Although increases in creatine kinase and myopathy have been reported, rhabdomyolysis and hepatotoxicity are rare. However, some patients may receive lipid-lowering therapy for as long as 50 years, and long-term safety over such a timespan remains unproven.

Summary of cost-effectiveness evidence
Review of existing cost-effectiveness literature
The literature searches identified 206 potentially relevant publications. Of these only five UK studies satisfied all inclusion and exclusion criteria and formed the basis of the review. These studies were assessed for quality using components of the BMJ and Eddy checklists. All scored well on modelling methodologies and presentation of results.

All five UK studies reported on cost per life-year gained (LYG), rather than cost per QALY. Four of the five studies had results below £30,000 in primary prevention treatment, varying between £8000 and £30,000 depending on baseline risk. One study estimated cost-effectiveness at £136,000, which appears anomalous compared with the other studies. Cost-effectiveness in secondary treatment was estimated in two studies and ranged from £6000 to £40,000.

As part of their industry submissions to the National Institute for Health and Clinical Excellence, Pfizer, Novartis, Bristol-Myers Squibb and AstraZeneca presented cost-effectiveness models. These were critiqued using the combined

BMJ and Eddy framework. Of the four models submitted, two (Pfizer and AstraZeneca) used the surrogate end-point of cholesterol lowering for predicting reductions in clinical end-points and two (Novartis and Bristol-Myers Squibb) used trial evidence on reductions in clinical end-points. The time-horizon in the four models varied between 5 years and lifetime. Overall, taking into account the differences in techniques and objectives, the results from all four models could be considered to be of a similar order of magnitude. The estimated cost per QALY for both secondary and primary prevention is typically below £10,000. The most significant difference between the model results is the secondary prevention results from the AstraZeneca model, which are markedly higher than the other evaluations. In this model, treatment is reported to be less cost-effective in secondary prevention than in primary prevention. The within-trial economic analysis of simvastatin by Merck Sharp & Dohme produced results in secondary prevention of a similar magnitude to the Novartis and Pfizer evaluations.

Base-case analysis

The cost-effectiveness of statins depends on the CHD risk in the population treated and the age and gender of the population under consideration. Cost-effectiveness results were presented for men and women aged 45–85 years in 10-year age bands.

In secondary prevention the cost per QALY was estimated to vary between around £10,000 and £17,000 between the ages of 45 and 85, with incremental cost-effectiveness ratios (ICERs) increasing with age, but with little difference between genders. These results are sensitive to the modelling time-frame and to the discount rates. The results of probabilistic sensitivity analysis showed that, using a threshold of £20,000 per QALY, statin therapy was cost-effective for all patients with a history of CHD.

In primary prevention the estimated ICERs varied according to risk level and age. This rose from around £20,000 to £28,000 for men between 3 and 0.5% CHD risk, and between £21,000 and £57,000 for women. There was significant variation with age within risk levels. At an annual CHD risk of 3%, the estimated cost per QALY ranged from £10,000 to £37,000 for men and from £14,000 to £48,000 for women between the ages of 45 and 85. At the age of 85 years the estimated cost per QALY rose from £37,000 and £48,000 for men and women, respectively, at 3% CHD risk, to around £105,000 and £111,000 for men and women at 0.5% CHD risk.

Alternative scenarios

Alternative scenarios also considered the cost-effectiveness in statins in the wider context of CVD risk and outcomes. For scenario 1 (CHD analysis with CVD outcomes) the ICERs were similar to the base-case results (CHD analysis). For scenario 2 (CVD analysis) the ICERs were substantially lower than the base-case results owing to the additional impact of statin treatment on reducing stroke and TIA events for all patients.

Conclusions

The cost-effectiveness modelling presented here has shown that statin therapy in secondary prevention is likely to be considered cost-effective when compared with other current standard treatments available to the NHS. In primary prevention, the cost-effectiveness ratios are dependent on the level of CHD risk and age, but the results, for the CVD analysis in particular, offer support for the more aggressive treatment recommendation issued by recent guidelines in UK.

Limitations of cost–utility estimates

One of the major limitations of the analyses is the requirement to extrapolate well beyond the time-frame of the trial period. This period of extrapolation will be longer for younger patients and therefore the results for the lower age bands are subject to greater uncertainty. In addition, the analyses for primary prevention extrapolated effectiveness results from higher risk primary prevention populations to the treatment of populations at much lower risk, and have to be viewed with caution.

The analyses are sensitive to the cost of statin, and the future cost of statins is a key unknown. Therefore, the cost-effectiveness results will need to be reviewed in the light of any significant changes in the price of statins.

These analyses do not take into account the costs of identifying and screening the relevant population. In primary prevention, as the risk threshold becomes lower the size of the population eligible for treatment increases. The number of patients who will require regular monitoring will expand, placing additional demands on staff and resources at GP surgeries.

Evidence on clinical end-points for rosuvastatin is awaited. Modelling clinical outcome on cholesterol lowering inherently favours drugs that are more potent at lowering cholesterol. In the absence of

strong and conclusive evidence on the exact relationship between cholesterol lowering and clinical end-points, cost-effectiveness results for rosuvastatin are subject to additional uncertainty.

The role of statins must be seen in the context of other interventions to reduce CHD risk, including smoking cessation, exercise and the use of diet, as well a range of drug treatments, such as antihypertensives, β-blockers and aspirin. Use of other interventions prior to statin prescribing to reduce CHD risk potentially has the effect of reducing an individual's risk to levels below which they would become eligible for statin treatment. A comparison of statins with alternative interventions to reduce CHD risk has not been addressed here.

Generalisability of the findings

The generalisability of the findings is limited by the exclusion, in some studies, of patients who were hypersensitive to or intolerant of statins, who were known to be unresponsive to statins, or who were not adequately compliant with study medication during a placebo run-in phase. A considerable proportion of patients with or at risk of CHD may have been excluded in this way. Consequently, the treatment effect may be reduced when statins are used in an unselected population.

There is a major question regarding the generalisability of the results of RCT evidence to routine clinical practice and the effectiveness of statins here could well be lower than suggested by the trials, particularly because of issues such as compliance and continuance. However, sensitivity analysis on compliance and continuance assumptions shows that the impact on cost-effectiveness results is not likely to be significant.

Recommendations for further research

Additional high-quality evidence on quality of life and compliance and continuance for patients on statins is required.

Large outcome studies at lower CHD/CVD risk thresholds would be useful to determine whether the relative risk reduction figures remain valid at lower risk levels and to determine the extent to which potential disutility due to statins may become an issue as treatment is extended to a vast proportion of the 'well' population.

Future service implementation research is important, particularly on effective policies for targeting low-risk populations. Research on the attitudes of low-risk patients and relatively healthy 45-year-olds to taking lifetime medication is required, along with research into the optimal methods of explaining risks and benefits of treatment to patients so that they can make informed choices.

Chapter 1

Aim of the review

The overall aim of this review is to evaluate the clinical effectiveness and cost-effectiveness of statins for the primary and secondary prevention of cardiovascular events in adults with, or at risk of, coronary heart disease (CHD).

Chapter 2

Background

Description of underlying health problem

Cardiovascular disease (CVD) – disease of the heart and blood vessels – has three major manifestations:

- CHD
- transient ischaemic attack (TIA) and stroke
- peripheral arterial disease (PAD).

CVD is the main cause of death in the UK. It accounted for nearly 238,000 deaths in 2002; about half of these were from CHD, and about a quarter from stroke. More importantly, CVD is one of the main causes of premature death (death in people aged under 75). In 2002, it caused over 67,000 premature deaths in the UK, accounting for 35% of premature deaths in men and 27% in women.[1] CVD is also a significant cause of morbidity.

CHD

CHD [also known as coronary artery disease (CAD) or ischaemic heart disease] is caused by the narrowing of the arteries that supply the heart, as a result of a gradual build-up of fatty material called atheroma. This can cause angina and myocardial infarction (MI; heart attack) as well as other forms of chronic heart disease.

MI is defined as permanent damage to an area of heart muscle as a result of interruption to the blood supply to the area caused by narrowed or blocked blood vessels. An MI usually causes severe pain in the centre of the chest, lasting for more than 30 minutes. This pain may spread to arms, neck, jaw, back or stomach. However, some MIs are 'silent' and produce little discomfort.

Angina is pain or discomfort in the chest or neighbouring parts of the body which is usually caused by a shortage of oxygen reaching the heart as a result of the narrowing of the coronary arteries. Stable angina occurs when the arteries are narrowed by stable fibrotic lesions.[2] It is triggered by exercise, emotion or extremes of temperature, and is normally relieved by rest, nitroglycerine or both. Unstable angina occurs when unstable plaques develop, which are prone to rupture or erosion.[2] It is characterised by symptoms of increased severity (in terms of ease of onset, duration, intensity, frequency or decreased responsiveness to medication), and may persist while the patient is at rest and emotional ease. Patients whose pain is accompanied by ST- and T-wave abnormalities, or who have lengthy episodes of pain at rest, are at increased risk of acute myocardial infarction (AMI) and death.[3]

Prevalence of disease

The prevalence of treated CHD rises with age. Overall, it has been estimated that 4.2% of men and 3.2% of women in England and Wales have treated CHD, but this figure rises from 0.01% of men and women aged under 35 years to over 20% of men and over 16% of women aged 75 years and over (*Table 1*).

Within England and Wales, the prevalence of treated CHD varies: the age-standardised rates for men and women alike are highest in Wales, the North West and Northern and Yorkshire regions, and lowest in North and South Thames. In both men and women, the prevalence of treated CHD rises with increasing deprivation.[4]

The prevalence of CHD also varies substantially by ethnic group. The prevalence of angina and MI is

TABLE 1 *Prevalence of treated CHD (%), England and Wales, 1998[4]*

	Age (years)							
Gender	0–34	35–44	45–54	55–64	65–74	75–84	≥85	All ages
Men	0.01	0.49	3.02	9.45	18.40	23.05	22.38	4.20
Women	0.01	0.07	1.30	4.93	11.15	16.66	17.41	3.24

TABLE 2 *Prevalence of angina and MI in England, 1999 (age-standardised percentages)[5]*

Ethnic group	Angina		MI	
	Men	**Women**	**Men**	**Women**
Black Caribbean	1.7	4.3	0.6	1.0
Indian	6.8	3.7	4.0	0.6
Pakistani	6.7	4.9	6.0	2.9
Bangladeshi	9.9	4.3	7.1	0.4
Chinese	2.0	0.8	1.3	–
Irish	5.6	3.7	4.1	2.7
General population	5.3	3.9	4.2	1.8

particularly high in those from the Indian subcontinent, and very low in those of Chinese origin (*Table 2*).

In 2003, 3.8% of men and 1.7% of women in England aged 16 years and over reported having had a heart attack at some time. The prevalence in both genders increased with age, more than 10% of men aged 65 and over reported having

had a heart attack. In 2003, 2.5% of men and 2.0% of women in England aged 16 and over reported currently having angina; again, the prevalence in both genders increased with age. In the younger age groups, the proportion reporting current angina was lower than the proportion who were Rose Angina Questionnaire positive for angina; however, people aged 65 and over reported having angina more frequently than they reported angina symptoms (*Table 3*).[6]

Incidence of primary CHD

The incidence of CHD is available from the Bromley Coronary Heart Disease Register (BCHDR).[7] All incident presentations of CHD were registered for Bromley Health District in South-East London (population of 186,053; men and women aged 25–74 years) for the period 1996–1998. The incidence of primary CHD events was reported as being 414 per 100,000 population per year in men and 147 per 100,000 population per year in women. Incidence rates were greater in older people in both genders, and at all ages were significantly higher in men than in women (*Table 4*).

TABLE 3 *Percentage of population aged 16 and over reporting CHD outcomes, by age, England, 2003[6]*

Gender	Age (years)							
	16–24	**25–34**	**35–44**	**45–54**	**55–64**	**65–74**	**>75**	**Total aged ≥16**
Ever having suffered a heart attack								
Men	–	–	0.8	2.2	6.7	12.1	15.7	3.8
Women	–	–	0.3	0.8	2.1	4.2	8.1	1.7
Currently having angina								
Men	–	–	0.4	1.6	4.4	8.2	10.3	2.5
Women	–	–	0.1	1.1	2.8	4.7	9.4	2.0
Rose Angina Questionnaire positive for angina								
Men	0.7	0.3	1.5	1.4	4.3	4.5	5.0	2.2
Women	1.1	0.9	1.2	2.0	3.5	4.0	5.2	2.3

TABLE 4 *Age- and gender-specific incidence rates per 100,000 population of primary CHD events*

Age (years)	Exertional angina		Unstable angina		AMI		Sudden cardiac death	
	Men	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**
25–34	0	0	0	0	4	3	0	0
35–44	19	6	5	0	52	3	5	3
45–54	129	53	45	19	124	13	30	6
55–64	449	229	97	48	235	61	117	26
65–74	520	250	201	64	420	150	235	100

Source: Bromley Coronary Heart Disease Register.[7]

TIA and stroke

TIA has been defined as a focal neurological deficit of sudden onset which lasts for less than 24 hours, is presumed to be of vascular origin, and is confined to an area of the brain or eye perfused by a specific artery.[8] In a substantial majority of cases, the symptoms last for less than 10 minutes.[9] Diagnosis is problematic because it is generally dependent on the patient's recollections, and also because the symptoms may be difficult to distinguish from those due to non-ischaemic causes such as migraine.[10]

Data from the General Practitioner Research Database (GPRD) for the years 1992–1996 indicate a mean annual age-adjusted UK incidence of new TIA of 1.90 per 1000 population. The incidence varies geographically, with the highest incidence (2.49 per 1000) in the former Yorkshire health region and the lowest (1.22 per 1000) in the Oxford region.[11] These figures suggest an annual UK incidence of over 100,000 new TIAs, a figure substantially in excess of the Stroke Association's estimate of between 30,000 and 40,000 TIAs per annum.[12] Moreover, the GPRD only records TIAs that come to medical attention, and is therefore likely to underestimate the true incidence of TIA: some patients do not seek medical advice because of the transient nature of their symptoms.

Stroke can be defined as neurological deficit of acute onset which leads to death or lasts for more than 24 hours, and which results from cerebral infarction or haemorrhage. There are two major types of stroke, with different pathophysiological mechanisms: ischaemic (occlusive or thromboembolic) stroke caused by cerebral infarction, and haemorrhagic stroke.[13] Approximately 80% of strokes in westernised countries are ischaemic strokes.[14] Haemorrhagic stroke is more often fatal than ischaemic stroke.[13] Observational studies suggest that lower cholesterol levels are associated with increased risks of haemorrhagic strokes; this association could be causal, or could be due to confounding by other factors such as alcohol intake.[14]

There are approximately 100,000 new cases of stroke per year in England and Wales.[11] Data from the GPRD for the years 1992–1996 indicate a mean annual age-adjusted UK incidence of new ischaemic stroke of 1.51 per 1000 population. This is supported by a prospective study carried out in Oxfordshire in the 1980s which found a crude annual incidence of clinically apparent first ever stroke of 1.60 per 1000 population [95%

TABLE 5 Annual incidence rates per 1000 population for first ever stroke, by age and gender, Oxfordshire 1981–1986[15]

Age (year)	Male	Female	Total
0–14	0.03	0.03	0.03
15–24	0.02	0.10	0.06
25–34	0.05	0.12	0.08
35–44	0.26	0.20	0.23
45–54	0.67	0.46	0.57
55–64	3.47	2.35	2.91
65–74	8.11	5.84	6.90
75–84	15.87	13.39	14.34
≥85	18.42	20.36	19.87
Total	1.50	1.71	1.60

confidence interval (CI) 1.48 to 1.72] (2.00 per 1000 when adjusted by age and gender to the 1981 population of England and Wales).[15] For further details, see *Table 5*.

Similarly, a community-based study carried out in East Lancashire in 1994/95 found an incidence of first ever stroke of 1.60 per 1000, adjusted for the England and Wales 1991 census population (1.26 per 1000 in men and 1.83 in women).[16] When adjusted to the 1981 census population for England and Wales, the incidence of first ever stroke was 1.43 per 1000 (1.21 per 1000 in men and 1.62 in women). When recurrent strokes were included, the total annual age- and gender-adjusted stroke incidence rate rose to 2.33 per 1000 population (2.08 per 1000 for men and 2.56 for women).[16]

As with TIA, the incidence of stroke varies geographically, the highest incidence (1.94 per 1000) again being in the former Yorkshire health region, and the lowest (1.15 per 1000) in the Oxford region.[11] In both men and women, the prevalence of stroke rises with increasing deprivation.[4] The prevalence of stroke also varies by ethnic group, being particularly high in men of black Caribbean origin (*Table 6*).

TABLE 6 Prevalence of stroke in England, 1999, by ethnic group (age-standardised percentages)[17]

Ethnic group	Men	Women
Black Caribbean	3.8	1.5
Indian	3.3	1.4
Pakistani	1.9	1.9
Bangladeshi	2.6	1.4
Chinese	1.9	0.6
Irish	2.0	2.3
General population	2.3	2.1

The South London Stroke Register (SLSR), a population-based register prospectively recording first in a lifetime strokes only, found that the mean age at first stroke was 73.9 years for white patients, 62.6 years for black patients and 66 years for others (Asian, Bangladeshi, Chinese, Indian, Pakistani and other). The age-adjusted incidence rate ratio for men compared with women was 1.34 (95% CI 1.19 to 1.50, $p < 0.001$), and for black people compared with white was 1.87 (95% CI 1.51 to 2.33, $p < 0.001$) in men and 2.65 (95% CI 2.09 to 3.34, $p < 0.001$) in women.[18]

PAD

PAD is defined as obstruction of the arteries carrying blood to the arms or, more commonly, the legs; it is usually caused by atherosclerosis.

In the UK, approximately 20% of adults aged 65–74 years have evidence of PAD, although only a quarter of these have symptoms.[19] Non-invasive testing has found a prevalence of symptomless PAD of up to 25% in men over 50.[20]

The most common symptom of PAD is intermittent claudication (pain in the calf or buttock brought on by exercise and relieved by rest). Intermittent claudication is two to five times more common in men than in women, with a reported prevalence of between 1 and 7% in men aged 50–75.[20] The prevalence increases in people with CHD risk factors such as cigarette smoking, diabetes, hypertension and hypercholesterolaemia.[21]

Aetiology, pathology and prognosis

Several risk factors for cardiovascular disease have been identified. These include:

- hyperlipidaemia, including:
  - hypercholesterolaemia [particularly high levels of low-density lipoprotein cholesterol (LDL-C)]
  - familial hypercholesterolaemia
  - familial combined hyperlipidaemia
- hyperapobetalipoproteinaemia
- cigarette smoking
- hypertension
- diabetes mellitus
- family history of premature CHD
- physical inactivity
- obesity
- male gender
- ethnicity
- increasing age.

Some of these factors (e.g. smoking, obesity and hypertension) can be modified, treated or controlled. Others (e.g. age, gender and ethnicity) cannot.

Blood cholesterol and CHD risk

The average level of blood cholesterol within a population is an important determinant of the CHD risk of the population.[22] However, although blood cholesterol is an important risk factor for CHD, it is by itself a relatively poor predictor of future CHD events.[23] It has been shown that, in British men aged 40–59, there is considerable overlap between the distribution of blood cholesterol concentrations in those who subsequently go on to suffer from CHD and the distribution in those who do not.[23] Consequently, other risk factors, such as tobacco smoking, diabetes, physical inactivity and obesity, need to be taken into account when defining individual risk of CHD.[23]

Cholesterol lowering is therefore only one of a number of methods of reducing the risk of CHD. CHD risk can also be reduced by changes in lifestyle, such as smoking cessation, exercise and the use of cholesterol-lowering diets, along with non-cholesterol drug treatments, including aspirin and antihypertensives. The cost-effectiveness of statins must be seen in the context of these other interventions.

Significance in terms of ill-health
Mortality and morbidity
CHD

It has been estimated that CHD is the leading single cause of disability in Europe, accounting for 9.7% of total disability-adjusted life-years. Since the incidence of CHD in England and Wales is relatively high, the proportion of disability attributable to CHD is likely to be higher in those countries than in the rest of Europe.[24]

In 2001, 105,895 deaths in England and Wales (19% of all deaths) were attributed to CHD (*Table 7*); 36,936 (35%) of these deaths occurred in people under the age of 75, accounting for 24% of premature deaths in men and 14% in women.[25] At all ages, death rates were higher in men than in women. This phenomenon cannot be attributed to the protective effects in women of endogenous oestrogen, or to gender differences in smoking rates, hypertension or mean cholesterol concentrations, and it has been suggested that it may be due to differences between men and women in their intake of, and response to, dietary fat.[26] However, although women tend to experience MI 10 years later than do men, their risk of dying in the first 60 days following their first MI is double that of men.[27]

TABLE 7 *Deaths attributed to CHD, England and Wales, 2001*[25]

Age (years)	No. (rate per 100,000 population per annum)						
	0–34	**35–44**	**45–54**	**55–64**	**65–74**	**≥75**	**Total**
Men	117 (1.0)	778 (20.2)	3,076 (90.4)	7,276 (265.7)	15,358 (750.0)	31,907 (2,191.7)	58,512 (230.8)
Women	24 (0.2)	167 (4.3)	641 (18.5)	2,166 (77.0)	7,333 (315.8)	37,052 (1,481.5)	47,383 (177.3)
Total	141 (0.6)	945 (12.2)	3,717 (54.1)	9,442 (170.1)	22,691 (519.3)	68,959 (1,742.8)	105,895 (203.3)

Within the UK, the premature death rate from CHD is higher in manual workers than in non-manual workers. It is also higher in South Asians living in the UK (Indians, Bangladeshis, Pakistanis and Sri Lankans) than in the population as a whole.[17]

In 2000/01, the latest year for which figures are available, 28,008 coronary artery bypass graft (CABG) operations were undertaken in the UK; 2881 of these combined CABG with another procedure.[17] In 2001, 33,830 percutaneous transluminal coronary angioplasties (PTCAs) were performed in England and Wales.[28]

The cost of CHD to the healthcare system in the UK was estimated at £1750 million in 1999. In addition, production losses from death and illness in those of working age and from the informal care of people with the disease are substantial, having been estimated to cost the UK economy about £5300 million in 1999.[17]

Stroke and TIA
Stroke is the third leading cause of death in industrialised countries, after CHD and cancer.[13] In 2002, the latest year for which data are available, 59,090 deaths in England and Wales were attributed to stroke; 11,441 (19%) of these deaths occurred in people under the age of 75, accounting for 5.7% of premature deaths in men and 6.9% in women.[1]

In industrialised countries, stroke is the leading cause of long-term disability.[13] It can cause physical and cognitive impairment and aphasia, and is associated with depression. The second Auckland Stroke Study found that 36% of stroke patients survived to 6 years. Of these survivors, 61% said they had not recovered completely from their stroke, 23% were in institutional care, compared with 8% of age- and gender-matched controls, and 42% required assistance with basic activities of daily living, compared with 18% of controls.[29]

People who have suffered a TIA are at increased risk of stroke. The Oxfordshire study found that the mean annual risk of stroke in the first 5 years following TIA was 5.9% (95% CI 4.3 to 7.5%); the risk was highest, at 11.6%, in the first year.[30] A recent reanalysis of data from the Oxfordshire Community Stroke Project found a risk of stroke of 8.6% (95% CI 4.8 to 12.4) at 7 days and 12.0% (95% CI 7.6 to 16.4) at 30 days after the patient's first ever TIA; if purely ocular TIAs were excluded, the estimated risk of stroke at 30 days was 14.3%.[31] These results are congruent with those of the largest study of short-term prognosis following TIA: this found that, in the 90-day period following the TIA, 10.5% of patients (180/1707) had a stroke, 2.6% (44/1707) were hospitalised with a cardiovascular event, and 2.6% (45/1707) died (almost half of these, 20/45, of stroke). Factors associated with an increased risk of stroke following TIA included age over 60, diabetes mellitus, symptoms lasting for over 10 minutes, and TIA accompanied by weakness or speech impairment.[32] It has been estimated that, without treatment, a quarter of people having a TIA will have a full-blown stroke within a few years.[12]

Patients who have suffered an AMI are also at increased risk of ischaemic stroke. A retrospective study in the USA and Puerto Rico found that about 2.5% (2532/111,023) of patients aged 65 and over who were discharged from acute hospitals with a principal diagnosis of AMI and without a terminal illness suffered an ischaemic stroke within 6 months of hospital discharge. The risk was higher in those aged 75 and over than in those aged under 75.[33]

PAD
In patients with intermittent claudication, the risk of death, at 5–10% a year, is three to four times

TABLE 8 *Age-adjusted relative risk (RR) of death over a 10-year period in individuals with PAD but without CVD at baseline*[34]

Cause of death	Men		Women	
	RR	**95% CI**	**RR**	**95% CI**
All causes	3.1	1.5 to 6.4	2.7	1.2 to 6.0
CVD	3.9	1.5 to 10.4	5.7	1.4 to 23.2
CHD	5.1	1.5 to 16.8	1.9	0.2 to 18.5
Other causes	2.3	0.8 to 6.8	1.9	0.7 to 5.2

TABLE 9 *Relative risk of death over a 10-year period in individuals with PAD but without CVD at baseline, adjusted for risk factors*[34]

Cause of death	RR	95% CI
All causes	3.1	1.8 to 5.3
CVD	6.3	2.6 to 15.0
CHD	4.3	1.4 to 12.8

higher than that of an age- and gender-matched population without claudication. The main causes of death are coronary and cerebrovascular events.[19] A Californian study found that, in people without a history of CVD, those identified as having PAD at baseline were at increased risk of death over a 10-year period relative to those without baseline PAD. The increased risk was largely due to increased mortality from CVD and CHD (*Table 8*). The increase in risk remained after adjusting for CVD risk factors such as cigarette smoking, systolic blood pressure, high-density lipoprotein (HDL) and LDL-C, triglycerides and body mass index (BMI) (*Table 9*), suggesting that the presence of PAD reflects a particular susceptibility to the development of atherosclerosis.[34]

Many patients with claudication have severely limited walking ability, and this adversely affects their occupational, social and leisure activities.[35] Some patients with intermittent claudication develop more critical ischaemia (pain at rest, ulceration or gangrene).[20] However, the proportion of patients with claudication who require amputation as a result of critical ischaemia is low (<1% a year).[19]

Quality of life
Various studies have addressed the impact of CVD on quality of life. A North American study compared quality of life 30 days, 6 months and 1 year after AMI in a randomly selected subgroup of 2600 US patients and 400 Canadian patients

taking part in the GUSTO trial. At one year, 16% of US patients reported that their general health was worse than before their MI, and 22% reported their physical capacity as worse; 13% reported their emotional state as worse. Of those who worked either for pay or in the home, 37% reported a change in their work activities due to their health. The median time before returning to work was 58 days (25th to 75th percentile 30 to 100 days) in the USA, where the pattern of treatment was more aggressive than in Canada, where the median time was 81 days (25th to 75th percentile 45 to 162 days).[36]

A Finnish study found that patients with CAD reported significantly poorer quality of life in all six dimensions of the Nottingham Health Profile than age- and gender-matched controls. The most obvious differences were seen in the dimensions of energy, pain, emotional reactions, sleep and physical mobility.[37]

A qualitative study was carried out in patients admitted to a district general hospital in the north of England with MI. At interview, 6 weeks after discharge and before cardiac rehabilitation, patients expressed concern about their symptoms, and about the impact of those symptoms on their ability to perform the activities of daily living. Breathlessness had the most detrimental effect on quality of life, because of the fears that it provoked, and because it disturbed sleep, leaving patients in a fragile physical and emotional state the next morning. Fatigue was also a problem, and many patients could not get through the day without a rest. Chest pain had least effect on quality of life, although it caused most worry. Participants who lived alone reported isolation and loneliness as they could not go shopping or visit friends because they tired so easily. Participants also reported feelings of depression and irritability.[38] This tallies with the findings of the Finnish study, suggesting that CHD interferes with a person's whole life by limiting physical mobility, disrupting sleep, and causing fatigue, fear and depression.

Current service provision

In 2004, the Department of Health stated that 1.8 million people (over 2% of the population) were currently receiving statin therapy.[39]

Data from the Myocardial Infarction National Audit Project (MINAP) show that, in 2003, 82.6% of patients were discharged from hospital on

statins after an MI. In 1.7% of the remaining patients, statins were contraindicated or not indicated, and in 7.9% they were not used; it is not known whether they were used in the remaining 7.8%.[1] However, many patients who would benefit are currently untreated. A recent review of cardiovascular and diabetes audits in the UK concluded that less than half of patients with CHD were on a statin or other lipid-lowering drug, and a significant proportion of those were on suboptimal doses.[40]

Current level of statin prescribing

The estimate of current statin prescribing is based on data from the 2003 Prescription Cost Analysis (PCA) data published on the Internet by the Department of Health.[41] PCA provides details of the number of items and the net ingredient cost of all prescriptions dispensed in the community in England. PCA data are based on the therapeutic grouping used in the British National Formulary (BNF). The classification in the report accessed is based on the September 2002 BNF (edition 44). Prescribing data are presented here as the number of tablets prescribed, for two reasons. First, the number of prescription items in PCA data does not represent packs of 28 tablets (the average across all statins is 38.6 tablets per prescription item). Secondly, the cost of these prescriptions

(*Table 10*) is based on the cost per tablet. *Table 10* shows the number of tablets dispensed in 2003 for each of the five statins.

Before July 2004, statins were only available on prescription. From July 2004, simvastatin (Zocor Heart-Pro 10 mg daily) has been available over the counter (OTC). The impact of this on the number and type of patients receiving statins is not yet known. For a fuller discussion of the issues raised by OTC treatment see Chapter 6.

Current service cost

Prescribing of lipid-regulating drugs (largely statins) has increased rapidly from the mid-1990s from £93 million in 1996 to £571 million in 2002.[42] The cost of prescribing statins in 2003 has been estimated from the PCA data. Cost is calculated by multiplying the number of tablets prescribed (*Table 10*) by the cost per tablet. For simvastatin, costs have been calculated for the branded and generic treatments separately and then aggregated. The price of statins is based on BNF September 2004 data.[43] The total prescribing cost for all statins in England in 2003 was approximately £640 million (*Table 11*). Adjusting this cost to take into account the population of Wales would imply a total cost for England and Wales of approximately £675 million.

TABLE 10 Number of statin prescriptions dispensed in England, 2003

Statin	No. of tablets (thousands)					
	10 mg	20 mg	40 mg	80 mg	Drug total	% of total
Atorvastatin (Lipitor)	206,246	90,512	35,739	5,471	**337,969**	37%
Fluvastatin (Lescol)		10,755	14,843	3,731	**29,329**	3%
Pravastatin (Lipostat)	19,401	29,678	46,085		**95,163**	10%
Rosuvastatin (Crestor)	8,249	1,335	406		**9,990**	1%
Simvastatin (Zocor + generics)	118,796	159,727	113,567	53,624	**445,714**	49%
Dosage total	**352,692**	**292,007**	**210,639**	**62,827**	**918,165**	**100%**

TABLE 11 Cost of statin prescribing in England, 2003

Statin	Cost (£,000)					
	10 mg	20 mg	40 mg	80 mg	Total drug cost	% of total
Atorvastatin (Lipitor)	£132,808	£95,975	£37,896	£5,801	**£272,481**	42.8%
Fluvastatin (Lescol)		£4,886	£6,743	£2,132	**£13,761**	2.2%
Pravastatin (Lipostat)	£11,211	£31,469	£48,866		**£91,546**	14.4%
Rosuvastatin (Crestor)	£5,312	£1,416	£430		**£7,158**	1.1%
Simvastatin (Zocor + generics)	£59,505	£115,446	£71,104	£6,033	**£252,088**	39.6%
Total by dosage	**£208,835**	**£249,191**	**£165,040**	**£13,966**	**£637,033**	**100.0%**

Statin prescribing has increased dramatically in recent years and this trend seems set to continue in view of the published evidence and introduction of national guidance (see below). The impact of generic statins (simvastatin in May 2003 and pravastatin in August 2004) on the NHS is difficult to evaluate and quantify in the short term; interpretation of prescribing data is subject to a number of caveats at this stage.[44]

In October 2003, the Department of Health issued a consultation letter addressing the significant differences between reimbursement and procurement price with respect to specified generics, including simvastatin.[45] Reimbursement prices were reduced, but further consultation and price adjustments were deemed necessary in July 2004 following a further fall in procurement price.

Events following the introduction of generics (including simvastatin) indicate that NHS prices for such medication may take some time to fall to levels that are perceived as significant in terms of budgetary impact. Owing to the complexity and changeable nature of these issues, a full discussion concerning the impact of generic statins is beyond the scope of this report. However, a brief discussion of the impact of generics on the NHS can be found in the section 'NHS impact' (p. 122).

Variation in services

Data from the Doctors' Independent Network (DIN) database indicated that, in 2001, only 56.3% of men and 41.1% of women with CHD received a prescription for lipid-lowering drugs (primarily statins); over 30% of those prescribed statins were prescribed a dose that was unlikely to achieve a mean reduction of 25% in total cholesterol. Detailed analysis of data from 1998 indicated that statin prescribing was influenced by age, with 45% of patients aged 35–64 receiving a statin compared with 10% of those aged 75–84 and only 1% of those aged over 85. Statin use was also strongly related to type of CHD: after adjustment for other factors, revascularised patients had an odds ratio of 3.92 for receiving statins compared with those with angina. Patients in deprived areas were less likely to receive statins than those in thriving areas. However, after adjusting for age, diagnosis and revascularisation, men were not significantly more likely to receive a statin than women.

Levels of statin prescribing differ widely between general practices. In 2002 primary care trusts (PCTs) in England showed a four-fold variation in prescribing of lipid-regulating agents, from 180 to 730 items per 1000 patients.[42]

Description of intervention

Identification of patients and important subgroups

Current Department of Health guidance recommends that patients with established CHD should receive statins and dietary advice to lower serum cholesterol concentrations either to less than 5 mmol l^{-1} (LDL-C to below 3 mmol l^{-1}) or by 25% (30% for LDL-C), whichever is greater. For primary prevention, drug intervention is recommended in patients with an absolute risk of developing CHD of 30% or more over 10 years.[46]

Several scoring systems are currently available which are designed to estimate an individual's CHD event risk, to aid the targeting of high-risk patients in primary prevention. Most of these scoring systems are derived from the Framingham prediction equations. The limitations of these equations are discussed in full in the section 'Effectiveness of statin treatment' p. 91. Moreover, routine calculation of risk is hampered by poor availability of data on risk factors, and there is a need for more systematic collection of these data in general practice.

Recent guidelines from the British Hypertension Society[47] have recommended a move away from CHD risk assessment towards CVD assessment. This is stated to be in recognition of the fact that in clinical practice both the patient and health professional will not be interested in fatal and non-fatal CHD alone, but in all CVD events, including stroke. This is consistent with the new Joint British Societies risk assessment charts and computer program. The previous Joint British Societies charts predicted the absolute 10-year CHD risk, whereas the new charts predict 10-year CVD risk (combined fatal and non-fatal stroke and CHD). The previous charts had a high uptake rate among health professionals and it is likely that the new charts will also be widely implemented.

Criteria for treatment

The evidence base for current treatment criteria has now been superseded by new trial evidence. The revised British Hypertension Society guidelines,[47] issued in 2004, have followed an international trend[48] towards lower risk thresholds and treatment targets.

Intervention

Statins act to lower cholesterol by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, an enzyme involved in cholesterol synthesis, particularly in the liver.[49] Inhibition of HMG CoA reductase lowers LDL-C levels by slowing down the production of cholesterol and increasing the liver's ability to remove the LDL-C that is already in the blood.[50] Because the body makes more cholesterol at night than during the day, it is recommended that some statins are taken in the evening.[50]

Statins are used both for the secondary prevention of coronary and cardiovascular events in patients with CHD (including a history of angina or AMI), peripheral arterial disease or a history of stroke, and for primary prevention in patients who are at increased risk of coronary events because of factors such as smoking, hypertension and diabetes mellitus. Although the benefits of treatment are independent of the initial cholesterol concentration, patients with elevated serum cholesterol (total serum cholesterol 5 mmol l^{-1} or greater) are likely to benefit most.[49] It is recommended that statins are used in conjunction with lifestyle measures (diet, smoking cessation and exercise) and other appropriate interventions (e.g. adequate control of chronic conditions such as hypertension and diabetes).

For both primary and secondary prevention of CHD, it is recommended that statin treatment be adjusted to achieve a total cholesterol concentration of less than 5 mmol l^{-1} (or a reduction of 20–25%, if this produces a lower concentration); the target for LDL-C should be below 3 mmol l^{-1} (or a reduction of about 30%, if lower).[49]

Because they affect the liver, statins are contraindicated in patients with active liver disease or persistently abnormal liver function tests, and should be used with caution in patients with a history of liver disease or a high alcohol intake. Liver function tests should be carried out before and within 1–3 months of starting therapy, and thereafter 6-monthly for 1 year, unless signs or symptoms suggestive of hepatotoxicity indicate that they should be carried out sooner. Treatment should be discontinued if serum transaminase concentration rises to, and persists at, three times the upper limit of the reference range.[49]

Statins are also contraindicated in pregnancy and breast-feeding. Untreated hypothyroidism also increases the risk of myositis with lipid-regulating drugs. However, in patients with hypothyroidism, adequate thyroid replacement therapy may itself resolve any lipid abnormality.[49]

Side-effects of statins include myalgia, myositis, myopathy and rhabdomyolysis (a very rare but significant side-effect), headache, altered liver function tests (rarely, hepatitis), paraesthesia, and gastrointestinal effects including abdominal pain, flatulence, diarrhoea, nausea and vomiting. Rash and hypersensitivity reactions (including angioedema and anaphylaxis) have been reported, but are rare.[49] Statins are carcinogenic in laboratory animals at two to seven times the plasma drug levels achieved with recommended doses in humans.[51]

Statins interact with a number of other medications. The risk of muscle toxicity increases when statins are used concomitantly with fibrates (e.g. gemfibrozil) or nicotinic acid (niacin) in lipid-regulating doses, or with immunosuppressants such as ciclosporin. With gemfibrozil, the risk is increased to such an extent that gemfibrozil and statins should not be used concomitantly. The concomitant use of statins with other lipid-lowering drugs (fibrates other than gemfibrozil, ezetimibe or nicotinic acid in lipid-lowering doses) should be undertaken with caution, and generally under specialist supervision.[49]

In addition, because some statins (particularly atorvastatin and simvastatin) are metabolised by cytochrome P450 (CYP3A4), concomitant use of potent inhibitors of this enzyme (e.g. 'azole' antifungal agents and HIV protease inhibitors) may increase plasma levels of those statins and thus increase the risk of side-effects such as rhabdomyolysis. The risk of serious myopathy is also increased when high doses of simvastatin are combined with less potent CYP3A4 inhibitors, including amiodarone, verapamil and diltiazem. Moreover, it appears that the consumption of even modest quantities of grapefruit juice can significantly increase exposure to simvastatin, thus increasing the risk of serious myopathy. Patients taking atorvastatin should also avoid drinking large quantities of grapefruit juice. These concerns do not apply to fluvastatin, which is metabolised by a different cytochrome P450 enzyme, or to pravastatin and rosuvastatin, which are not substantially metabolised by cytochrome P450.[52]

Five statins are currently licensed for use in the UK:

- atorvastatin
- fluvastatin
- pravastatin

- rosuvastatin
- simvastatin.

Summary of product characteristics
Characteristics of the five statins licensed for use in the UK are summarised in *Table 12*.

Atorvastatin
Atorvastatin is a synthetic statin. It is licensed in the UK for use as an adjunct to diet in primary hypercholesterolaemia, heterozygous familial hypercholesterolaemia, homozygous familial hypercholesterolaemia, or combined (mixed) hyperlipidaemia in patients who have not responded adequately to diet or other non-pharmacological measures.[53]

The usual starting dose is 10 mg daily. This may be increased at intervals of at least 4 weeks to a maximum of 80 mg once daily (alternatively, in patients with heterozygous familial hypercholesterolaemia, a maximum dose of 40 mg may be combined with a bile acid sequestrant).[53]

Potential side-effects, in addition to those common to all statins [see the section 'Intervention' (p. 11)], include insomnia, dizziness, hypoaesthesia, arthralgia, back pain and asthenia; uncommonly, alopecia, amnesia, anorexia, malaise, muscle cramps, thrombocytopenia and tinnitus; rarely, peripheral neuropathy, pancreatitis and peripheral oedema; and very rarely, erythema multiforme, hypoglycaemia, hyperglycaemia, peripheral neuropathy and Stevens–Johnson syndrome.[53]

Atorvastatin is marketed in the UK by Parke-Davis as Lipitor®.[53] Lipitor contains atorvastatin as atorvastatin calcium trihydrate, and is available in 28-tab packs of 10-, 20-, 40- and 80-mg tablets at a net price of £18.03 for the 10-mg dose and £29.69 for the other three doses.[49]

Fluvastatin
Fluvastatin is also a synthetic statin. It is licensed in the UK for use:

- as an adjunct to diet in patients with primary hypercholesterolaemia or mixed dyslipidaemia
- in patients with primary hypercholesterolaemia and concomitant CHD who do not respond adequately to dietary control
- in patients with CHD for the secondary prevention of coronary events after percutaneous coronary intervention.[54]

For lipid lowering, the recommended starting dose of fluvastatin is 40 mg daily in the evening.

However, in mild cases, 20 mg daily may be sufficient. The dose may be increased to 80 mg daily. Following percutaneous coronary intervention (PCI), the recommended daily dose is 80 mg.[54]

Potential side-effects, in addition to those common to all statins [see the section 'Intervention' (p. 11)], include insomnia and, very rarely, dysaesthesia, hypoesthesia, peripheral neuropathy, oedema, angioedema, thrombocytopenia, vasculitis and lupus erythematosus-like reactions.[54]

Fluvastatin is marketed in the UK by Novartis as Lescol® and, in a modified-release form, as Lescol XL. Both contain fluvastatin as sodium salt. Lescol is available as 20- and 40-mg capsules at a cost of £12.72 per 28-cap pack or £25.44 for a 56-cap pack of the 40-mg dose. Lescol XL is available only as 80-mg tablets, at a cost of £16.00 for a 28-tab pack; it is therefore not appropriate for initial dose titration.[49]

Pravastatin
Pravastatin is a natural statin found in fungi. It is licensed in the UK for use:

- as an adjunct to diet in patients with primary hypercholesterolaemia or mixed dyslipidaemia who have not responded adequately to dietary control and other non-pharmacological treatments (e.g. exercise, weight reduction)
- as an adjunct to diet in patients with moderate or severe hypercholesterolaemia and at high risk of a first cardiovascular event
- as an adjunct to the correction of other risk factors in patients with previous MI or unstable angina, with either normal or raised cholesterol levels
- in patients receiving immunosuppressive therapy following solid organ transplantation.[55]

Potential side-effects, in addition to those common to all statins [see the section 'Intervention' (p. 11)], include arthralgia and muscle cramps; rarely, dizziness, sleep disturbance, insomnia, vision disturbance, scalp/hair abnormality, abnormal urination, sexual dysfunction and fatigue; and, very rarely, peripheral perineuropathy and and pancreatitis.[55]

Pravastatin is taken orally once daily, preferably in the evening, with or without food. The recommended dose range for hypercholesterolaemia is 10–40 mg daily. A starting dose of 10 mg daily is recommended in patients with moderate or severe renal impairment or significant hepatic impairment. A starting dose

TABLE 12 Summary of product characteristics

Statin	Licensed indication	Contraindications other than hypersensitivity to the drug or any of the excipients, active liver disease (including unexplained persistent serum transaminase elevation), pregnancy and breast-feeding	Interactions associated with an increased risk of myopathy or possible enhanced anticoagulant effect other than ciclosporin, fibrates, gemfibrozil and niacin (nicotinic acid) in lipid-regulating doses	Side-effects other than reversible myositis, headache, altered liver function tests (rarely, hepatitis), paraesthesia and gastrointestinal effects
Atorvastatin[53]	Primary hypercholesterolaemia, heterozygous or homozygous familial hypercholesterolaemia, mixed dyslipidaemia	None	Erythromycin, clarithromycin, azole antifungals, protease inhibitors, large quantities of grapefruit juice	Insomnia, dizziness, hypoaesthesia, arthralgia, back pain, asthenia; uncommonly, alopecia, amnesia, anorexia, malaise, muscle cramps, thrombocytopenia, tinnitus; rarely, peripheral neuropathy, pancreatitis, peripheral oedema; very rarely, erythema multiforme, hypoglycaemia, hyperglycaemia, peripheral neuropathy, Stevens–Johnson syndrome
Fluvastatin[54]	Primary hypercholesterolaemia or mixed dyslipidaemia; primary hypercholesterolaemia and CHD; CHD and prior PCI	None	Warfarin or other coumarin derivatives, phenytoin	Insomnia; very rarely, dysaesthesia, hypoaesthesia, peripheral neuropathy, oedema, angioedema, thrombocytopenia, vasculitis, lupus erythematosus-like reactions
Pravastatin[55]	Primary hypercholesterolaemia or mixed dyslipidaemia; moderate or severe hypercholesterolaemia and high risk of a first CV event; MI or unstable angina; immunosuppressive therapy following solid organ transplantation	None	None	Arthralgia, muscle cramps; rarely, dizziness, sleep disturbance, insomnia, vision disturbance, scalp/hair abnormality, abnormal urination, sexual dysfunction, fatigue; very rarely, peripheral polyneuropathy, pancreatitis
Rosuvastatin[57]	Hypercholesterolaemia/dyslipidaemia	Severe renal impairment, myopathy, concomitant ciclosporin. The 40-mg dose is contraindicated in patients with predisposing factors for myopathy	Vitamin K antagonists (e.g. warfarin)	Dizziness, asthenia, proteinuria; arthralgia; very rarely, polyneuropathy
Simvastatin[59]	Primary hypercholesterolaemia or mixed dyslipidaemia; homozygous familial hypercholesterolaemia, atherosclerotic cardiovascular disease or diabetes mellitus	Concomitant administration of potent CYP3A4 inhibitors	Itraconazole, ketoconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin, nefazodone, amiodarone, verapamil, diltiazem, coumarin anticoagulants, large quantities of grapefruit juice	Rarely, alopecia, anaemia, asthenia, paraesthesia, dizziness, peripheral neuropathy, muscle cramps

of 20 mg daily is recommended for transplant patients receiving immunosuppressive therapy.[55]

Pravastatin is marketed in the UK by Bristol-Myers Squibb Pharmaceuticals as Lipostat®. Lipostat contains pravastatin sodium, and is available in 28-tab packs of 10-, 20- and 40-mg tablets at a price of £16.18 for the 10-mg dose and £29.69 for the 20- and 40-mg doses.[49]

Pravastatin is also available as a generic formulation in 28-tab packs of 10-, 20- and 40-mg tablets. Prices vary depending on the costing source and manufacturer:

- BNF-listed generic pravastatin: 10 mg = £15.76, 20 mg = £28.80, 40 mg = £29.01[43]
- Almus: 10 mg = £8.5, 20 mg =£13.75, 40 mg = £21.60[56]
- Alpharma: 10 mg = £16.18, 20 mg = £29.69, 40 mg = £29.69[56]
- Ivax: 10 mg = £14.26, 20 mg = £26.72, 40 mg = £28.20.[56]

Rosuvastatin
Rosuvastatin is a synthetic statin. It is licensed in the UK for use:

- as an adjunct to diet in patients with primary hypercholesterolaemia (type IIa, including heterozygous familial hypercholesterolaemia) or mixed dyslipidaemia (type IIb) when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate
- in patients with homozygous familial hypercholesterolaemia as an adjunct to diet and other lipid-lowering treatments or if such treatments are not appropriate.[57]

In addition to the contraindications common to all statins, rosuvastatin is contraindicated in patients with severe renal impairment and in those taking ciclosporin. The 40-mg dose is contraindicated in patients with predisposing factors for myopathy/rhabdomyolysis (e.g. moderate renal impairment, hypothyroidism, personal or family history of hereditary muscular disorders, alcohol abuse, Asian origin) and in those taking fibrates.[57]

Potential side-effects, in addition to those common to all statins [see the section 'Intervention' (p. 11)], include dizziness, asthenia, proteinuria and, rarely, arthralgia.[57]

The recommended starting dose is 10 mg once daily, increased if necessary after not less than 4 weeks to 20 mg once daily. Further increasing the dose to 40 mg should only be considered in patients with severe hypercholesterolaemia and high cardiovascular risk (especially those with familial hypercholesterolaemia); specialist supervision is recommended.

Rosuvastatin is marketed in the UK by AstraZeneca as Crestor®, which contains rosuvastatin calcium. It is available in 28-tab packs of 10-, 20- and 40-mg tablets at a cost of £18.03 for the 10-mg dose and £29.69 for the 20-mg and 40-mg doses.[49]

Consultation has begun on the possibility of licensing a 5-mg dose.[58]

Simvastatin
Simvastatin is a semisynthetic statin based on lovastatin (a natural statin found in fungi). It is licensed in the UK for use in:

- patients with primary hypercholesterolaemia or mixed dyslipidaemia who have not responded adequately to diet and other non-pharmacological measures (e.g. exercise, weight reduction)
- patients with homozygous familial hypercholesterolaemia who have not responded adequately to diet and other non-pharmacological measures (e.g. exercise, weight reduction)
- patients with manifest atherosclerotic cardiovascular disease or diabetes mellitus, as an adjunct to correction of other cardiovascular risk factors and other cardioprotective therapy.[59]

In addition to the contraindications common to all statins, simvastatin is contraindicated in patients taking potent CYP3A4 inhibitors.[59]

Potential side-effects, in addition to those common to all statins [see the section 'Intervention' (p. 11)], include, rarely, alopecia, anaemia, asthenia, dizziness, peripheral neuropathy and muscle cramps.[59]

Simvastatin is licensed for use in 5–80 mg daily doses, given orally as a single dose in the evening. The 80-mg dose is only recommended in patients with severe hypercholesterolaemia and at high risk of cardiovascular complications. The usual starting dose is 10–20 mg daily. However, in patients who require a large reduction in LDL-C, or who are at high risk of CHD, the usual dose is 20–40 mg, and in homozygous familial hypercholesterolaemia the

recommended dose is 40 mg per day in the evening, or 80 mg per day in three divided doses. Adjustments to dose should be made at intervals of not less than 4 weeks.[59]

However, the maximum dose is 10 mg daily in patients taking ciclosporin, gemfibrozil, other fibrates (except fenofibrate) or lipid-lowering doses of niacin, and 20 mg daily in patients taking the antiarrhythmic drug amiodarone or the calcium-channel blocker verapamil.[59]

Simvastatin should not be taken concomitantly with itraconazole, ketoconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin and nefadozone, or grapefruit juice. Caution should be exercised when combining simvastatin with ciclosporin, verapamil or diltiazem.[60]

Simvastatin is now also available OTC at a dose of 10 mg per day for patients at moderate (10–15%) 10-year risk of a major coronary event. The risk assessment model approved by the Medicines and Healthcare Regulatory Authority for this purpose suggests that individuals with the following characteristics are likely to be at moderate risk of an event:

- men aged 55 or more
- men aged 45–54 and postmenopausal women over 55 who have one or more of the following risk factors:
  - smoking (currently or stopped in the past 5 years)
  - family history of premature CHD (heart attack or angina in a father or brother before the age of 55, or in a mother or sister before the age of 65)
  - South Asian ethnicity (family originating from, for example, India, Pakistan, Bangladesh or Sri Lanka)
  - Overweight (BMI >25 kg/m^2) or central obesity (waist >102 cm in men, >88 cm in women).[61]

Simvastatin is marketed in the UK by Merck Sharp & Dohme (MSD) as Zocor®. Zocor is available in 28-tab packs of 10-, 20-, 40- and 80-mg tablets at a cost of £18.03 for the 10-mg dose and £29.69 for the other three doses.[49]

Simvastatin is also available as a generic formulation in 28-tab packs of 10-, 20- and 40-mg tablets at a price of £5.78 for the 10-mg dose, £7.80 for the 20-mg dose, £15.60 for the 40-mg dose and £28.77 for the 80-mg dose.[43]

This report reviews the evidence for the five licensed statins at all doses and in all populations with or at risk of CVD. Because many statins are used outside their licensed indications, this review is not restricted to statins used in accordance with the licensed indications detailed above.

Personnel involved
GP and nurse time is required to provide high-quality coronary prevention. Potential reduction in the treatment threshold for statins will have significant workload implications, in terms of identifying patients, testing and prescribing. As the number of patients on statins increases there will be additional resources required for monitoring of these patients. A recent survey of GPs reported that current limitations to delivering better coronary prevention were reported as lack of nurse and doctor time, and other organisational issues relating to buildings, staffing and use of computers.[62] These problems will be exacerbated as more patients become eligible for statin treatment.

Length of treatment
There is evidence to suggest that the risk of a coronary event in patients who stop taking statins, or who change to an ineffective dose, is at least as high as the risk in similar individuals who have never taken statins.[63] In theory, therefore, statin therapy, once commenced, should be lifelong. However, as with any long-term medication, there are issues of compliance. These issues are discussed in the section 'Continuance and compliance' (p. 60).

Chapter 3
Effectiveness

Systematic review of evidence for clinical effectiveness

Search strategy

The search aimed to identify all literature relating to the clinical effectiveness of statins for the prevention of coronary events. The main searches were conducted between November 2003 and April 2004.

Sources searched

Nine electronic bibliographic databases were searched: MEDLINE, EMBASE, Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CCTR), Database of Abstracts of Reviews of Effectiveness (DARE), Science Citation Index, NHS Economic Evaluation Database (NHS EED), Health Technology Assessment Database (NHS HTA) and CINAHL. In addition, the reference lists of relevant articles and sponsor submissions were handsearched.

Search terms

A copy of the MEDLINE search strategy is given in Appendix 1. Search strategies for the other databases are available on request.

Search restrictions

No language, study/publication or date restrictions were applied to the main searches.

Inclusion criteria

- Participants: adults (defined as age >18 years) with, or at risk of, CHD
- interventions:
  - atorvastatin
  - fluvastatin
  - pravastatin
  - rosuvastatin
  - simvastatin
- comparators:
  - placebo
  - other statins
  - 'usual care'
  - 'no statin treatment'
- outcome measures:
  - all-cause mortality
  - cardiovascular mortality
  - CHD mortality

- stroke mortality
- other cardiovascular events (e.g. non-fatal MI, angina, surgical revascularisation, non-fatal stroke)
- adverse events (including cancer and trauma), when reported in studies that also report relevant mortality, morbidity or quality of life outcomes
- health-related quality of life (HRQoL)
- cost.

  Data relating to surrogate end-points (such as total cholesterol, LDL-C and HDL-C) were used only where information on clinical end-points was unavailable
- methodology:
  - randomised controlled trials (RCTs) of at least 6 months' (defined as 26 weeks) duration. Trials were accepted as RCTs if the allocation of subjects to treatment groups was described by the authors as either randomised or double-blind.

Exclusion criteria

- Studies considered methodologically unsound
- studies of multi-interventional therapies where the effect of the statin could not be separated out.

Discussion of interventions

Studies using other interventions in addition to statin therapy were included only if the treatment received by the intervention and control groups was identical in all respects other than the use of statin therapy.

Discussion of comparators

The original intention of this review was to consider only studies in which statins were compared with either placebo or other statins, and this is the approach taken in the base-case scenario. However, on expert clinical advice, and because of the paucity of placebo-controlled studies in relation to some statins and some patient groups, studies in which the comparator was 'usual care' or 'no statin treatment' were also reviewed, and data from these studies were included in secondary analyses. Again following expert clinical advice, studies that compared two doses of the same statin were also included.

It is evident that the nature of the comparator will affect the nature of the results obtained from any given study. Placebo-controlled studies are in theory the easiest to interpret, although many of the studies reviewed here display a level of cross-over that complicates study findings. However, for ethical reasons, placebo-controlled studies are not always appropriate (in particular, in secondary prevention, and in primary prevention in very high-risk groups such as patients with familial hypercholesterolaemia). Some studies in these patient groups have therefore compared one statin with another, whereas others have compared a statin with usual care. Although in principle these studies are very relevant to clinical practice, in reality their results are difficult to interpret because of the potential range of therapies (including statins) offered to patients in the control groups, and because of the questions that arise regarding the comparability of 'usual care' in the countries in which the studies were conducted with usual care in the UK. It is perhaps unfortunate that the studies that compared a statin with usual care did not instead make use of the opportunity to compare that statin with a specific standard treatment.

Discussion of outcome measures
Clinical outcomes
Studies may report a substantial number of clinical outcomes. Some, such as all-cause mortality, seem reasonably self-explanatory. Others are less straightforward, and these are discussed briefly below.

Unstable angina
Studies that report unstable angina as an outcome do not always define exactly what outcome they are recording. In studies of primary prevention, it seems probable that they refer to the development of unstable angina in patients who were free of angina at baseline. However, in studies of secondary prevention, many participants had angina at study entry, and it is therefore difficult, without further explanation, to know how to interpret data relating to unstable angina. Some of these studies do indeed specify that they are recording either the number of patients who developed new or worsening unstable angina or the number who were hospitalised for unstable angina during the course of the study. It should be noted that hospitalisation for unstable angina is a health service utilisation outcome; as such, it will be influenced by local practice so that, although the relative risk of hospitalisation should be generally applicable, the absolute risk of hospitalisation may not be generalisable to other contexts.[23]

Stroke
The data relating to cholesterol levels and stroke outcomes are complex. A meta-analysis of data from prospective observational studies found no significant association between total cholesterol and risk of stroke mortality, after adjusting for other relevant variables, but noted that this lack of association might conceal a positive association between elevated cholesterol levels and atherothrombotic (ischaemic) stroke on the one hand, and low cholesterol levels and haemorrhagic stroke on the other.[64] If so, statin therapy might be expected to reduce the risk of the more common ischaemic stroke while increasing the risk of the rarer haemorrhagic stroke. However, it has been suggested that the association of haemorrhagic stroke and low cholesterol seen in several observational studies could be due to confounding with alcohol consumption and other factors.[65] Moreover, the use of cholesterol-lowering agents in patients with elevated cholesterol levels seldom reduces cholesterol to the level associated with an increased risk of haemorrhagic stroke.[66]

Unfortunately, few of the RCTs of statin therapy that report stroke outcomes differentiate between types of stroke. However, as haemorrhagic stroke is more often fatal than ischaemic stroke,[13] it is possible that statin therapy may be associated with a reduction in the risk of non-fatal stroke, but not necessarily with a comparable reduction in the risk of fatal stroke.

Composite end-points
Many studies report composite end-points (generally CHD death plus non-fatal MI, sometimes with the addition of stroke or coronary revascularisation). They frequently do so because they are not powered to achieve a statistically significant result in relation to each of these end-points individually. The combination of CHD death with non-fatal MI seems appropriate, as it combines more and less severe manifestations of the same disease process to produce a robust measure of effectiveness. The addition of undifferentiated stroke is more questionable because of the possibility, noted above, that statins increase the risk of haemorrhagic stroke while offering protection against ischaemic stroke. The inclusion in composite end-points of health service utilisation outcomes such as revascularisation rates makes it difficult to generalise from the composite outcome as procedure rates may differ markedly between locations.[23]

Surrogate end-points
Ideally, this review would only include studies that reported relevant clinical end-points. However, the

absence of completed studies of rosuvastatin that report such end-points necessitated a more flexible approach. Consequently, data relating to surrogate end-points from studies of rosuvastatin with a duration of 26 weeks or longer were compared with the equivalent data drawn from included studies of other statins. As a result, the strength of the evidence for rosuvastatin is weaker than that for those statins that report clinical outcomes, as it depends on extrapolation from surrogate to clinical end-points on the basis of evidence from other statins, which are different in their chemical composition, may have different pleiotrophic effects and are therefore not likely to be fully comparable in this respect.

Adverse effects
Issues relating to drug toxicity assume considerable importance in relation to statins because of:

- the very large number of patients who may be prescribed or may purchase statins
- the fact that many of these individuals do not have symptomatic disease
- the fact that they may then take those drugs for life.

RCTs generally cannot provide definitive information about drug toxicity. They may underestimate the incidence of drug-related adverse events for several reasons: their populations may not be wholly typical of the target population (RCTs tend to exclude older participants, those with co-morbidities and those with known sensitivity to statins), and they may monitor the health of those populations more carefully than might be done in normal practice. In addition, RCTs are not powered to identify rare, although potentially serious, adverse events (such as the raised incidence of rhabdomyolysis which led to the withdrawal of cerivastatin). Finally, RCTs do not always measure, or report, all potential side-effects.[67] Because of this, data drawn from the studies included in the systematic review will be supplemented, when relevant, with evidence from other sources (e.g. postmarketing surveillance).

Continuance and compliance
The extent to which patients take a therapy in the intended manner will clearly affect the actual efficacy of that therapy. There are two aspects to this issue:

- continuance: the length of time for which the patient continues to take the medication (also referred to as adherence or persistence)

- compliance: the extent to which the medication is taken each day as prescribed.

Thus, some patients may demonstrate good continuance, in that they persist with the medication for a long period, but poor compliance. Other patients may demonstrate perfect compliance for a relatively short period, but then completely cease taking the medication. Yet other patients may demonstrate partial compliance in the form of occasional missed doses or occasional extra doses: such partial compliance may be erratic, or may be consistent but different from what the physician prescribed.[68] Insull and colleagues associate partial compliance (defined as taking 20–79% of the prescribed medication) with inconsistent dosing, whereby patients take the drug in an erratic pattern of near-perfect compliance interspersed with multiple omission of single doses or of two or more consecutive days' doses.[69]

Compliance and continuance can be assessed by a number of methods, including:

- patient recall (e.g. self-reported questionnaire)
- pill counts
- self-recorded diaries
- electronic devices that record the date and time of opening of the drug containers
- direct measurements of therapeutic response, such as blood tests (these may be confounded by an unknown degree of variation in therapeutic response)
- repeat prescriptions.

However, none of these methods is ideal in terms of determining whether or when the patients actually took the medication. For example, it has been estimated that careful questioning will detect over 50% of non-compliant patients, but even patients who admit to missing medication during the previous day or week tend to overestimate their actual rate of compliance.[70] Moreover, a study of the proportion of medication taken would not necessarily identify partial compliance if this took the form of either extra doses or deviations from the prescribed time of dose. In a controlled trial of fluvastatin versus placebo, electronic monitoring was used in a random sample of patients: although mean compliance as measured by the number of doses taken was found to be 94% (range 54–110%), mean compliance as measured by the number of days on which the correct number of doses was taken was only 81% (range 36–100%), and mean compliances to the prescribed morning and evening dosing schedules

(i.e. within ±6 hours) were only 71% (range 23–100%).[69] Thus, the compliance reported by the included studies, which is largely based on pill counts, is likely to overestimate the actual degree of compliance with the study regimen.

Unsurprisingly, it has been found that continuance and compliance with a medication are related to a number of properties of that medication, including its tolerability, convenience of administration, the patient's perception of its safety, and quality of life while on treatment.[71] Thus, compliance decreases as the complexity, cost and duration of the regimen increase. Although compliance has little relation to sociodemographic factors, patients with psychological problems are less likely to comply with treatment, whereas those with physical disabilities caused by the disease are more likely to do so.[72] The risk of non-continuance or non-compliance with prescribed medication is particularly high in patients with asymptomatic chronic diseases or risk factors that require long-term preventive medication.[71] Because such treatments bring no immediately apparent benefits, patients are less well motivated to comply long term, and find any minor side-effects less acceptable.[73]

Discussion of methodology
The review of clinical effectiveness was limited to studies of 26 weeks and over. This decision was made because of the evidence from large studies which published survival curves, such as the Heart Protection Study (HPS),[74] suggesting that statin therapy does not immediately impact on the number of patients having a major vascular event. Moreover, as clinical events are relatively infrequent outcomes in RCTs of statin therapy, the number recorded in short studies will be very small. As a consequence of both these factors, the shorter the study the greater the likelihood that the relative incidence of clinical events in the treatment and control groups will be disproportionately influenced by chance, and that, in consequence, the effectiveness of statin therapy will be underestimated.

Sifting
The references identified by the literature searches were sifted in three stages. All studies were first screened for relevance by title, and the abstracts of those that were not excluded at this stage were read. Finally, all studies which seemed from their abstracts to be potentially relevant were obtained for a full reading (for studies that did not provide abstracts, the full studies were screened).

Data extraction strategy
Data were extracted by one reviewer, using a customised data extraction form based on that proposed by the NHS Centre for Reviews and Dissemination (CRD).[75] Extracted data were checked by another reviewer.

Where available, the following data were reviewed:

- all-cause mortality
- CVD mortality
- CHD mortality
- stroke mortality
- fatal MI
- non-fatal MI
- unstable angina
- stable angina
- TIA
- PAD
- CABG
- PTCA
- quality of life
- adverse effects
- continuance and compliance.

Quality assessment strategy
The quality of RCTs was assessed according to criteria based on those proposed by the NHS CRD.[75]

Meta-analysis strategy
Studies that met the review's entry criteria were eligible for inclusion in the meta-analyses provided that they reported outcomes in terms of the number of subjects suffering clinical outcomes, as only this would allow calculation of the relative risk of subjects in the intervention group developing each outcome, compared with subjects in the control group. Studies that reported only numbers of events, or event rates (i.e. numbers of events per hundred or thousand patient-years), could not be included in the meta-analyses as this would have violated the basic statistical assumption that the occurrence of one event does not increase the likelihood of a subsequent event:[76] once a subject has suffered one cardiovascular event, the risk of a subsequent event increases (see Chapter 2). It was also impossible to include in the meta-analyses studies that only presented results in the form of relative risks, relative hazards or odds ratios, without the underlying numbers. Because of the number of relevant studies, and the tight timescale of the review, it was not considered feasible to contact the authors for missing data.

The meta-analyses combine study data first by individual statin and then overall. The overall analysis was undertaken at the request of the

National Institute for Health and Clinical Excellence (NICE); the approach has precedents in earlier systematic reviews such as that by Ross and colleagues.[77] Similarly, the meta-analyses combine data from all studies except for those in transplant patients and people with familiar hypercholesterolaemia because it was believed that statins were likely to have a similar effect in all patients with, or at risk of, CHD. However, separate meta-analyses were carried out of studies of primary and secondary prevention, and relevant subgroup analyses were also undertaken.

Meta-analysis was carried out using Review Manager.[78] The random-effects model was used, to allow generalisation beyond the sample of patients represented by the studies included in the meta-analysis; this model also provides wider, more conservative, confidence intervals than the fixed-effects model.[67] Unless stated otherwise, relative risks for individual studies were also calculated using Review Manager.

Absolute risks and numbers needed to treat (NNT) were also calculated for some key outcomes, using GraphPad.[79] Both of these statistics involve a time element: they indicate the absolute risk of an event, or the number needed to treat to avoid an event, over a specific period. Consequently, it is not possible to include studies of different lengths in these analyses, which have therefore been carried out only for key studies of primary and secondary CHD prevention.

In the above series of meta-analyses the trial data on each outcome are analysed separately. The implication of this is that the impact of statins on each outcome is independent. To incorporate correlations between outcomes in the economic analyses a Bayesian meta-analysis was also undertaken. This analysis has the advantage that the relative risks can be defined in a form suitable for inclusion in the economic modelling; that is, in terms of the relative risks conditional on no death.

The Bayesian meta-analysis provides distributions of relative risks of various events for treatment versus control. The events considered were CVD death, CHD death, non-fatal stroke, non-fatal MI and unstable angina.

The five events were considered separately and the same underlying probability model was used in each case. For the event in question, denoting

$n_{c,i}$: the number of control group patients in trial i

$n_{c,i}$: the number of treatment group patients in trial i

$r_{c,i}$: the number of occurrences of the event in the control group in trial i

$r_{t,i}$: the number of occurrences of the event in the treatment group in trial i

$p_{c,i}$: the probability of the event in the control group in trial i

$p_{t,i}$: the probability of the event in the treatment group in trial i

RR_i : the relative risk $p_{t,i}/p_{c,i}$ in trial i

it was then assumed that

$$r_{c,I} \sim \text{Binomial}(n_{c,i}, p_{c,i})$$
$$r_{t,I} \sim \text{Binomial}(n_{t,i}, p_{t,i})$$

A fairly non-informative prior was assumed for the control group probability $p_{c,I}$ in each trial:

$$p_{c,I} \sim \text{Beta}(0.5, 0.5)$$

It was then assumed that relative risk in trial was independent of the baseline (control) probability, with prior uncertainty about the relative risk described by

$$\log RR_i \sim N(m, s^2)$$

with m interpreted as the population relative risk, the parameter ultimately of interest, and s describing between-trial heterogeneity. Prior uncertainty about m and s was described by

$$m \sim N(0, 100^2)$$
$$s \sim U[0,3]$$

The alternatives $m \sim N(0, 10^2)$ and $s \sim U[0,2]$ were also considered, without any visible change in the results.

The above model for each event was implemented in the software package WinBUGS to obtain a sample of values from the posterior distribution of m, the population relative risk. Summary statistics were generated based on 10,000 randomly sampled values.

Presentation of results

The evidence from placebo-controlled studies for the clinical effectiveness of statins in patients with, or at risk of, CHD (other than transplant patients or those with familial hypercholesterolaemia) is presented first. These placebo-controlled studies were grouped on the basis of the presence or absence of clinical CHD or CVD at study entry, and results will therefore

be presented for each of the following groups in turn:

- all patients
- patients free of known CHD or CVD at baseline (primary CVD prevention)
- patients free of known CHD at baseline (primary CHD prevention)
- patients with CHD at baseline (secondary CHD prevention)
- patients with CVD (including CHD) at baseline (secondary CVD prevention) (*Table 13*).

It should be emphasised that the primary CVD prevention category includes only studies in which no patients were known to have CHD or other CVD at study entry. The primary CHD prevention category included studies in which no patients were known to have CHD at study entry; thus, it included all studies of primary CVD prevention as well as other studies in which some or all patients had some form of CVD other than CHD at study entry. The secondary CHD prevention category included only studies in which all patients were said to have CHD at study entry. The secondary CVD category included studies in which all patients were said to have either CHD or CVD at study entry; it thus included all studies of secondary CHD prevention as well as some studies in which all subjects had CVD, although not necessarily CHD, at study entry (*Table 13*).

It should be remembered that, as CHD is a specific manifestation of CVD, all patients with CHD by definition have CVD; thus, all subjects in the studies in the secondary CHD prevention category have CVD at baseline. However, not all patients with CVD have CHD, and therefore the secondary CVD prevention category includes subjects who may not have CHD at baseline. It should moreover be noted that the secondary prevention categories are not homogeneous in that some studies recruited patients with any evidence of existing coronary or cardiovascular disease, whereas others only recruited patients who had recently suffered a definite MI, and who were therefore at a substantially higher risk of death.[80]

To enable the utilisation of data from a number of large studies [HPS,[74] PROSPER,[81] West of Scotland Coronary Prevention Study (WOSCOPS)[82]] undertaken in mixed populations, the evidence from all placebo-controlled studies, including studies of statins in primary and secondary prevention, was analysed together.

The evidence from non-placebo-controlled trials is then presented, grouped by comparator, in the following order:

- comparisons with other statins
- comparisons with 'usual care'
- comparisons with 'no statin treatment'
- dose comparisons.

The evidence relating to the following specific groups will then be discussed in turn:

- women
- people with diabetes
- people aged 65 and over
- cardiac transplant recipients
- renal transplant recipients
- people with familial hypercholesterolaemia
- ethnic minorities.

Finally, evidence relating to the following outcomes will be discussed:

- quality of life
- adverse events
- continuance and compliance with statin therapy.

Review of clinical effectiveness: results

Quantity and quality of research available
Number and type of studies of clinical efficacy identified
The electronic literature searches identified 8308 potentially relevant articles. Of these, 157 articles were identified by the sifting process as relating to 40 RCTs that met the inclusion criteria (*Figure 1*).

TABLE 13 *Prevention categories: subjects with CHD or CVD at study entry*

Prevention category	CHD at study entry	CVD at study entry
Primary CVD prevention	No subjects	No subjects
Primary CHD prevention	No subjects	Some or all subjects
Secondary CHD prevention	All subjects	All subjects
Secondary CVD prevention	Some or all subjects	All subjects

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┌─────────────────────────────┐
│ Potentially relevant articles identified
│ and screened for retrieval:
│ n = 8308                    │
└─────────────────────────────┘
              │                         ┌─────────────────────────────┐
              │────────────────────────▶│ Papers rejected at the title stage:
              │                         │ n = 7405                    │
              ▼                         └─────────────────────────────┘
┌─────────────────────────────┐
│ Total abstracts screened:   │
│ n = 903                     │
└─────────────────────────────┘
              │                         ┌─────────────────────────────┐
              │────────────────────────▶│ Papers rejected at the abstract stage:
              │                         │ n = 604                     │
              ▼                         └─────────────────────────────┘
┌─────────────────────────────┐
│ Total full papers screened: │
│ n = 299                     │
└─────────────────────────────┘
              │                         ┌─────────────────────────────┐
              │────────────────────────▶│ Full papers excluded:
              │                         │ n = 142                     │
              ▼                         └─────────────────────────────┘
┌─────────────────────────────┐
│ Total full papers accepted: n = 157
│ (relating to 40 studies of clinical
│ effectiveness)              │
└─────────────────────────────┘
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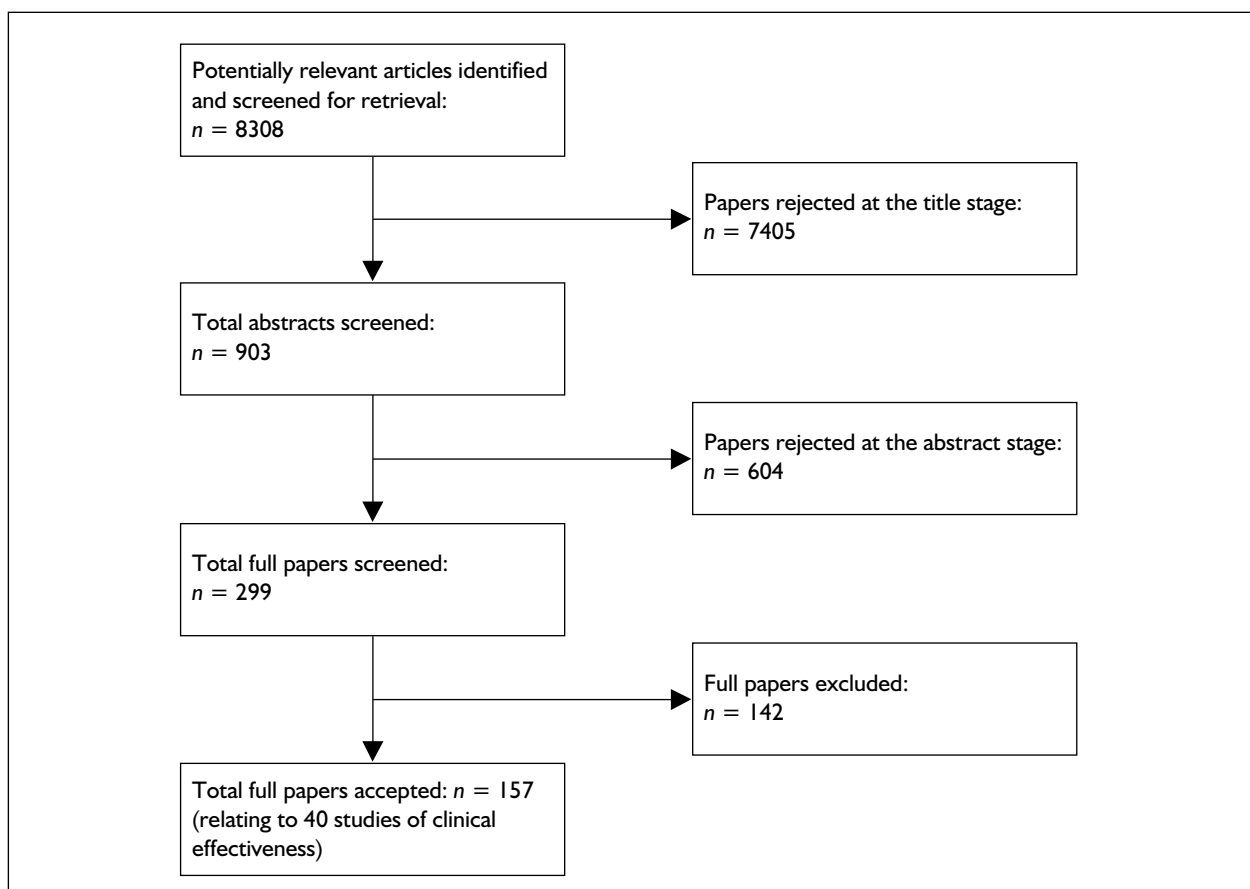
FIGURE 1 *Summary of study selection and exclusion: electronic literature searches*

A further five relevant studies (3T,[83] 4D,[84] ASAP,[85] DALI[86] and Sato, 2001[87]), which were reported in articles identified by the electronic literature searches, had been rejected during the sifting process as their relevance was not apparent; they were subsequently identified from citations, as were three studies (the ALLIANCE,[88] ESTABLISH[89] and REVERSAL[90] studies) that were not picked up by the electronic searches.

Number and type of studies included
A total of 48 individual RCTs met the review inclusion criteria. A full list of these studies, with the identified papers relating to them, may be found in Appendix 2.

In addition, a further 13 potentially relevant studies were identified which are still ongoing, or for which the data are unavailable; these are listed in Appendix 3.

Number and type of studies excluded, with reasons
As may be seen from *Figure 1*, a very large number of studies identified by the electronic literature searches did not meet the inclusion criteria, and

were therefore excluded as part of the sifting process. It is not practical to provide details of all these studies, and details are therefore given only of those studies that were excluded at the full paper stage, and then only if the reason for exclusion is not immediately apparent from the full text. Such studies, and the reasons for their exclusion, are listed in Appendix 4. For clarity, this appendix also lists all those clinical trials discussed in the company submissions that did not meet the inclusion criteria, together with at least one reason for their exclusion.

Tabulation of quality of studies
The quality of studies relating to each intervention is tabulated in Appendix 5.

It is only possible here to comment on the quality of those studies as reported in published articles. A surprising number of studies (19/48) did not provide enough information to allow the reader to judge whether the allocation of patients to treatment groups was truly random, even using generous criteria (e.g. assuming that randomisation that was said to be by minimisation or block randomisation was performed by computer or

23

some other adequate technique, even if that was not specified). Even fewer studies (27/48) indicated whether allocation to treatment groups was adequately concealed.

Most studies were double blind. However, only one (LIPS) assessed the success of the blinding process, and then only informally. In that study, anecdotal evidence suggested that many patients were aware of their total cholesterol levels, as these had been tested by their primary care physicians, and were therefore no longer blinded to the effects of treatment.[91] Clearly, this may also have occurred in other studies. If patients in the control group were aware of their cholesterol levels, they may have sought to reduce them either by modifying their behaviour or by seeking non-study lipid-lowering therapy, thus reducing the apparent effect of the study therapy.

Many studies reported the presence of cointerventions that were not equally distributed between treatment groups and therefore potentially influenced the study outcome. Such cointerventions most commonly took the form of statin or other lipid-lowering therapy in the control group. The probable impact of such cointerventions is discussed in the section 'Placebo-controlled studies: discussion of results' (p. 40). Of the studies that do not report such cointerventions, only two (FLARE,[92] LiSA[93]) specifically stated that the use of non-study lipid-lowering therapies was prohibited during the study. In a third study, by Mehra, no use appeared to have been made of non-study lipid-lowering therapies.[94]

Placebo-controlled studies
Quantity and quality of research available: placebo-controlled studies
Twenty-eight RCTs were identified that compared a statin with placebo and reported relevant outcomes: 4D, 4S, Aronow (2003), ASCOT-LLA, CAIUS, CARDS, CARE, CIS, DALI, FLARE, FLORIDA, HPS, KAPS, LIPID, LIPS, LiSA, MAAS, Mohler 2003, Mondillo 2003, Oxford Cholesterol Study, PLAC I, PLAC II, PMSG, PREDICT, PROSPER, REGRESS, SCAT and WOSCOPS. Of these, five used atorvastatin (4D, ASCOT-LLA, CARDS, DALI, Mohler 2003), four fluvastatin (FLARE, FLORIDA, LIPS, LiSA), 11 pravastatin (CAIUS, CARE, KAPS, LIPID, PLAC I, PLAC II, PMSG, PREDICT, PROSPER, REGRESS, WOSCOPS) and eight simvastatin (4S, Aronow 2003, CIS, HPS, MAAS, Mondillo 2003, Oxford Cholesterol Study, SCAT) (for further details, see Appendix 6). These studies are set out by prevention category in *Table 14*.

The majority of studies used statins at the maximum recommended dose. Thus, three of the four fluvastatin studies (FLARE, FLORIDA, LIPS) used the maximum dose of 80 mg; the LiSA study increased the starting dose of 40 mg to 80 mg 6 weeks after randomisation if the decrease in LDL-C was less than 30%.[93] Similarly, all but two of the pravastatin studies used the maximum dose of 40 mg; in the remaining two (PLAC II and PMSG), the dose could be increased to 40 mg in participants whose LDL-C levels had not responded to the starting dose of 20 mg.[95,96] Three of the simvastatin studies (Aronow 2003,

TABLE 14 *Placebo-controlled studies by prevention category*

Primary CVD prevention	Primary CHD prevention	Secondary CHD prevention	Secondary CVD prevention	Mixed primary and secondary prevention
CAIUS[107]	CAIUS[107]	4S[97]	4S[97]	4D[84]
CARDS[103]	CARDS[103]	CARE[111]	CARE[111]	HPS[74]
	ASCOT-LLA[102]	CIS[98]	CIS[98]	KAPS[133]
	DALI[86]	FLARE[108]	FLARE[108]	Oxford Cholesterol Study[101]
		FLORIDA[109]	FLORIDA[109]	PMSG[96]
		LIPID[112]	LIPID[112]	PROSPER[81]
		LIPS[110]	LIPS[110]	WOSCOPS[82]
		LiSA[93]	LiSA[93]	
		MAAS[100]	MAAS[100]	
		PLAC I[113]	PLAC I[113]	
		PLAC II[95]	PLAC II[95]	
		PREDICT[114]	PREDICT[114]	
		REGRESS[115]	REGRESS[115]	
		SCAT[116]	SCAT[116]	
			Aronow 2003[118]	
			Mohler 2003[21]	
			Mondillo 2003[105]	

HPS, Mondillo 2003) used 40 mg throughout; this is the maximum dose recommended for all patients except those at extremely high risk of cardiovascular events [see the section 'Summary of product characteristics' (p. 12)]. Of the remaining five simvastatin studies, three (4S, CIS, SCAT) used a starting dose of 20 mg, which could be increased to 40 mg if this was necessary to achieve an adequate reduction in LDL-C.[97–99] MAAS used a 20-mg dose throughout,[100] while in the Oxford Cholesterol Study, which did not present results for clinical effectiveness by treatment arm, one arm was randomised to 20 mg and one to 40 mg.[101] By contrast, the atorvastatin studies generally used doses well below the maximum dose of 80 mg: ASCOT-LLA and CARDS used a fixed dose of 10 mg,[102,103] and the 4D study a fixed dose of 20 mg.[84] Only the small DALI[86] and Mohler[21] studies used an 80-mg dose: each had two treatment arms, one on a fixed dose of 10 mg and the other on 80 mg.

Assessment of effectiveness: placebo-controlled studies

As noted earlier, the evidence from all the placebo-controlled studies will be presented first. Evidence will then be presented in relation to the different prevention categories in turn, starting with primary CVD prevention (patients free of known CHD or CVD at baseline), followed by primary CHD prevention (patients free of known CHD at baseline), then by secondary CHD prevention (patients with CHD at baseline) and finally secondary CVD prevention (patients with CVD, including CHD, at baseline).

Assessment of effectiveness of statins: all placebo-controlled trials

Many of the studies that report mortality data are too small to show a statistically significant effect. However, meta-analysis of data from all studies that provided such data in usable form indicates that statins are associated with a reduction in the risk of all-cause mortality, cardiovascular mortality, CHD mortality and fatal MI, but not of stroke mortality (*Figures 2–4*). (Only forest plots for key outcomes are included here; those for other outcomes may be found in Appendix 7.) Studies that were excluded from any meta-analysis of clinical outcomes because they had not published such data in usable form were 4D, for which only preliminary data were available, indicating a non-significant reduction in the primary end-point of combined cardiac death, non-fatal MI and stroke,[104] and the Oxford Cholesterol Study, which collected data on the number of patients who suffered all-cause, CHD and other vascular

mortality, non-fatal MI and stroke, but only published these data in an interim report which did not attribute such outcomes to treatment groups.[101] Mondillo 2003 did not report any clinical outcomes other than walking distances.[105]

Many studies were also too small to show a statistically significant effect in relation to non-fatal outcomes. However, meta-analysis of data from all studies that provided such data in usable form indicates that statins are associated with a reduction in the risk of non-fatal stroke, TIA, non-fatal MI (*Figure 5*), unstable angina and hospitalisations for unstable angina. In the only study that reported this outcome,[102] statin treatment was also found to be associated with a reduction in relative risk of chronic stable angina (RR 0.59, 95% CI 0.38 to 0.90).

Because few studies reported the effect of statins on PAD, the results were not statistically significant even when combined. However, one of the studies included in the meta-analysis was carried out in patients with stable intermittent claudication.[21] This found that statin therapy was associated with a significant reduction in the incidence of peripheral arterial events (worsening claudication, development of rest ischaemia, peripheral revascularisation and limb amputation), suggesting that statins may have a beneficial effect on PAD, at least in this patient group.

Statin treatment was also found to be associated with a reduction in both CABG and PTCA.

The most robust results are demonstrated in relation to the composite end-point of CHD mortality plus non-fatal MI (*Figure 6*).

The fact that statin therapy is associated with a statistically significant reduction in the risk of non-fatal stroke, but not of fatal stroke, may be due to a differential effect on haemorrhagic and non-haemorrhagic stroke. Only three studies differentiated between types of stroke. Two of these provided data in a form that enabled them to be combined in a meta-analysis.[74,97] The results show that, although statin therapy was not shown to have an effect on haemorrhagic stroke, it reduced the risk of non-haemorrhagic stroke (*Figures 7* and *8*).

These results are supported by those of the third study, the LIPID study[106] in which statin therapy was associated with a significant reduction in the risk of non-haemorrhagic stroke but not of haemorrhagic stroke (*Table 15*). Thus, statin therapy appears to be associated with a reduced
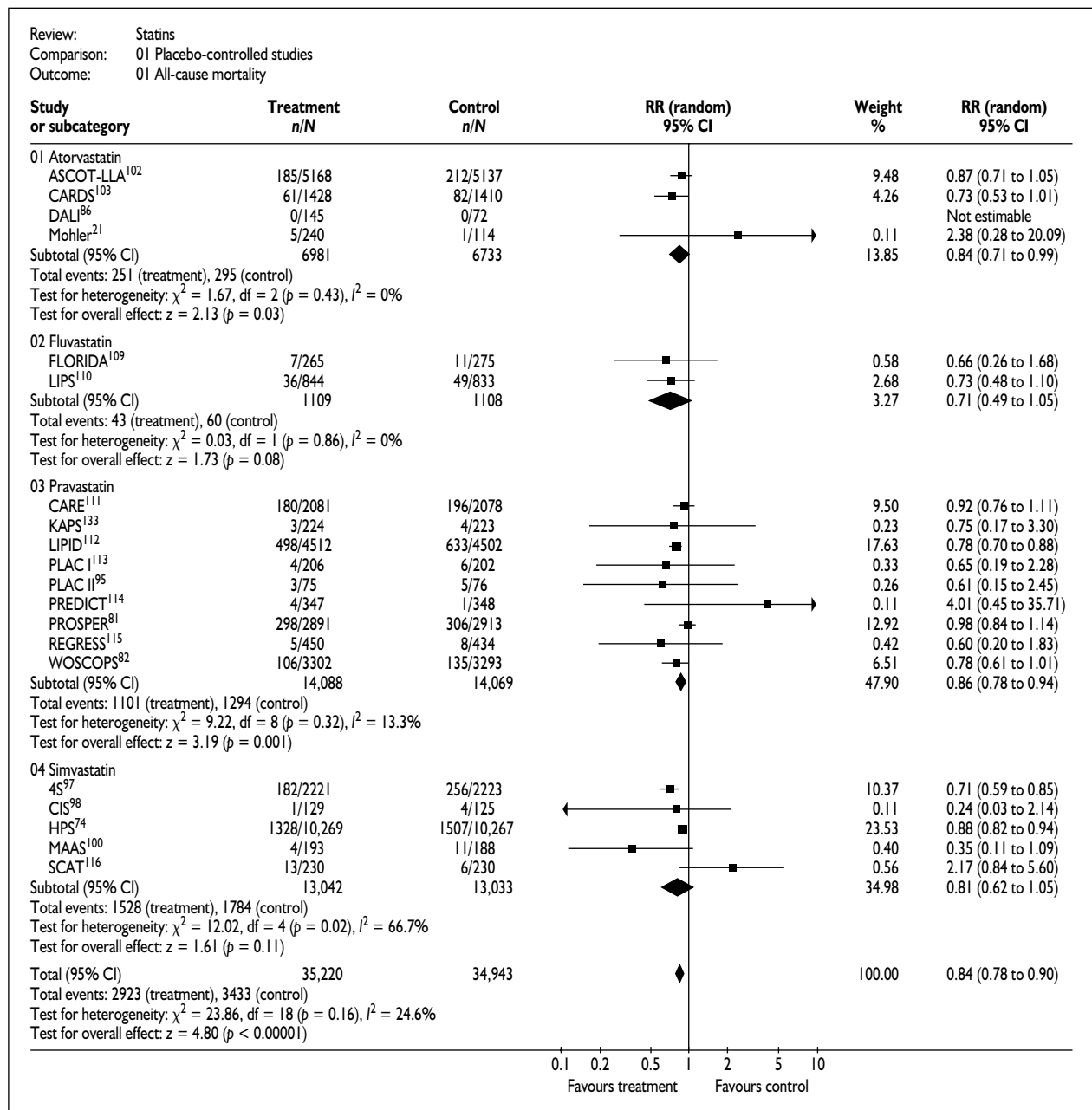
FIGURE 2 *Placebo-controlled studies: effect of statins on all-cause mortality*

risk of the more common, non-haemorrhagic, stroke and has not been shown to increase the risk of haemorrhagic stroke.

Overall, therefore, the evidence indicates that statins are associated with a reduction in the risk of all-cause, cardiovascular and CHD mortality, and of a number of non-fatal outcomes (non-fatal MI, non-fatal stroke, TIA, angina and coronary revascularisation). No effect has been demonstrated in respect of stroke mortality.

On the evidence available from the placebo-controlled trials, it is barely possible to

differentiate between the different statins in relation to any outcome: although the point estimates of their effect sizes may vary, the confidence intervals overlap in each case except for non-fatal MI, where simvastatin can just be differentiated from pravastatin (*Figure 5*). Head-to-head comparisons of one statin with another are reviewed in the section 'Direct statin–statin comparisons' (p. 42).

As noted in the section 'Quantity and quality of research available: placebo-controlled studies' (p. 24), although most studies of fluvastatin and pravastatin and simvastatin either used, or had the

Review: Statins
Comparison: 80 Placebo-controlled studies: CHD mortality
Outcome: 01 CHD mortality

Study or subcategory	Treatment n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
01 Atorvastatin					
DALI[86]	0/145	0/72			Not estimable
Mohler[21]	2/240	1/114		0.09	0.95 (0.09 to 10.37)
CARDS[103]	21/1428	25/1410		1.52	0.83 (0.47 to 1.47)
Subtotal (95% CI)	1813	1596		1.61	0.84 (0.48 to 1.46)
Total events: 23 (treatment), 26 (control)					
Test for heterogeneity: $\chi^2 = 0.01$, df = 1 ($p = 0.91$), $I^2 = 0\%$					
Test for overall effect: $z = 0.63$ ($p = 0.53$)					
02 Fluvastatin					
FLARE[108]	3/409	7/425		0.28	0.45 (0.12 to 1.71)
LiSA[93]	2/187	4/178		0.18	0.48 (0.09 to 2.57)
FLORIDA[109]	2/265	9/275		0.22	0.23 (0.05 to 1.06)
LIPS[110]	13/844	24/833		1.13	0.53 (0.27 to 1.04)
Subtotal (95% CI)	1705	1711		1.80	0.46 (0.27 to 0.79)
Total events: 20 (treatment), 44 (control)					
Test for heterogeneity: $\chi^2 = 0.99$, df = 3 ($p = 0.80$), $I^2 = 0\%$					
Test for overall effect: $z = 2.84$ ($p = 0.004$)					
03 Pravastatin					
PMSG[96]	0/530	3/532		0.06	0.14 (0.01 to 2.77)
KAPS[133]	2/224	2/223		0.13	1.00 (0.14 to 7.01)
PLAC I[113]	3/206	3/202		0.20	0.98 (0.20 to 4.80)
REGRESS[115]	3/450	5/434		0.25	0.58 (0.14 to 2.41)
WOSCOPS[82]	38/3302	52/3293		2.91	0.73 (0.48 to 1.10)
CAIUS[107]	1/151	0/154		0.05	3.06 (0.13 to 74.51)
CARE[111]	96/2081	119/2078		7.33	0.81 (0.62 to 1.05)
LIPID[112]	287/4512	373/4502		22.89	0.77 (0.66 to 0.89)
PROSPER[81]	94/2891	122/2913		7.22	0.78 (0.60 to 1.01)
Subtotal (95% CI)	14,347	14,331		41.03	0.77 (0.69 to 0.86)
Total events: 524 (treatment), 679 (control)					
Test for heterogeneity: $\chi^2 = 2.45$, df = 8 ($p = 0.96$), $I^2 = 0\%$					
Test for overall effect: $z = 4.56$ ($p < 0.00001$)					
04 Simvastatin					
4S[97]	111/2221	189/2223		9.77	0.59 (0.47 to 0.74)
MAAS[100]	4/193	4/188		0.27	0.97 (0.25 to 3.84)
CIS[98]	1/129	2/125		0.09	0.48 (0.04 to 5.28)
SCAT[116]	7/230	4/230		0.34	1.75 (0.52 to 5.90)
Aronow[118]	3/34	6/35		0.30	0.51 (0.14 to 1.89)
HPS[74]	587/10,269	707/10,267		44.79	0.83 (0.75 to 0.92)
Subtotal (95% CI)	13,076	13,068		55.56	0.74 (0.57 to 0.96)
Total events: 713 (treatment), 912 (control)					
Test for heterogeneity: $\chi^2 = 9.64$, df = 5 ($p = 0.09$), $I^2 = 48.1\%$					
Test for overall effect: $z = 2.26$ ($p = 0.02$)					
Total (95% CI)	30,941	30,706		100.00	0.77 (0.72 to 0.83)
Total events: 1280 (treatment), 1661 (control)					
Test for heterogeneity: $\chi^2 = 16.80$, df = 20 ($p = 0.67$), $I^2 = 0\%$					
Test for overall effect: $z = 7.15$ ($p < 0.00001$)					

0.1   0.2   0.5   1   2   5   10
Favours treatment   Favours control

FIGURE 3 *Placebo-controlled studies: effect of statins on CHD mortality*

potential to use, those statins at their maximum recommended dose, the same was not true of atorvastatin. It could therefore be argued that atorvastatin may have the potential to achieve greater reductions in clinical events than are demonstrated by the trials included in this review. However, it is not clear to what extent increasing the dose of atorvastatin above 10 mg would increase its clinical effectiveness. Neither of the two small studies that used 10-mg and 80-mg doses was powered to demonstrate a difference between them in terms of vascular events,[21,86] and

the 4D study, which used a 20-mg dose, has yet to report. Moreover, although the DALI study found that the 80-mg dose achieved a significantly greater reduction in LDL-C than did the 10-mg dose,[86] Mohler and colleagues found no significant difference between the two doses.[21] Thus, it is currently not clear to what extent the use of higher doses of atorvastatin would achieve greater LDL-C lowering, or whether any lipid-lowering effects would be beneficial in terms of clinical end-points or would be associated with an increased risk of adverse events.

Review: Statins
Comparison: 01 Placebo-controlled studies
Outcome: 02 Fatal MI

Study or subcategory	Treatment n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
01 Atorvastatin					
CARDS[103]	8/1428	20/1410		6.24	0.39 (0.17 to 0.89)
DALI[86]	0/145	0/72			Not estimable
Mohler[21]	1/240	1/114		0.55	0.48 (0.03 to 7.53)
Subtotal (95% CI)	1813	1596		6.79	0.40 (0.18 to 0.88)

Total events: 9 (treatment), 21 (control)
Test for heterogeneity: $\chi^2 = 0.02$, df = 1 ($p = 0.90$), $I^2 = 0\%$
Test for overall effect: $z = 0.63$ ($p = 0.53$)

02 Fluvastatin					
FLORIDA[109]	2/265	3/275		0.48	0.15 (0.01 to 2.86)
LiSA[93]	2/187	3/178		1.32	0.63 (0.11 to 3.75)
Subtotal (95% CI)	452	453		1.79	0.43 (0.09 to 1.98)

Total events: 2 (treatment), 6 (control)
Test for heterogeneity: $\chi^2 = 0.71$, df = 1 ($p = 0.40$), $I^2 = 0\%$
Test for overall effect: $z = 1.08$ ($p = 0.28$)

03 Pravastatin					
CAIUS[107]	1/151	0/154		0.41	3.06 (0.13 to 74.51)
CARE[111]	24/2081	38/2078		16.16	0.63 (0.38 to 1.05)
KAPS[133]	0/224	2/223		0.45	0.20 (0.01 to 4.12)
LIPID[112]	53/4512	89/4502		36.52	0.59 (0.42 to 0.83)
PLAC I[113]	1/206	1/202		0.54	0.98 (0.06 to 15.57)
PMSG[96]	0/530	2/532		0.45	0.20 (0.01 to 4.17)
PREDICT[114]	1/347	0/348		0.41	3.01 (0.12 to 73.60)
REGRESS[115]	1/450	1/434		0.54	0.96 (0.06 to 15.37)
WOSCOPS[82]	17/3302	33/3293		12.24	0.51 (0.29 to 0.92)
Subtotal (95% CI)	11,803	11,766		67.73	0.59 (0.46 to 0.76)

Total events: 98 (treatment), 166 (control)
Test for heterogeneity: $\chi^2 = 3.53$, df = 8 ($p = 0.90$), $I^2 = 0\%$
Test for overall effect: $z = 4.11$ ($p < 0.0001$)

04 Simvastatin					
4S[97]	30/2221	63/2223		22.42	0.48 (0.31 to 0.73)
MAAS[100]	1/193	2/188		0.73	0.49 (0.04 to 5.33)
SCAT[116]	1/230	1/230		0.54	1.00 (0.06 to 15.89)
Subtotal (95% CI)	2644	2641		23.69	0.49 (0.32 to 0.74)

Total events: 32 (treatment), 66 (control)
Test for heterogeneity: $\chi^2 = 0.27$, df = 2 ($p = 0.87$), $I^2 = 0\%$
Test for overall effect: $z = 3.38$ ($p = 0.0007$)

Total (95% CI)	16,712	16,456		100.00	0.55 (0.45 to 0.67)

Total events: 141 (treatment), 259 (control)
Test for heterogeneity: $\chi^2 = 5.95$, df = 15 ($p = 0.98$), $I^2 = 0\%$
Test for overall effect: $z = 5.77$ ($p < 0.00001$)

```
0.1   0.2    0.5    1    2    5    10
   Favours treatment    Favours control
```

FIGURE 4 *Placebo-controlled studies: effect of statins on fatal MI*

Assessment of effectiveness of statins in patients free of CVD at baseline (primary CVD prevention)
The evidence for the effectiveness of statins in primary CVD prevention rests on two placebo-controlled RCTs (CAIUS[107] and CARDS[103]), and on subgroup analyses in three placebo-controlled studies of CHD prevention (ASCOT-LLA[102]) or populations with mixed CVD status (PROSPER[81] and WOSCOPS[82]). However, these latter studies only presented data relating to patients without CVD at study entry in relation to the following composite end-points:

- fatal CHD and non-fatal MI (ASCOT-LLA and WOSCOPS)

- fatal CHD, non-fatal MI and fatal or non-fatal stroke (PROSPER).

Moreover, two of these studies (PROSPER and WOSCOPS) did not stratify randomisation to take into account prior disease status. In the ASCOT-LLA study, randomisation was by minimisation, and it is not specified whether this took prior disease status into account. Consequently, the subgroup analyses from PROSPER and WOSCOPS are not, and those from the ASCOT-LLA study may not be, true randomised comparisons.

The two studies that were carried out specifically in patients without CVD differed in their

Review:	Statins					
Comparison:	84 Placebo-controlled studies: non-fatal MI					
Outcome:	01 Non-fatal MI					

Study or subcategory	Treatment n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
01 Atorvastatin					
DALI[86]	0/145	1/72		0.10	0.17 (0.01 to 4.04)
ASCOT-LLA[102]	60/5168	108/5137		7.79	0.55 (0.40 to 0.76)
Mohler[21]	5/240	2/114		0.39	1.19 (0.23 to 6.03)
CARDS[103]	25/1428	41/1410		3.78	0.60 (0.37 to 0.98)
Subtotal (95% CI)	6981	6733		12.06	0.57 (0.44 to 0.74)

Total events: 90 (treatment), 152 (control)
Test for heterogeneity: $\chi^2 = 1.44$, df = 3 ($p = 0.70$), $I^2 = 0\%$
Test for overall effect: $z = 4.21$ ($p < 0.0001$)

Study or subcategory	Treatment n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
02 Atorvastatin					
FLARE[108]	3/409	10/425		0.63	0.31 (0.09 to 1.12)
LiSA[93]	0/187	1/178		0.10	0.32 (0.01 to 7.74)
LIPS[110]	30/844	38/833		4.10	0.78 (0.49 to 1.25)
Subtotal (95% CI)	1440	1436		4.83	0.69 (0.45 to 1.07)

Total events: 33 (treatment), 49 (control)
Test for heterogeneity: $\chi^2 = 1.97$, df = 2 ($p = 0.37$), $I^2 = 0\%$
Test for overall effect: $z = 1.67$ ($p = 0.09$)

Study or subcategory	Treatment n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
03 Pravastatin					
PMSG[96]	0/530	4/532		0.12	0.11 (0.01 to 2.07)
KAPS[133]	3/224	6/223		0.55	0.50 (0.13 to 1.97)
PLAC I[113]	7/206	16/202		1.34	0.43 (0.18 to 1.02)
REGRESS[115]	7/450	12/434		1.19	0.56 (0.22 to 1.42)
WOSCOPS[82]	143/3302	204/3293		13.05	0.70 (0.57 to 0.86)
CAIUS[107]	1/151	2/154		0.18	0.51 (0.05 to 5.56)
CARE[111]	182/2081	231/2078		14.75	0.79 (0.65 to 0.95)
PREDICT[114]	4/347	4/348		0.55	1.00 (0.25 to 3.98)
PROSPER[81]	222/2891	254/2913		15.68	0.88 (0.74 to 1.05)
Subtotal (95% CI)	10,182	10,177		47.41	0.78 (0.70 to 0.87)

Total events: 569 (treatment), 733 (control)
Test for heterogeneity: $\chi^2 = 7.66$, df = 8 ($p = 0.47$), $I^2 = 0\%$
Test for overall effect: $z = 4.57$ ($p < 0.00001$)

Study or subcategory	Treatment n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
04 Simvastatin					
4S[97]	164/2221	270/2223		14.72	0.61 (0.51 to 0.73)
CIS[98]	1/129	5/125		0.23	0.19 (0.02 to 1.64)
SCAT[116]	10/230	9/230		1.30	1.11 (0.46 to 2.68)
HPS[74]	357/10,269	574/10,267		19.45	0.62 (0.55 to 0.71)
Subtotal (95% CI)	12,849	12,845		35.70	0.62 (0.56 to 0.69)

Total events: 532 (treatment), 858 (control)
Test for heterogeneity: $\chi^2 = 2.87$, df = 3 ($p = 0.41$), $I^2 = 0\%$
Test for overall effect: $z = 8.90$ ($p < 0.00001$)

Study or subcategory	Treatment n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
Total (95% CI)	31,452	31,191		100.00	0.68 (0.62 to 0.76)

Total events: 1224 (treatment), 1792 (control)
Test for heterogeneity: $\chi^2 = 25.21$, df = 19 ($p = 0.15$), $I^2 = 24.6\%$
Test for overall effect: $z = 7.27$ ($p < 0.00001$)

0.1 0.2 0.5 1 2 5 10
Favours treatment   Favours control

FIGURE 5 *Placebo-controlled studies: effect of statins on non-fatal MI*

populations: CARDS recruited patients with type 2 diabetes from the UK and Republic of Ireland (a high-risk primary prevention population), while CAIUS was conducted in a Mediterranean population with ultrasonographic evidence of early carotid artery atherosclerosis. The ASCOT-LLA study was a factorial study evaluating atorvastatin in hypertensive patients without a history of CHD who were also receiving aggressive antihypertensive treatment with either a β-blocker or a calcium antagonist[102] (again, a high-risk primary prevention population; for further details, see Appendix 6). Of the studies with mixed populations, PROSPER was specifically carried out in elderly patients[81] and WOSCOPS in men.[82]

Meta-analysis indicates that, in patients without clinical CVD, statins are associated with a statistically significant reduction in the risk of non-fatal MI, and of CHD death plus non-fatal MI. There was also a statistically significant reduction in the composite end-point of CHD death, non-

29

Review: Statins
Comparison: 91 Placebo-controlled studies: CHD death plus non-fatal MI
Outcome: 01 CHD death plus non-fatal MI

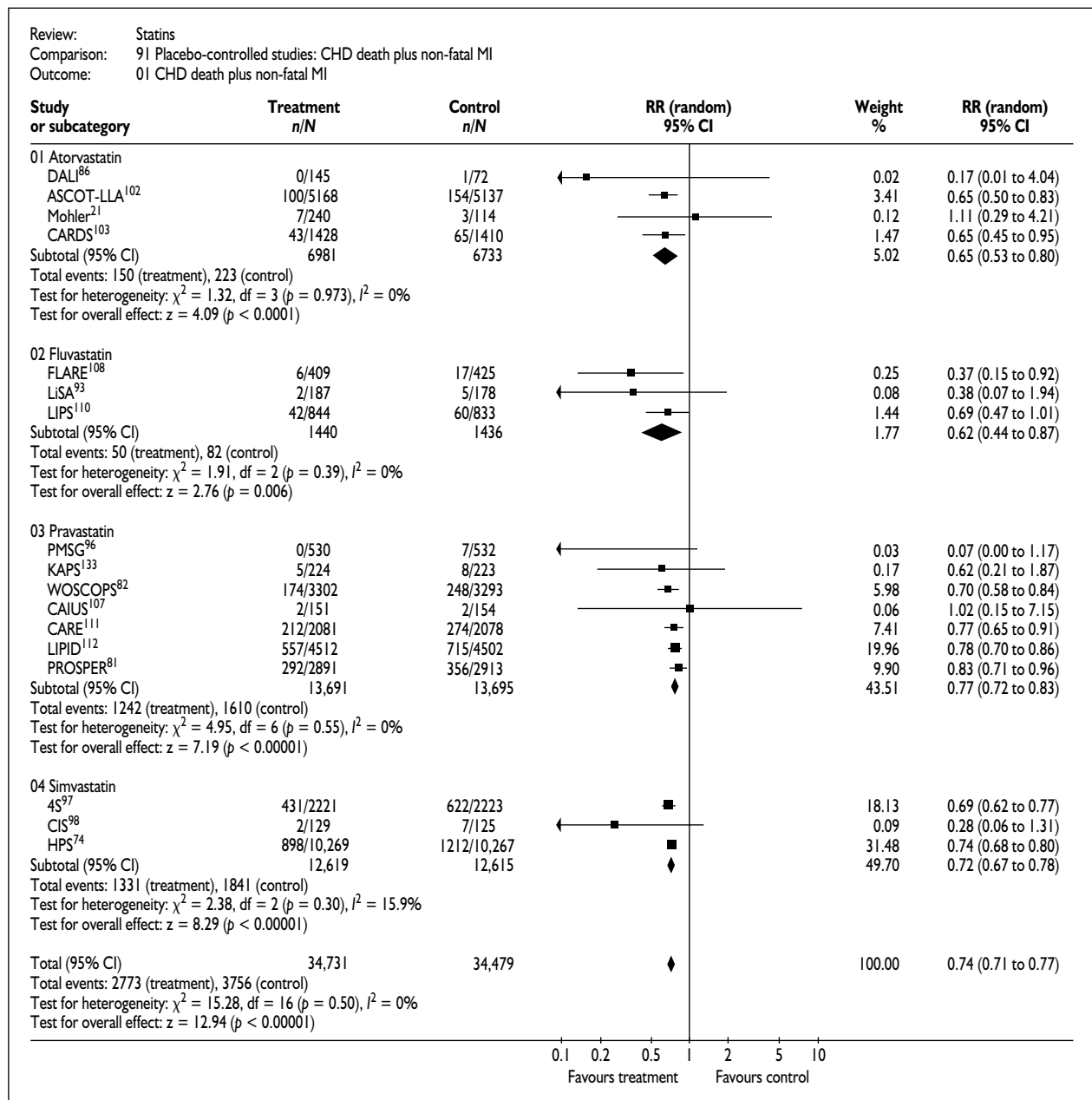| Study or subcategory	Treatment n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
01 Atorvastatin					
DALI[86]	0/145	1/72		0.02	0.17 (0.01 to 4.04)
ASCOT-LLA[102]	100/5168	154/5137		3.41	0.65 (0.50 to 0.83)
Mohler[21]	7/240	3/114		0.12	1.11 (0.29 to 4.21)
CARDS[103]	43/1428	65/1410		1.47	0.65 (0.45 to 0.95)
Subtotal (95% CI)	6981	6733		5.02	0.65 (0.53 to 0.80)
Total events: 150 (treatment), 223 (control)					
Test for heterogeneity: $\chi^2 = 1.32$, df = 3 ($p = 0.973$), $I^2 = 0\%$					
Test for overall effect: $z = 4.09$ ($p < 0.0001$)					
02 Fluvastatin					
FLARE[108]	6/409	17/425		0.25	0.37 (0.15 to 0.92)
LiSA[93]	2/187	5/178		0.08	0.38 (0.07 to 1.94)
LIPS[110]	42/844	60/833		1.44	0.69 (0.47 to 1.01)
Subtotal (95% CI)	1440	1436		1.77	0.62 (0.44 to 0.87)
Total events: 50 (treatment), 82 (control)					
Test for heterogeneity: $\chi^2 = 1.91$, df = 2 ($p = 0.39$), $I^2 = 0\%$					
Test for overall effect: $z = 2.76$ ($p = 0.006$)					
03 Pravastatin					
PMSG[96]	0/530	7/532		0.03	0.07 (0.00 to 1.17)
KAPS[133]	5/224	8/223		0.17	0.62 (0.21 to 1.87)
WOSCOPS[82]	174/3302	248/3293		5.98	0.70 (0.58 to 0.84)
CAIUS[107]	2/151	2/154		0.06	1.02 (0.15 to 7.15)
CARE[111]	212/2081	274/2078		7.41	0.77 (0.65 to 0.91)
LIPID[112]	557/4512	715/4502		19.96	0.78 (0.70 to 0.86)
PROSPER[81]	292/2891	356/2913		9.90	0.83 (0.71 to 0.96)
Subtotal (95% CI)	13,691	13,695		43.51	0.77 (0.72 to 0.83)
Total events: 1242 (treatment), 1610 (control)					
Test for heterogeneity: $\chi^2 = 4.95$, df = 6 ($p = 0.55$), $I^2 = 0\%$					
Test for overall effect: $z = 7.19$ ($p < 0.00001$)					
04 Simvastatin					
4S[97]	431/2221	622/2223		18.13	0.69 (0.62 to 0.77)
CIS[98]	2/129	7/125		0.09	0.28 (0.06 to 1.31)
HPS[74]	898/10,269	1212/10,267		31.48	0.74 (0.68 to 0.80)
Subtotal (95% CI)	12,619	12,615		49.70	0.72 (0.67 to 0.78)
Total events: 1331 (treatment), 1841 (control)					
Test for heterogeneity: $\chi^2 = 2.38$, df = 2 ($p = 0.30$), $I^2 = 15.9\%$					
Test for overall effect: $z = 8.29$ ($p < 0.00001$)					
Total (95% CI)	34,731	34,479		100.00	0.74 (0.71 to 0.77)
Total events: 2773 (treatment), 3756 (control)					
Test for heterogeneity: $\chi^2 = 15.28$, df = 16 ($p = 0.50$), $I^2 = 0\%$					
Test for overall effect: $z = 12.94$ ($p < 0.00001$)					

```
0.1   0.2   0.5   1   2   5   10
   Favours treatment   Favours control
```

FIGURE 6 *Placebo-controlled studies: effect of statins on CHD mortality plus non-fatal MI*

fatal MI, any stroke or coronary revascularisation. However, the studies were too small to demonstrate statistically significant effects in relation to other clinical outcomes (see Appendix 8, *Table 107* and *Figures 47–52*).

Two of the studies that provided subgroup data relating to patients without prior CVD reported combined data on CHD death plus non-fatal MI in a form that did not allow them to be included in a meta-analysis. The ASCOT-LLA investigators calculated that, in patients without prior CVD, statin treatment was associated with an unadjusted hazard ratio in relation to this outcome of 0.61

(95% CI 0.46 to 0.81),[102] while the WOSCOPS investigators calculated that, in such patients, statin treatment was associated with a risk reduction of 33% (95% CI 15 to 46%).[82] These figures are not incompatible with the results of the meta-analysis presented in *Table 16*.

The WOSCOPS investigators also calculated a risk reduction of 33% (95% CI 15 to 46%) for a composite end-point of CHD death, non-fatal MI, fatal or non-fatal stroke and coronary revascularisation in patients without CVD at baseline.[82] This is again not incompatible with the relative risk of that same end-point of 0.64 (95%
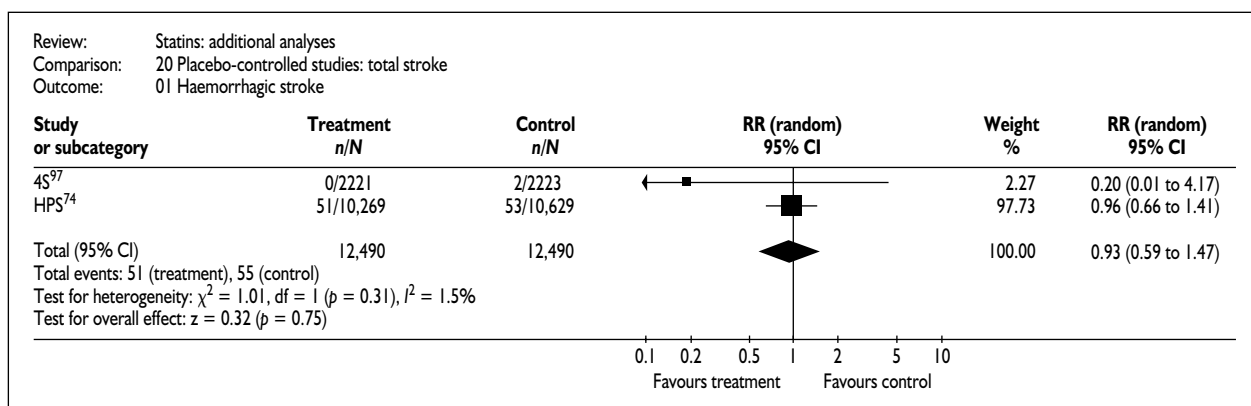
```
Review:        Statins: additional analyses
Comparison:    20 Placebo-controlled studies: total stroke
Outcome:       01 Haemorrhagic stroke
```

Study or subcategory	Treatment n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
4S[97]	0/2221	2/2223		2.27	0.20 (0.01 to 4.17)
HPS[74]	51/10,269	53/10,629		97.73	0.96 (0.66 to 1.41)
Total (95% CI)	12,490	12,490		100.00	0.93 (0.59 to 1.47)

Total events: 51 (treatment), 55 (control)
Test for heterogeneity: $\chi^2 = 1.01$, df = 1 ($p = 0.31$), $I^2 = 1.5\%$
Test for overall effect: $z = 0.32$ ($p = 0.75$)

```
        0.1   0.2   0.5   1   2   5   10
        Favours treatment    Favours control
```

FIGURE 7 *Placebo-controlled studies: effect of statins on haemorrhagic stroke*

```
Review:        Statins: additional analyses
Comparison:    20 Placebo-controlled studies: total stroke
Outcome:       02 Non-haemorrhagic stroke
```

Study or subcategory	Treatment n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
4S[97]	29/2221	49/2221		9.55	0.59 (0.38 to 0.93)
HPS[74]	290/10,269	409/10,267		90.45	0.71 (0.61 to 0.82)
Total (95% CI)	12,490	12,490		100.00	0.70 (0.61 to 0.80)

Total events: 319 (treatment), 458 (control)
Test for heterogeneity: $\chi^2 = 0.54$, df = 1 ($p = 0.46$), $I^2 = 0\%$
Test for overall effect: $z = 5.03$ ($p < 0.0001$)

```
        0.1   0.2   0.5   1   2   5   10
        Favours treatment    Favours control
```

FIGURE 8 *Placebo-controlled studies: effect of statins on non-haemorrhagic stroke*

TABLE 15 *Effect of statin therapy on types of stroke: the LIPID study[106]*

Outcome	% of patients		Risk reduction (%)	95% CI	p
	Pravastatin (n = 4512)	Placebo (n = 4502)			
Haemorrhagic stroke	0.4	0.2	NR		0.28
Non-haemorrhagic stroke	3.4	4.4	23	5–38	0.02

NR, not reported.

CI 0.48 to 0.84) calculated from data presented in CARDS relating to the number of patients who had CHD death, non-fatal MI, fatal or non-fatal stroke, or CABG or other surgery as their primary end-point.

Assessment of effectiveness of statins in patients free of CHD at baseline (primary CHD prevention)
The evidence for the effectiveness of statins in patients without prior CHD rests on the CAIUS and CARDS studies discussed above, DALI, which compared two doses of atorvastatin with placebo in patients with type 2 diabetes (a high-risk primary prevention population),[86] and the full ASCOT-LLA study. The subgroup data from PROSPER[81] and WOSCOPS,[82] noted above, relating to patients without CVD at study entry, are also relevant here. In addition, HPS,[74] a factorial study evaluating both simvastatin and antioxidant vitamins (for further details, see Appendix 6), presented subgroup data relating to patients without CHD at study entry, although
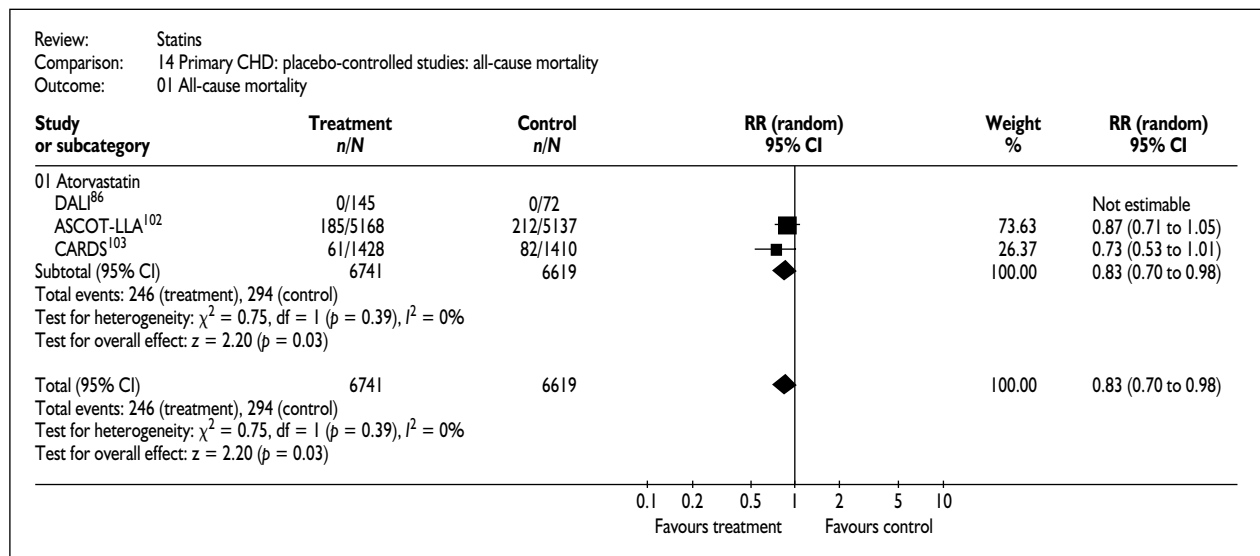
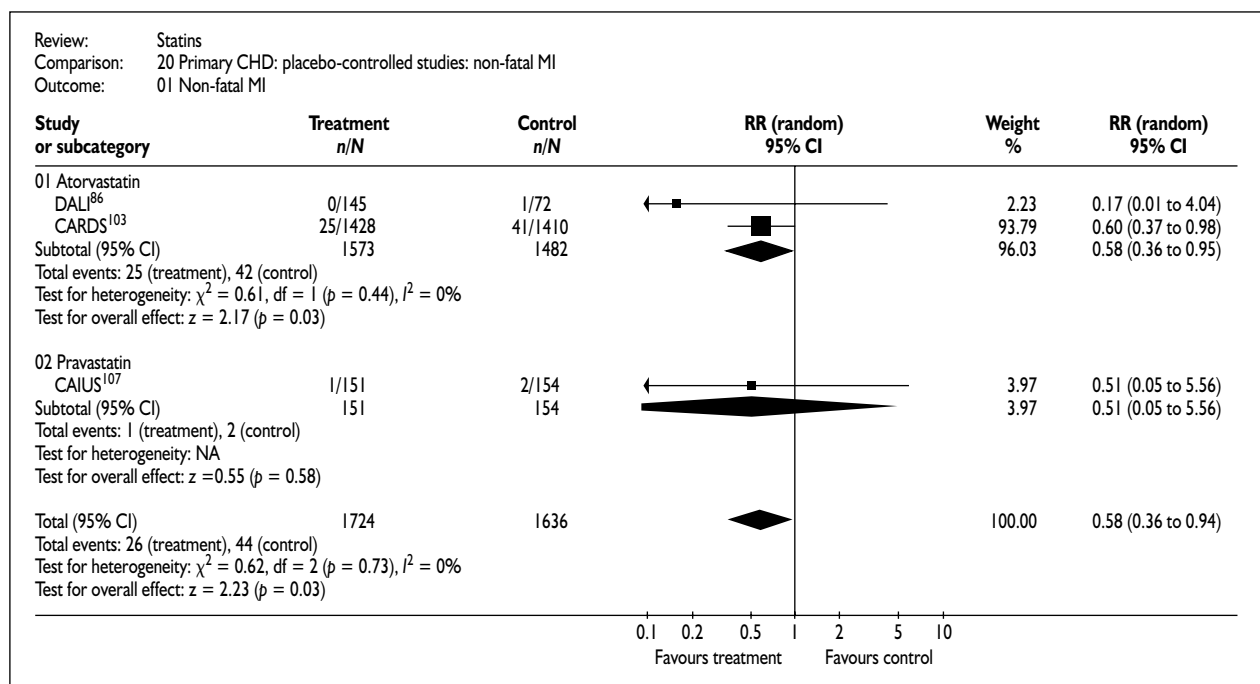**FIGURE 9** *Placebo-controlled studies: statins in primary CHD prevention – all-cause mortality*

FIGURE 10 *Placebo-controlled studies: statins in primary CHD prevention – non-fatal MI. NA, not applicable.*

only in relation to the first major vascular event (coronary death, non-fatal MI, fatal or non-fatal stroke or any revascularisation).

Meta-analysis indicates that, in patients without clinical CHD, statin therapy is associated with a statistically significant reduction in the risk of all-cause mortality, non-fatal MI, stable angina, CHD death plus non-fatal MI, and a composite of coronary death, non-fatal MI, fatal or non-fatal stroke or any revascularisation (*Figures 9–13*).

However, the studies were again too small to demonstrate significant results in relation to other fatal events, non-fatal stroke, PAD, unstable angina or coronary revascularisation (see Appendix 9, *Table 108* and *Figures 53–60*).

Assessment of effectiveness of statins in patients with CHD at baseline (secondary CHD prevention)
There is a larger body of evidence relating to the use of statins in patients with symptomatic CHD. Fourteen placebo-controlled studies were identified
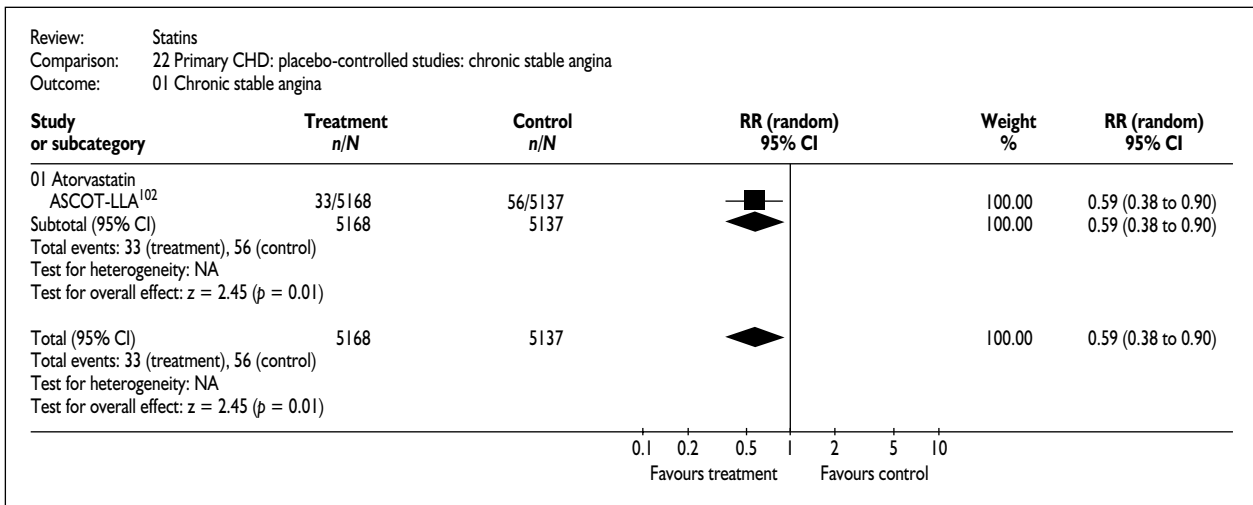
FIGURE 11 *Placebo-controlled studies: statins in primary CHD prevention – chronic stable angina*
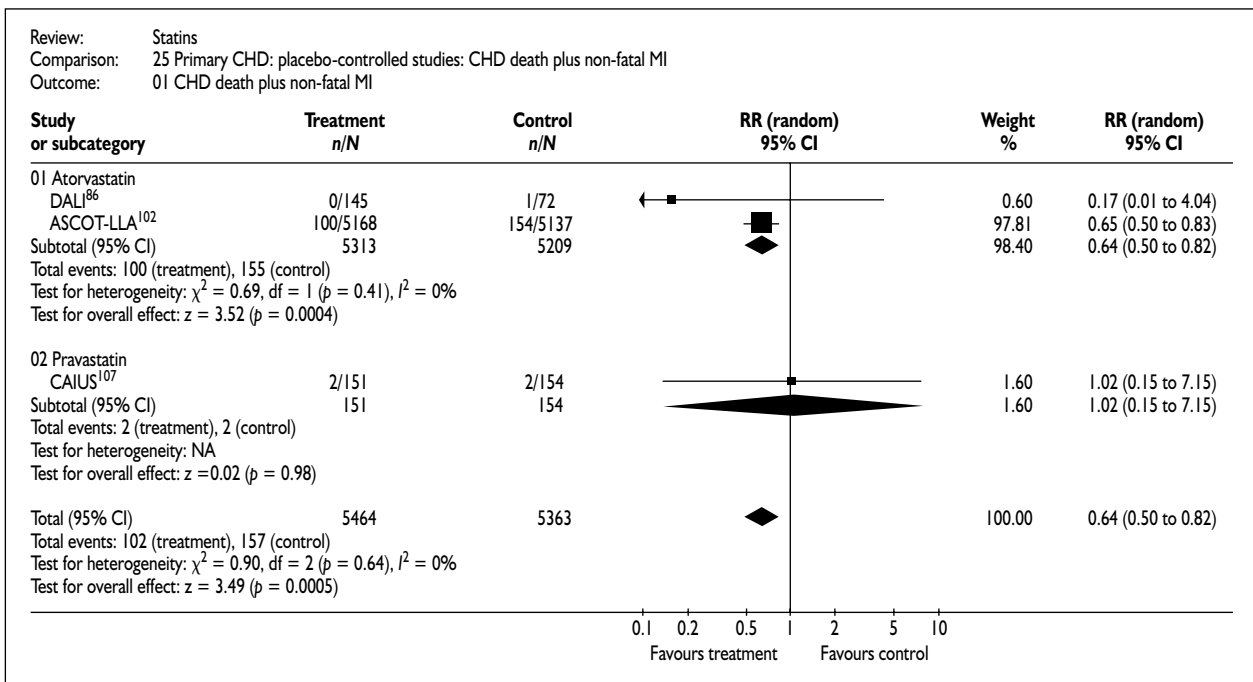
FIGURE 12 *Placebo-controlled studies: statins in primary CHD prevention – CHD death plus non-fatal MI*

that were carried out in this patient group and reported relevant clinical outcomes: LiSA,[93] FLARE,[108] FLORIDA,[109] LIPS,[110] CARE,[111] LIPID,[112] PLAC I,[113] PLAC II,[95] PREDICT,[114] REGRESS,[115] MAAS,[100] 4S,[97] CIS[98] and SCAT.[116] In addition, one study in a mixed population (HPS) presented data relating to a subgroup of patients with prior CHD, although only in relation to a composite end-point, first major vascular event (i.e. coronary death, non-fatal MI, fatal or non-fatal stroke or any revascularisation).[74]

Meta-analysis of the relevant data indicates that, in patients with clinical CHD, statin treatment was associated with a statistically significant reduction in the risk of all-cause mortality, cardiovascular mortality and CHD mortality, fatal and non-fatal MI, unstable angina and hospitalisation for unstable angina, non-fatal stroke, PAD, coronary revascularisation and a composite of CHD death and non-fatal MI (*Figures 14–24*). (For other analyses, see Appendix 10, *Table 109* and *Figures 61–64*.
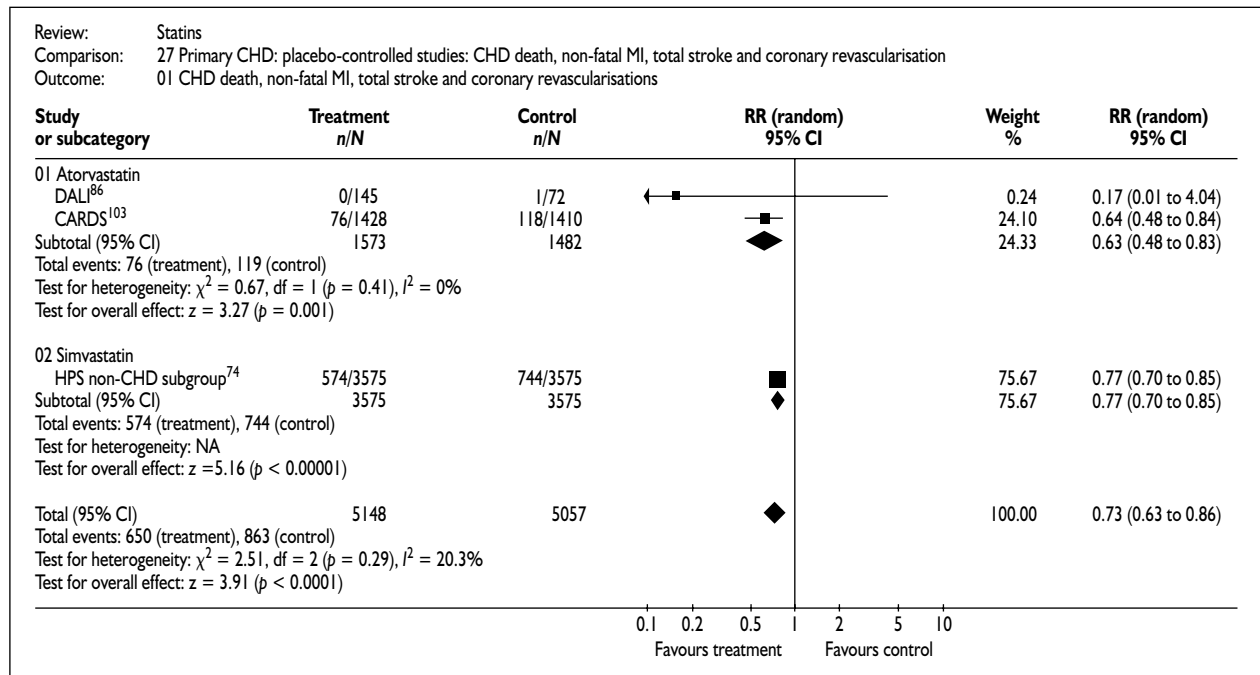
Review: Statins
Comparison: 27 Primary CHD: placebo-controlled studies: CHD death, non-fatal MI, total stroke and coronary revascularisation
Outcome: 01 CHD death, non-fatal MI, total stroke and coronary revascularisations

Study or subcategory	Treatment n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
01 Atorvastatin					
DALI[86]	0/145	1/72		0.24	0.17 (0.01 to 4.04)
CARDS[103]	76/1428	118/1410		24.10	0.64 (0.48 to 0.84)
Subtotal (95% CI)	1573	1482		24.33	0.63 (0.48 to 0.83)
Total events: 76 (treatment), 119 (control)					
Test for heterogeneity: $\chi^2 = 0.67$, df = 1 ($p = 0.41$), $I^2 = 0\%$					
Test for overall effect: $z = 3.27$ ($p = 0.001$)					
02 Simvastatin					
HPS non-CHD subgroup[74]	574/3575	744/3575		75.67	0.77 (0.70 to 0.85)
Subtotal (95% CI)	3575	3575		75.67	0.77 (0.70 to 0.85)
Total events: 574 (treatment), 744 (control)					
Test for heterogeneity: NA					
Test for overall effect: $z = 5.16$ ($p < 0.00001$)					
Total (95% CI)	5148	5057		100.00	0.73 (0.63 to 0.86)
Total events: 650 (treatment), 863 (control)					
Test for heterogeneity: $\chi^2 = 2.51$, df = 2 ($p = 0.29$), $I^2 = 20.3\%$					
Test for overall effect: $z = 3.91$ ($p < 0.0001$)					

0.1 0.2 0.5 1 2 5 10
Favours treatment   Favours control

FIGURE 13 *Placebo-controlled studies: statins in primary CHD prevention – CHD death, non-fatal MI, fatal or non-fatal stroke and coronary revascularisation*

Review: Statins
Comparison: 06 Secondary CHD: placebo-controlled studies
Outcome: 01 All-cause mortality

Study or subcategory	Treatment n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
01 Fluvastatin					
FLORIDA[109]	7/265	11/275		1.47	0.66 (0.26 to 1.68)
LIPS[110]	36/844	49/833		6.67	0.73 (0.48 to 1.10)
Subtotal (95% CI)	1109	1108		8.14	0.71 (0.49 to 1.05)
Total events: 43 (treatment), 60 (control)					
Test for heterogeneity: $\chi^2 = 0.03$, df = 1 ($p = 0.86$), $I^2 = 0\%$					
Test for overall effect: $z = 1.73$ ($p = 0.08$)					
02 Pravastatin					
CARE[111]	180/2081	196/2078		22.65	0.92 (0.76 to 1.11)
LIPID[112]	498/4512	633/4502		40.10	0.78 (0.70 to 0.88)
PLAC I[113]	4/206	6/202		0.83	0.65 (0.19 to 2.28)
PLAC II[95]	3/75	5/76		0.67	0.61 (0.15 to 2.45)
PREDICT[114]	4/347	1/348		0.27	4.01 (0.45 to 35.71)
REGRESS[115]	5/450	8/434		1.05	0.60 (0.20 to 1.83)
Subtotal (95% CI)	7671	7640		65.56	0.81 (0.74 to 0.89)
Total events: 694 (treatment), 849 (control)					
Test for heterogeneity: $\chi^2 = 4.50$, df = 5 ($p = 0.48$), $I^2 = 0\%$					
Test for overall effect: $z = 4.27$ ($p < 0.0001$)					
03 Simvastatin					
4S[97]	182/2221	356/2223		24.60	0.71 (0.59 to 0.85)
CIS[98]	1/129	4/125		0.28	0.24 (0.03 to 2.14)
SCAT[116]	13/230	6/230		1.42	2.17 (0.84 to 5.60)
Subtotal (95% CI)	2580	2578		26.30	0.90 (0.36 to 2.27)
Total events: 196 (treatment), 266 (control)					
Test for heterogeneity: $\chi^2 = 6.10$, df = 2 ($p = 0.05$), $I^2 = 67.2\%$					
Test for overall effect: $z = 0.22$ ($p = 0.82$)					
Total (95% CI)	11,360	11,326		100.00	0.80 (0.71 to 0.89)
Total events: 933 (treatment), 1175 (control)					
Test for heterogeneity: $\chi^2 = 11.93$, df = 10 ($p = 0.29$), $I^2 = 16.2\%$					
Test for overall effect: $z = 3.92$ ($p < 0.0001$)					

0.1 0.2 0.5 1 2 5 10
Favours treatment   Favours control

FIGURE 14 *Placebo-controlled studies: statins in secondary CHD prevention – all-cause mortality*

```
Review:        Statins
Comparison:    31 Secondary CHD: placebo-controlled studies: cardiovascular mortality
Outcome:       01 Cardiovascular mortality
```

Study or subcategory	Treatment n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
01 Fluvastatin					
FLORIDA[109]	6/265	11/275		1.10	0.57 (0.21 to 1.51)
Subtotal (95% CI)	265	275		1.10	0.57 (0.21 to 1.51)
Total events: 6 (treatment), 11 (control)					
Test for heterogeneity: NA					
Test for overall effect: z = 1.14 (p = 0.26)					
02 Pravastatin					
PLAC I[113]	3/206	3/202		0.42	0.98 (0.20 to 4.80)
CARE[111]	112/2081	130/2078		17.58	0.86 (0.67 to 1.10)
LIPID[112]	33/4512	433/4502		56.32	0.76 (0.67 to 0.87)
Subtotal (95% CI)	6799	6782		74.32	0.79 (0.70 to 0.89)
Total events: 446 (treatment), 566 (control)					
Test for heterogeneity: $\chi^2 = 0.78$, df = 2 (p = 0.68), $I^2 = 0\%$					
Test for overall effect: z = 3.96 (p < 0.0001)					
03 Simvastatin					
4S[97]	136/2221	207/2223		24.39	0.66 (0.53 to 0.81)
CIS[98]	1/129	2/125		0.19	0.48 (0.04 to 5.28)
Subtotal (95% CI)	2350	2348		24.58	0.66 (0.53 to 0.81)
Total events: 137 (treatment), 209 (control)					
Test for heterogeneity: $\chi^2 = 0.06$, df = 1 (p = 0.80), $I^2 = 0\%$					
Test for overall effect: z = 3.98 (p < 0.0001)					
Total (95% CI)	9414	9405		100.00	0.75 (0.68 to 0.83)
Total events: 589 (treatment), 786 (control)					
Test for heterogeneity: $\chi^2 = 3.35$, df = 5 (p = 0.65), $I^2 = 0\%$					
Test for overall effect: z = 5.51 (p < 0.00001)					

```
        0.1   0.2   0.5   1    2    5    10
              Favours treatment    Favours control
```

FIGURE 15 *Placebo-controlled studies: statins in secondary CHD prevention – CVD mortality*

After the conclusion of the placebo-controlled phase of the 4S trial, which lasted for a median of 5.4 years, patients were followed up for a further 5 years. During that 5-year period, when more than 80% of patients in each group were treated with lipid-lowering drugs, the relative risks of mortality were close to unity. However, over the whole 10.4-year period, the original simvastatin group had a reduced risk of all-cause and CHD mortality relative to the original placebo group,[117] suggesting that benefit may be gained from earlier rather than deferred statin therapy.

Assessment of effectiveness of statins in patients with CVD (including CHD) at baseline (secondary CVD prevention)

The evidence for the effectiveness of statins in patients with prior CVD is derived primarily from the studies of statins in secondary CHD prevention discussed in the section 'Assessment of effectiveness of statins in patients free of CHD at baseline (primary CHD prevention)' (p. 31). However, it also draws on the findings of three relatively small studies (Mohler 2003,[21] Aronow 2003[118] and Mondillo 2003[105]) in patients with intermittent claudication. In addition, ASCOT-

LLA and WOSCOPS reported data relating to subgroups with vascular disease at baseline; however, these results should be treated with caution because, as noted above, the subgroup analysis from WOSCOPS is not, and that from ASCOT-LLA may not be, a true randomised comparison.

It might be argued that two of the three studies in patients with intermittent claudication[21,105] may be classified as primary CHD prevention, as they do not specify whether any participants had CHD at baseline. However, since all of the participants in these studies had symptomatic CVD at baseline, it seemed more appropriate to categorise them as secondary CVD prevention.

As the additional studies are small, and do not report data relating to all end-points, the changes to the tabulation of the effects of statins in secondary CHD prevention are few and so small as to be barely worth mentioning (see Appendix 11).

The two studies that reported subgroup data did so in a form that did not allow them to be included in the meta-analysis. Both provided data

Review: Statins
Comparison: 32 Secondary CHD: placebo-controlled studies: CHD mortality
Outcome: 01 CHD mortality

Study or subcategory	Treatment n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
01 Fluvastatin					
FLARE[108]	3/409	7/425		0.65	0.45 (0.12 to 1.71)
LiSA[93]	2/187	4/178		0.41	0.48 (0.09 to 2.57)
FLORIDA[109]	2/265	9/275		0.51	0.23 (0.05 to 1.06)
LIPS[110]	13/844	24/833		2.62	0.53 (0.27 to 1.04)
Subtotal (95% CI)	1705	1711		4.19	0.46 (0.27 to 0.79)
Total events: 20 (treatment), 44 (control)					
Test for heterogeneity: $\chi^2 = 0.99$, df = 3 (p = 0.80), I^2 = 0%					
Test for overall effect: z = 2.84 (p = 0.004)					
02 Pravastatin					
PLAC I[113]	3/206	3/202		0.46	0.98 (0.20 to 4.80)
REGRESS[115]	3/450	5/434		0.58	0.58 (0.14 to 2.41)
CARE[111]	96/2081	119/2078		17.08	0.81 (0.62 to 1.05)
LIPID[112]	287/4512	373/4502		53.31	0.77 (0.66 to 0.89)
Subtotal (95% CI)	7249	7216		71.43	0.78 (0.68 to 0.88)
Total events: 389 (treatment), 500 (control)					
Test for heterogeneity: $\chi^2 = 0.34$, df = 3 (p = 0.95), I^2 = 0%					
Test for overall effect: z = 3.88 (p = 0.0001)					
03 Simvastatin					
4S[97]	111/2221	189/2223		22.76	0.59 (0.47 to 0.74)
MAAS[100]	4/193	4/188		0.62	0.97 (0.25 to 3.84)
CIS[98]	1/129	2/125		0.21	0.48 (0.04 to 5.28)
SCAT[116]	7/230	4/230		0.79	1.75 (0.52 to 5.90)
Subtotal (95% CI)	2773	2766		24.38	0.69 (0.45 to 1.05)
Total events: 123 (treatment), 199 (control)					
Test for heterogeneity: $\chi^2 = 3.47$, df = 3 (p = 0.32), I^2 = 13.5%					
Test for overall effect: z = 1.75 (p = 0.08)					
Total (95% CI)	11,727	11,693		100.00	0.72 (0.64 to 0.80)
Total events: 532 (treatment), 743 (control)					
Test for heterogeneity: $\chi^2 = 10.71$, df = 11 (p = 0.47), I^2 = 0%					
Test for overall effect: z = 6.00 (p < 0.00001)					

0.1 0.2 0.5 1 2 5 10
Favours treatment | Favours control

FIGURE 16 *Placebo-controlled studies: statins in secondary CHD prevention – CHD mortality*

relating to the effect of statins on the composite end-point of CHD death plus non-fatal MI: in the ASCOT-LLA CVD subgroup, the investigators calculated the unadjusted hazard ratio to be 0.80 (0.45 to 1.42, p = 0.4376), while in WOSCOPS the risk reduction was calculated to be 29% (–4 to 51%, p = 0.075). Both results are broadly similar to the relative risk of 0.74 (95% CI 0.68 to 0.79) calculated in the present meta-analysis.

Placebo-controlled studies: summary of results
The results reported above, and summarised in *Table 16*, suggest that, relative to placebo, in both primary and secondary prevention, statin therapy is associated with a statistically significant reduction in the risk of all-cause mortality and non-fatal MI, and of a composite end-point of CHD death plus non-fatal MI; in primary prevention, it is also associated with a reduction in the risk of stable angina. In secondary prevention, statin therapy is associated with a statistically

significant reduction in the risk of cardiovascular mortality, CHD mortality, fatal MI, non-fatal stroke, PAD, unstable angina and coronary revascularisation. As the confidence intervals for each outcome in each prevention category overlap, it is not possible to differentiate, in terms of relative risk, between the effectiveness of statins in primary and secondary prevention.

Although there is no significant difference, in terms of relative risk, between the effectiveness of statins in primary and secondary prevention, there is a difference in terms of absolute risk reduction, and therefore in terms of the number needed to treat to avoid an event. Because, as noted in the section 'Meta-analysis strategy' (p. 20), both absolute risk and numbers needed to treat include a time dimension, it is not possible to base those estimates on data from all the studies that have been combined in the meta-analyses of relative risk, as these vary in length. Therefore, for primary CHD

```
Review:        Statins
Comparison:    35 Secondary CHD: placebo-controlled studies: fatal MI
Outcome:       01 Fatal MI
```

Study or subcategory	Treatment n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
01 Fluvastatin					
LiSA[93]	2/187	3/178		1.65	0.63 (0.11 to 3.75)
FLORIDA[109]	0/265	3/275		0.60	0.15 (0.01 to 2.86)
Subtotal (95% CI)	452	453		2.25	0.43 (0.09 to 1.98)
Total events: 2 (treatment), 6 (control)					
Test for heterogeneity: $\chi^2 = 0.71$, df = 1 ($p = 0.40$), $I^2 = 0\%$					
Test for overall effect: z = 1.08 ($p = 0.28$)					
02 Pravastatin					
PLAC I[113]	1/206	1/202		0.68	0.98 (0.06 to 15.57)
REGRESS[115]	1/450	1/434		0.68	0.96 (0.06 to 15.37)
CARE[111]	24/2081	38/2078		20.29	0.63 (0.38 to 1.05)
PREDICT[114]	1/347	0/348		0.51	3.01 (0.12 to 73.60)
LIPID[112]	53/4512	89/4502		45.84	0.59 (0.42 to 0.83)
Subtotal (95% CI)	7596	7564		68.01	0.62 (0.47 to 0.82)
Total events: 80 (treatment), 129 (control)					
Test for heterogeneity: $\chi^2 = 1.21$, df = 4 ($p = 0.88$), $I^2 = 0\%$					
Test for overall effect: z = 3.40 ($p = 0.0007$)					
03 Simvastatin					
4S[97]	30/2221	63/2223		28.15	0.48 (0.31 to 0.73)
MAAS[100]	1/193	2/188		0.91	0.49 (0.04 to 5.33)
SCAT[116]	1/230	1/230		0.68	1.00 (0.06 to 15.89)
Subtotal (95% CI)	2644	2641		29.74	0.49 (0.32 to 0.74)
Total events: 32 (treatment), 66 (control)					
Test for heterogeneity: $\chi^2 = 0.27$, df = 2 ($p = 0.87$), $I^2 = 0\%$					
Test for overall effect: z = 3.38 ($p = 0.0007$)					
Total (95% CI)	10,692	10,658		100.00	0.57 (0.45 to 0.72)
Total events: 114 (treatment), 201 (control)					
Test for heterogeneity: $\chi^2 = 3.19$, df = 9 ($p = 0.96$), $I^2 = 0\%$					
Test for overall effect: z = 4.81 ($p < 0.00001$)					

```
0.1  0.2      0.5    1     2    5    10
   Favours treatment   Favours control
```

FIGURE 17 *Placebo-controlled studies: statins in secondary CHD prevention – fatal MI*

prevention, absolute risk and numbers needed to treat were derived from the largest study of primary CHD prevention, the ASCOT-LLA study, which has a median follow-up of 3.3 years (*Table 17*).

Numbers needed to treat to avoid key outcomes were also calculated for the three largest studies of secondary CHD prevention: 4S, CARE and LIPID (*Table 18*). The length of time to which the treatment effect applies is 5.0 years for CARE, 5.4 years for 4S and 6.1 years for LIPID.

Unfortunately, the studies included in *Tables 17* and *18* do not provide data on the number of patients suffering CHD mortality, non-fatal MI or any stroke, so the number needed to treat to avoid any of these three outcomes cannot be calculated, as the addition of the figures relating to patients who had suffered a stroke to the total of patients who had suffered CHD death or a non-fatal MI would incur the risk of double-counting.

Because the studies differ in length, the absolute risk reduction and numbers needed to treat relate to different lengths of time. Nonetheless, it is clear that the number of people needed to treat to avoid an event is lower in secondary prevention than in primary prevention, even though the ASCOT-LLA population was a primary prevention population which was at relatively high risk of a cardiovascular event. At first sight, it seems surprising that the absolute risk of CHD mortality or non-fatal MI is so much higher, and the number needed to treat to avoid such an event consequently considerably smaller, in the 4S study compared with the CARE and LIPID trials. This does not seem to be due to differences in the study populations, and is more likely to be due to the level of cross-over in those trials: fewer than 1% of patients in 4S who were randomised to placebo received lipid-lowering drugs,[97] compared with 8% in CARE[111] and 24% in LIPID.[112]

37

Review: Statins
Comparison: 36 Secondary CHD: placebo-controlled studies: non-fatal MI
Outcome: 01 Non-fatal MI

Study or subcategory	Treatment n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
01 Fluvastatin					
FLARE[108]	3/409	10/425		1.28	0.31 (0.09 to 1.12)
LiSA[93]	0/187	1/178		0.21	0.32 (0.01 to 7.74)
LIPS[110]	30/844	38/833		8.92	0.78 (0.49 to 1.25)
Subtotal (95% CI)	1440	1436		10.41	0.69 (0.45 to 1.07)
Total events: 33 (treatment), 49 (control)					
Test for heterogeneity: $\chi^2 = 1.97$, df = 2 ($p = 0.37$), $I^2 = 0\%$					
Test for overall effect: z = 1.67 ($p = 0.09$)					
02 Pravastatin					
PLAC I[113]	7/206	16/202		2.77	0.43 (0.18 to 1.02)
REGRESS[115]	7/450	12/434		2.45	0.56 (0.22 to 1.42)
CARE[111]	182/2081	231/2078		40.12	0.79 (0.65 to 0.95)
PREDICT[114]	4/347	4/348		1.11	1.00 (0.25 to 3.98)
Subtotal (95% CI)	3084	3062		46.45	0.76 (0.64 to 0.91)
Total events: 200 (treatment), 263 (control)					
Test for heterogeneity: $\chi^2 = 2.37$, df = 3 ($p = 0.50$), $I^2 = 0\%$					
Test for overall effect: z = 3.05 ($p = 0.002$)					
03 Simvastatin					
4S[97]	164/2221	270/2223		40.00	0.61 (0.51 to 0.73)
CIS[98]	1/129	5/125		0.47	0.19 (0.02 to 1.64)
SCAT[116]	10/230	9/230		2.68	1.11 (0.46 to 2.68)
Subtotal (95% CI)	2580	2578		43.15	0.66 (0.40 to 1.08)
Total events: 175 (treatment), 284 (control)					
Test for heterogeneity: $\chi^2 = 2.87$, df = 2 ($p = 0.24$), $I^2 = 30.2\%$					
Test for overall effect: z = 1.67 ($p = 0.10$)					
Total (95% CI)	7104	7076		100.00	0.69 (0.59 to 0.79)
Total events: 408 (treatment), 596 (control)					
Test for heterogeneity: $\chi^2 = 9.82$, df = 9 ($p = 0.37$), $I^2 = 8.3\%$					
Test for overall effect: z = 5.06 ($p < 0.00001$)					

0.1 0.2 0.5 1 2 5 10
Favours treatment   Favours control

FIGURE 18 *Placebo-controlled studies: statins in secondary CHD prevention – non-fatal MI*

It is important that patients with CHD risk factors other than, or additional to, elevated cholesterol levels should receive appropriate treatment for those risk factors, both because of their potential contribution to CHD risk and because they may also be associated with other health problems (as in the case of smoking and lung cancer, or diabetes and diabetic retinopathy and neuropathy). However, it is not clear to what extent optimising the treatment of CHD risk factors other than cholesterol impacts on the effectiveness of statins. One placebo-controlled trial, ASCOT-LLA, recruited hypertensive patients with total cholesterol concentrations of 6.5 mmol l^{-1} or lower; these patients received aggressive antihypertensive therapy.[102] In that study, the relative risk of CHD death plus non-fatal MI (0.65, 95% CI 0.50 to 0.83) was comparable with the overall result of the meta-analysis (RR 0.74, 95% CI 0.71 to 0.77; see *Figure 7*).

Placebo-controlled studies: results from Bayesian meta-analysis

A Bayesian meta-analysis was undertaken in addition to the classical meta-analysis reported in the preceding sections. The Bayesian evidence synthesis provides the same inputs to the model as the classical meta-analysis; namely, the relative risk of the effect of statins for the event states in the model. The Bayesian method has the important benefit of being able to incorporate correlations between outcomes in the subsequent economic analysis.

Since some of the five events are mutually exclusive, conditional relative risks were considered as shown in *Table 19*.

The relative risks from the Bayesian analysis are generally similar to those from the standard meta-analysis, given in the first column of *Table 16*.
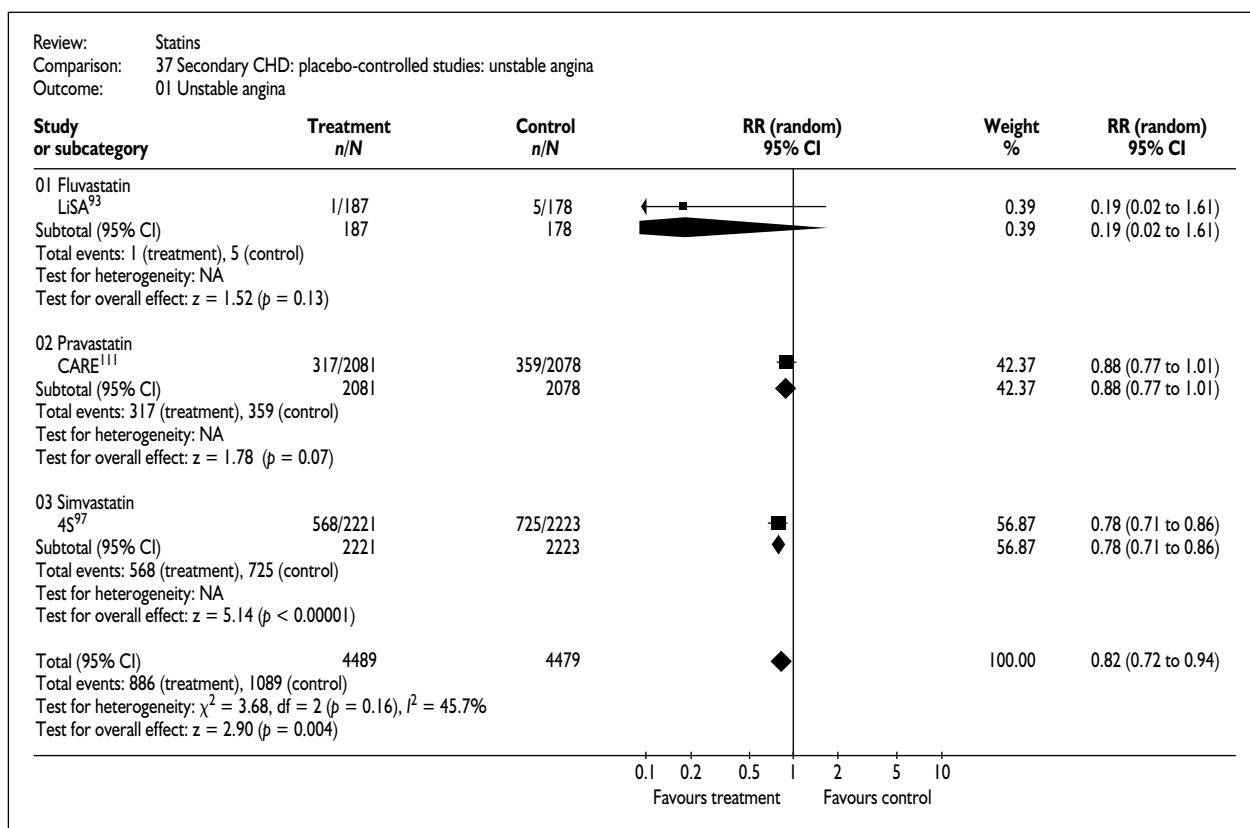
FIGURE 19 *Placebo-controlled studies: statins in secondary CHD prevention – unstable angina*
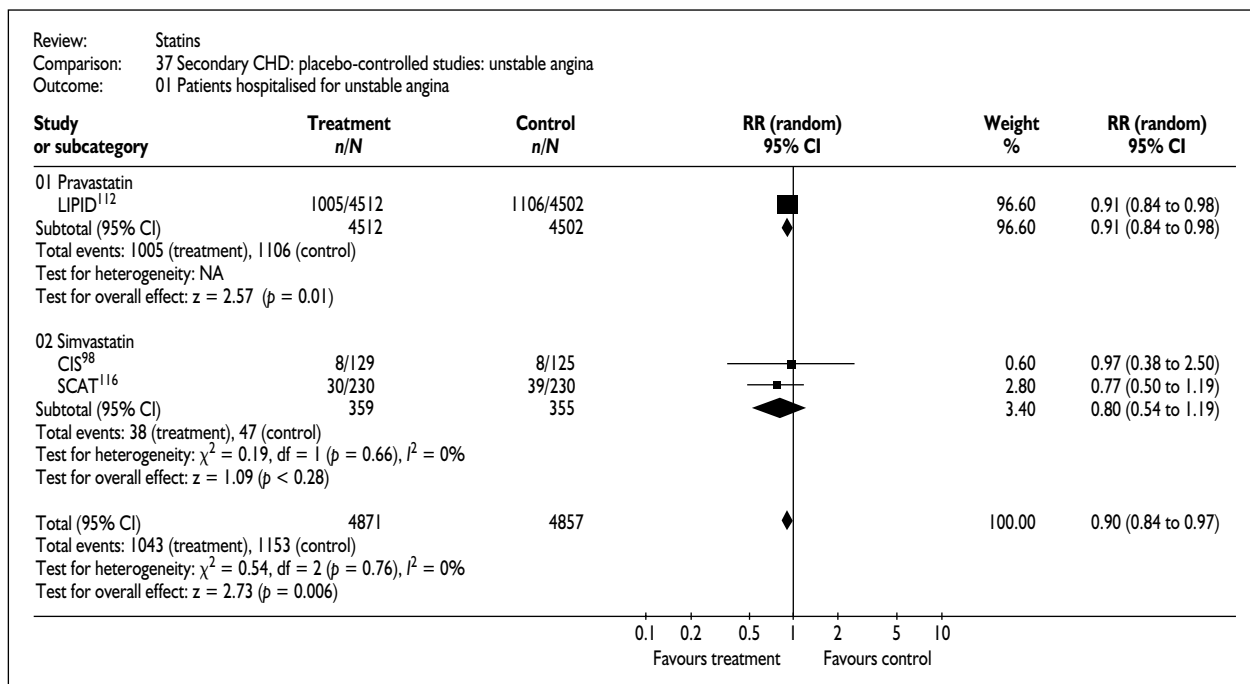
FIGURE 20 *Placebo-controlled studies: statins in secondary CHD prevention – hospitalisation for unstable angina*

Review: Statins
Comparison: 06 Secondary CHD: placebo-controlled studies
Outcome: 02 Non-fatal stroke

Study or subcategory	Treatment n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
01 Pravastatin					
CARE[111]	42/2081	71/2078		37.47	0.59 (0.41 to 0.86)
LIPID[112]	147/4512	177/4502		61.54	0.83 (0.67 to 1.03)
PLAC I[113]	0/206	2/202		0.99	0.20 (0.01 to 4.06)
Subtotal (95% CI)	6799	6782		100.00	0.72 (0.53 to 0.97)

Total events: 189 (treatment), 250 (control)
Test for heterogeneity: $\chi^2 = 3.11$, df = 2 ($p = 0.21$), $I^2 = 35.8\%$
Test for overall effect: $z = 2.13$ ($p = 0.03$)

| Total (95% CI) | 6799 | 6782 | | 100.00 | 0.72 (0.53 to 0.97) |

Total events: 189 (treatment), 250 (control)
Test for heterogeneity: $\chi^2 = 3.11$, df = 2 ($p = 0.21$), $I^2 = 35.8\%$
Test for overall effect: $z = 2.13$ ($p = 0.03$)

0.1 0.2 0.5 1 2 5 10
Favours treatment   Favours control

FIGURE 21 *Placebo-controlled studies: statins in secondary CHD prevention – non-fatal stroke*

Review: Statins
Comparison: 39 Secondary CHD: placebo-controlled studies: new or worsening intermittent claudication
Outcome: 01 New or worsening intermittent claudication

Study or subcategory	Treatment n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
03 Simvastatin					
4S[97]	52/2221	81/2223		100.00	0.64 (0.46 to 0.91)
Subtotal (95% CI)	2221	2223		100.00	0.64 (0.46 to 0.91)

Total events: 52 (treatment), 81 (control)
Test for heterogeneity: NA
Test for overall effect: $z = 2.53$ ($p = 0.01$)

| Total (95% CI) | 2221 | 2223 | | 100.00 | 0.64 (0.46 to 0.91) |

Total events: 52 (treatment), 81 (control)
Test for heterogeneity: NA
Test for overall effect: $z = 2.53$ ($p = 0.01$)

0.1 0.2 0.5 1 2 5 10
Favours treatment   Favours control

FIGURE 22 *Placebo-controlled studies: statins in secondary CHD prevention – new or worsening intermittent claudication*

In the case of relative risk of CVD death in *Table 18*, this is the risk of CVD death having excluded CHD death and is therefore most comparable with stroke mortality from *Table 16*. In both cases the confidence intervals cross 1, indicating that the impact is non-significant.

Placebo-controlled studies: discussion of results
The results from the placebo-controlled trials are likely to be conservative as a result of the degree of cross-over (use of lipid-lowering therapies, in particular statins, in the placebo arm, and non-compliance with study therapy in the statin arm) reported in many studies. In some studies, the use of lipid-lowering therapy in the placebo arm was preplanned. For example, in ASCOT-LLA, patients whose dyslipidaemia was judged by their

physician to require additional lipid-lowering therapy could receive open-label treatment in addition to trial treatment: after 3 years of follow-up, 9% of the placebo group had been prescribed open-label statins.[102] Similarly, in LIPS, patients whose total cholesterol exceeded 7.2 mmol l^{-1} for 3 months or longer could discontinue study therapy at the investigator's discretion and receive an open-label statin or other lipid-lowering therapy. As a result, 10.7% of patients in the treatment arm and 24% in the placebo arm started taking other lipid-lowering medications (mainly statins) before their first major adverse cardiac event or completion of follow-up.[110] In the LIPID study, although study personnel and patients remained unaware of lipid results from the core laboratory,[119] the patient's general care was at the

Review:	Statins
Comparison:	42 Secondary CHD: placebo-controlled studies: CABG or PTCA
Outcome:	01 CABG or PTCA

Study or subcategory	Treatment n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
01 Fluvastatin					
LiSA[93]	0/87	0/178			Not estimable
LIPS[110]	167/844	193/833		17.08	0.85 (0.71 to 1.03)
Subtotal (95% CI)	1031	1011		17.08	0.85 (0.71 to 1.03)
Total events: 167 (treatment), 193 (control)					
Test for heterogeneity: NA					
Test for overall effect: z = 1.68 (p = 0.09)					
02 Pravastatin					
CARE[111]	294/2081	391/2078		22.23	0.75 (0.65 to 0.86)
PREDICT[114]	66/347	75/348		9.22	0.88 (0.66 to 1.19)
LIPID[112]	585/4512	708/4502		27.26	0.82 (0.74 to 0.91)
Subtotal (95% CI)	6940	6928		58.70	0.80 (0.74 to 0.87)
Total events: 945 (treatment), 174 (control)					
Test for heterogeneity: $\chi^2 = 1.55$, df = 2 (p = 0.46), $I^2 = 0\%$					
Test for overall effect: z = 5.43 (p < 0.00001)					
03 Simvastatin					
4S[97]	252/2221	383/2223		21.08	0.66 (0.57 to 0.76)
CIS[98]	5/129	4/125		0.68	1.21 (0.33 to 4.41)
SCAT[116]	13/320	28/230		2.50	0.46 (0.25 to 0.87)
Subtotal (95% CI)	2580	2578		24.22	0.65 (0.56 to 0.76)
Total events: 270 (treatment), 415 (control)					
Test for heterogeneity: $\chi^2 = 2.01$, df = 2 (p = 0.37), $I^2 = 0.5\%$					
Test for overall effect: z = 5.67 (p < 0.00001)					
Total (95% CI)	10,551	10,517		100.00	0.77 (0.69 to 0.85)
Total events: 1382 (treatment), 1782 (control)					
Test for heterogeneity: $\chi^2 = 11.10$, df = 6 (p = 0.09), $I^2 = 46.0\%$					
Test for overall effect: z = 4.94 (p < 0.00001)					

0.1 0.2 0.5 1 2 5 10
Favours treatment   Favours control

FIGURE 23 *Placebo-controlled studies: statins in secondary CHD prevention – coronary revascularisation*

discretion of the patient's own doctor, and this allowed changes in lipid treatment to be made in the light of local cholesterol results.[120] The investigators recognised that the difference in the incidence of events between treatment groups was likely to have been reduced by the large numbers of patients in the placebo group who ultimately received cholesterol-lowering therapy outside the study combined with those in the pravastatin group who discontinued treatment.[112]

In other studies, the use of lipid-lowering drugs in the placebo arm was not preplanned. When the results of 4S were published in 1994 (less than half way through SCAT), the SCAT investigators deemed it unethical to keep on placebo patients whose total cholesterol persistently exceeded 5.5 mmol l^{-1}. Consequently, the protocol was modified to permit such patients to be identified and reallocated, in a double-blind fashion, to simvastatin. It is not stated how many patients this affected.[116] In addition, in LIPS, there was anecdotal evidence that many patients were aware of their total cholesterol levels as these had been tested by primary care physicians who were not

involved in LIPS; as a result, these patients were no longer blinded to their treatment allocation.[91]

Only two studies reported mean statin use in both the placebo and treatment arms, enabling an estimate of the extent to which the intention-to-treat (ITT) analysis might underestimate the full potential effect of statin treatment. In HPS, average statin use during the scheduled treatment period was said to be 85% in the simvastatin-allocated group and 17% in the placebo-allocated group; thus, the average absolute difference in statin use between all those randomised to simvastatin and all those randomised to placebo was 67% (85 – 17%), suggesting that the ITT analyses represent the effects of about two-thirds of the statin group taking 40 mg per day simvastatin.[74] However, non-study statin use in the placebo arm was not random, but was more common in patients with diagnosed CHD at entry, in younger participants and, particularly, in those with higher baseline total cholesterol or LDL-C, and therefore the reduction in the apparent effect of therapy in the statin arm may be even greater than suggested. In CARDS, mean non-compliance
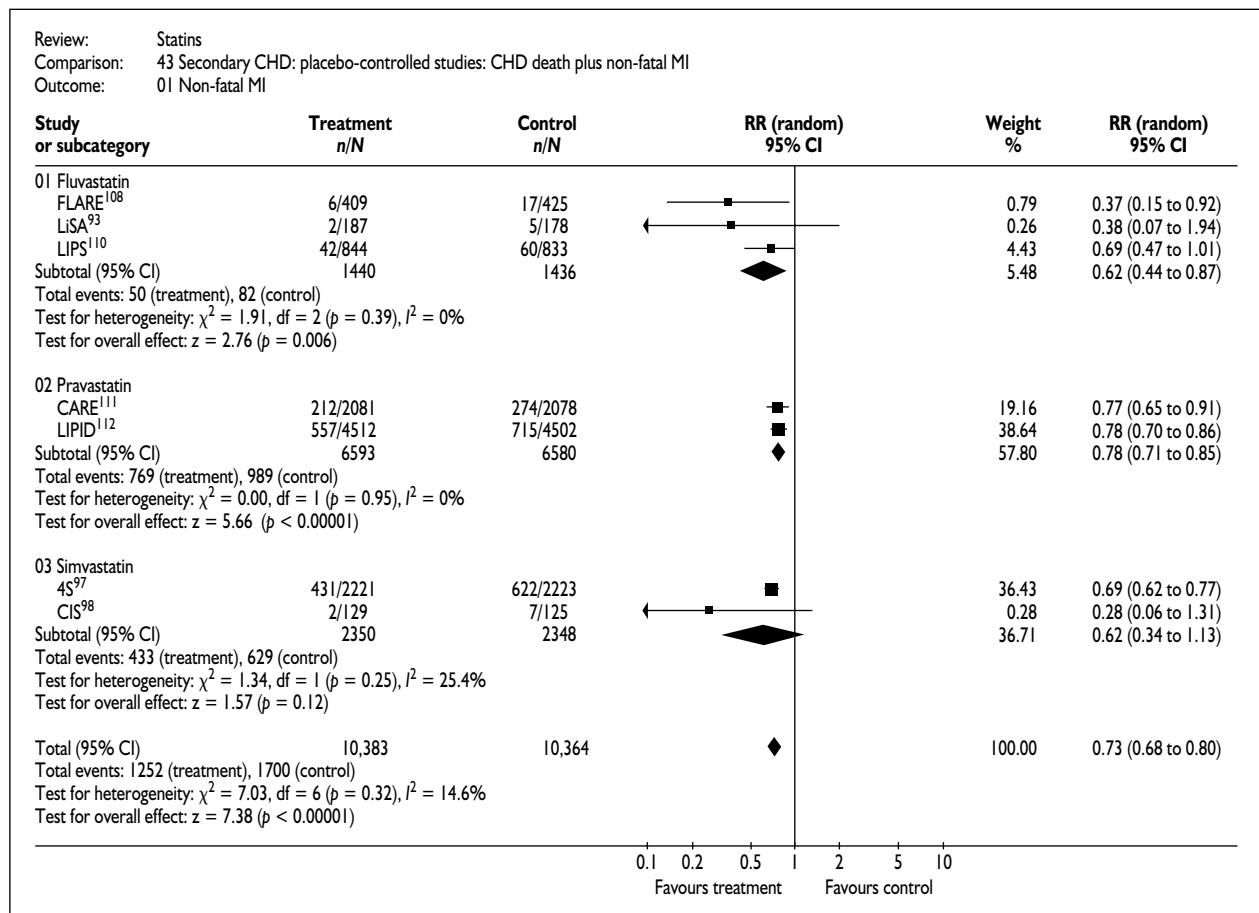
FIGURE 24 *Placebo-controlled studies: statins in secondary CHD prevention – CHD death plus non-fatal MI*

in the study arm was 15% and mean statin use in the placebo arm 9%,[103] suggesting a potential reduction of 24% in the treatment effect.

The generalisability of the results reported above is limited by the exclusion, in some studies, of patients who were hypersensitive to or intolerant of statins,[93,121,122] who were known to be unresponsive to statins,[74,115,122,123] or who were not adequately compliant with study medication during a placebo run-in phase.[120,121] A considerable proportion of potential participants may have been excluded in this way: in HPS, around 30% of those who entered the run-in phase either chose not to continue in the study or were deemed unlikely to be compliant in the long term.[121]

Direct statin–statin comparisons
Quantity and quality of research available: direct statin–statin comparisons
Three studies were identified which directly compared two different statins and which reported clinical outcomes. All three were in patients with symptomatic CHD. The 3T study compared

atorvastatin with simvastatin in adults with CHD and dyslipidaemia.[83] PROVE IT-TIMI compared atorvastatin with pravastatin in patients who had been hospitalised with acute coronary syndrome (either AMI or high-risk unstable angina) in the previous 10 days.[124] The REVERSAL study compared atorvastatin with pravastatin in patients requiring coronary angiography for a clinical indication.[90] (For further details of these studies, see Appendix 12.)

A further two studies of 6 months or longer were identified which compared the LDL-C-lowering efficacy of rosuvastatin (5 and 10 mg) with that of atorvastatin in patients with hypercholesterolaemia in northern Europe (study 4522IL/0026[125]) and with that of pravastatin or simvastatin in similar patients in the USA (study 4522IL/0028[126]). These studies did not report clinical outcomes. In both studies, each statin was started at the lowest stated dose, and this dose was maintained for a 12-week period. During the following 40-week period, the dose could be sequentially doubled at weeks 12, 20, 28, 36 and 44 in study 4522IL/0026,[125] and at

TABLE 16 Placebo-controlled trials of statin therapy: relative risk of event by prevention category (95% CI)

Outcome	All studies	Primary CVD prevention	Primary CHD prevention	Secondary CHD prevention	Secondary CVD prevention
All-cause mortality	0.84 (0.78 to 0.90)[a]	0.73 (0.53 to 1.01)	0.83 (0.70 to 0.98)[a]	0.80 (0.71 to 0.89)[a]	0.80 (0.71 to 0.89)[a]
Cardiovascular mortality	0.79 (0.74 to 0.85)[a]	0.67 (0.40 to 1.10)	0.83 (0.63 to 1.08)	0.75 (0.68 to 0.83)[a]	0.75 (0.68 to 0.83)[a]
CHD mortality	0.77 (0.72 to 0.83)[a]	0.86 (0.49 to 1.52)	0.86 (0.49 to 1.52)	0.72 (0.64 to 0.80)[a]	0.72 (0.64 to 0.80)[a]
Stroke mortality	0.92 (0.74 to 1.14)	0.20 (0.02 to 1.69)	0.20 (0.02 to 1.69)	1.07 (0.67 to 1.71)	1.08 (0.67 to 1.72)
Non-fatal stroke	0.75 (0.63 to 0.90)	0.66 (0.38 to 1.15)	0.66 (0.38 to 1.15)	0.72 (0.53 to 0.97)[a]	0.75 (0.59 to 0.95)
TIA	0.79 (0.68 to 0.91)	No data	No data	0.66 (0.37 to 1.17)	0.66 (0.37 to 1.17)
PAD	0.61 (0.13 to 2.78)	No data	0.59 (0.66 to 1.56)	0.64 (0.46 to 0.91)	0.58 (0.42 to 0.80)[a]
Fatal MI	0.55 (0.44 to 0.67)[a]	0.60 (0.12 to 3.04)	0.60 (0.12 to 3.04)	0.57 (0.45 to 0.72)[a]	0.57 (0.45 to 0.72)[a]
Non-fatal MI	0.70 (0.63 to 0.77)[a]	0.60 (0.37 to 0.97)[a]	0.58 (0.36 to 0.94)[a]	0.69 (0.59 to 0.79)[a]	0.69 (0.61 to 0.78)[a]
Stable angina	0.59 (0.38 to 0.90)[a]	No data	0.59 (0.38 to 0.90)[a]	No data	No data
Unstable angina	0.82 (0.74 to 0.90)[a]	0.77 (0.29 to 2.06)	0.87 (0.53 to 1.43)	0.82 (0.72 to 0.94)[a]	0.82 (0.72 to 0.94)[a]
Patients hospitalised for unstable angina	0.88 (0.84 to 0.94)[a]	No data	No data	0.90 (0.84 to 0.97)[a]	0.90 (0.84 to 0.97)[a]
CABG	0.74 (0.67 to 0.82)[a]	No data	No data	0.76 (0.66 to 0.87)[a]	0.76 (0.66 to 0.87)[a]
PTCA	0.78 (0.68 to 0.90)[a]	No data	No data	0.79 (0.67 to 0.94)[a]	0.79 (0.67 to 0.94)[a]
CABG + PTCA	0.75 (0.70 to 0.81)[a]	0.72 (0.49 to 1.21)	0.72 (0.43 to 1.21)	0.77 (0.69 to 0.85)[a]	0.77 (0.69 to 0.85)[a]
CHD death plus non-fatal MI	0.74 (0.71 to 0.77)[a]	0.66 (0.46 to 0.96)[a]	0.64 (0.50 to 0.82)[a]	0.73 (0.68 to 0.80)[a]	0.74 (0.69 to 0.79)[a]

[a] Statistically significant ($p < 0.05$).

TABLE 17 Primary CHD prevention: absolute risk reduction and NNT

ASCOT-LLA study	Risk of event in placebo arm	Absolute risk reduction (95% CI)	NNT for approximately 3 years to avoid an event (95% CI)
All-cause mortality	4.13%	0.55% (–0.20 to 1.29)	183[a]
CHD mortality	NR		
Total stroke	2.36%	0.63% (0.09 to 1.18)	158 (84.8 to 1141.4)
CHD mortality + non-fatal MI	3.00%	1.06% (0.46 to 1.66)	95 (60.2 to 215.5)

[a] CIs not calculated because the 95% CI for the absolute risk reduction extends from a negative number (indicating that treatment may be harmful) to a positive number (indicating that treatment may be beneficial).

TABLE 18 *Secondary CHD prevention: absolute risk reduction and NNT*

Study/outcome	Risk of event in placebo arm	Absolute risk reduction (95% CI)	NNT to avoid an event (95% CI)
4S			
All-cause mortality	11.52%	3.32% (1.57 to 5.07)	31 (19.7 to 63.6)
CHD mortality	8.50%	3.50% (2.03 to 4.98)	29 (20.1 to 49.2)
Total stroke	NR		
CHD mortality + non-fatal MI	27.98%	8.57% (6.09 to 11.06)	12 (9.0 to 16.4)
CARE			
All-cause mortality	9.43%	0.78% (−0.96 to 2.53)	128[a]
CHD mortality	5.73%	1.11% (−0.23 to 2.46)	90[a]
Total stroke	3.66%	1.16% (0.11 to 2.21)	87 (45.3 to 915.6)
CHD mortality + non-fatal MI	13.19%	3.00% (1.05 to 4.95)	34 (20.2 to 95.5)
LIPID			
All-cause mortality	14.06%	3.02% (1.66 to 4.39)	34 (22.8 to 60.4)
CHD mortality	8.29%	1.92% (0.85 to 3.00)	52 (33.3 to 117.7)
Total stroke	4.53%	0.79% (−0.04 to 1.61)	128[a]
CHD mortality + non-fatal MI	15.88%	3.54% (2.10 to 4.97)	29 (20.1 to 47.6)

[a] CIs not calculated because the 95% CI for the absolute risk reduction extends from a negative number (indicating that treatment may be harmful) to a positive number (indicating that treatment may be beneficial).

TABLE 19 *Relative risks from Bayesian meta-analysis*

	No. of trials	Mean	2.5th percentile	Median	97.5th percentile
RR of CHD death	27	0.740	0.640	0.741	0.824
RR of CVD death, conditional on no CHD death	12	0.854	0.601	0.851	1.106
RR of unstable angina, conditional on no death	7	0.716	0.293	0.754	0.990
RR of non-fatal MI, conditional on no death	24	0.656	0.553	0.657	0.746
RR of non-fatal stroke, conditional on no death	11	0.769	0.634	0.769	0.906

weeks 20, 28, 36 and 44 in study 4522IL/0028,[126] up to the maximum stated dose (for details, see Appendix 12).

In study 4522IL/0026, mean doses over the 40-week titration period were as follows:

- group 1: 9.3 mg per day rosuvastatin
- group 2: 13.4 mg per day rosuvastatin
- group 3: 20.8 mg per day atorvastatin.[125]

In study 4522IL/0028, mean doses over the 40-week titration period were as follows:

- group 1: not reported
- group 2: 13.8 mg per day rosuvastatin
- group 3: 32.6 mg per day pravastatin
- group 4: 36.3 mg per day simvastatin.[126]

Assessment of effectiveness: direct statin–statin comparisons
Although the PROVE IT-TIMI and REVERSAL studies compared the same interventions, it was not possible to combine their results in a meta-analysis because PROVE IT-TIMI only reported the percentage of patients in each arm, rather than the number, who experienced an event. The results of the individual studies are therefore summarised in *Table 20*.

Rosuvastatin appeared to be more effective than atorvastatin, pravastatin and simvastatin in reducing total cholesterol and LDL-C (*Table 21*). However, it should be noted that the study investigators were able to increase the dose of rosuvastatin to 80 mg, a dose that is not licensed in the UK; the other statins were used within their current licensed doses.

Direct statin–statin comparisons: discussion
As may be seen, the only statistically significant results are those reported by the PROVE IT-TIMI investigators for hospitalisations for unstable angina, coronary revascularisations and two composite end-points; in each case, the results favour atorvastatin. However, no significant

TABLE 20 *Direct statin–statin comparisons: statins in secondary CHD prevention: relative risk, or relative risk reduction, of event with atorvastatin compared with pravastatin or simvastatin*

Outcome	3T: atorvastatin 20–40 mg per day vs simvastatin 20–40 mg per day	PROVE IT-TIMI: atorvastatin 80 mg per day vs pravastatin 40 mg per day (risk reductions calculated by investigators)	REVERSAL: atorvastatin 80 mg per day vs pravastatin 40 mg per day
All-cause mortality	NR	28%, $p = 0.07$	1.00 (0.06 to 15.92)
Total stroke	2.90 (0.12 to 70.97)	–9%, ns	1.00 (0.06 to 15.92)
Total MI	0.32 (0.01 to 7.89)	13%, ns	0.57 (0.17 to 1.93)
Hospitalisation for unstable angina	NR	29%, $p = 0.02$	NR
Coronary revascularisations	NR	14%, $p = 0.04$	NR
CHD death or non-fatal MI	NR	18%, $p = 0.06$	NR
CHD death, non-fatal MI or coronary revascularisation	NR	14%, $p = 0.029$	NR
All-cause mortality, MI, hospitalisation for documented unstable angina, revascularisation (performed at least 30 days after randomisation) stroke	NR	16% (95% CI 5 to 26%), $p = 0.005$	NR

ns, not significant.

TABLE 21 *Mean percentage change in lipid variables from baseline at 52 weeks (standard error)*

	Rosuvastatin 5–80 mg per day	Rosuvastatin 10–80 mg per day	Atorvastatin 10–80 mg per day	Pravastatin 20–40 mg per day	Simvastatin 20–80 mg per day
Study 4522IL/0026[125]					
Total cholesterol	–34 (0.9)	–38 (1.0)	–33 (0.9)	NA	NA
LDL-C	–47 (1.2)	–53 (1.2)	–44 (1.1)	NA	NA
HDL-C	+2 (1.3)	+3 (1.4)	–1 (1.3)	NA	NA
Triglycerides	–20 (2.4)	–21 (2.6)	–19 (2.4)	NA	NA
LDL-C/HDL-C	–48 (1.3)	–54 (1.4)	–43 (1.3)	NA	NA
Total cholesterol/HDL-C	–35 (1.1)	–40 (1.1)	–32 (1.0)	NA	NA
Study 4522IL/0028[126]					
Total cholesterol	–30.1 (1.1)	–34.2 (1.1)	NA	–22.8 (1.1)	–27.0 (1.1)
LDL-C	–41.6 (1.4)	–48.0 (1.4)	NA	–31.6 (1.4)	–37.9 (1.4)
HDL-C	+4.5 (1.3)	+7.6 (1.3)	NA	+4.5 (1.4)	+6.2 (1.3)
Triglycerides	–15.8 (2.6)	–18.0 (2.7)	NA	–9.3 (2.7)	–14.1 (2.6)
LDL-C/HDL-C	–43.3 (1.5)	–51.1 (1.6)	NA	–34.1 (1.6)	–40.8 (1.5)
Total cholesterol/HDL-C	–32.3 (1.3)	–38.2 (1.3)	NA	–25.6 (1.3)	–30.4 (1.3)

NA, not applicable.

difference was found between atorvastatin and pravastatin in terms of the most important composite end-point, CHD mortality plus non-fatal MI. The investigators found the results of the PROVE IT-TIMI study difficult to interpret because of the difficulty, if not impossibility, of determining whether any benefit seen in the atorvastatin group was due solely to the aggressive reduction in LDL-C, compared with the moderate reduction achieved with the lower dose of pravastatin (median LDL-C fell from 2.74 mmol l^{-1} in each group to 2.46 mmol l^{-1} in the pravastatin group and 1.60 mmol l^{-1} in the atorvastatin group, $p < 0.001$), or to individual or inherent differences in the statins themselves.[124] In practice, however, this seems to be of little relevance as both statins were used at their maximum licensed dose.

TABLE 22 *Results from major placebo-controlled studies*

Study	Mean baseline LDL-C (mmol l⁻¹)	Length of follow-up	Intervention	Mean change from baseline in LDL-C		Change in LDL-C in treatment group relative to placebo group	CHD death + non-fatal MI: RR (95% CI)
				Treatment group	Placebo group		
ASCOT-LLA	3.4	3.3 years	Atorvastatin 10 mg per day	NR	NR	–29%	0.65 (0.50 to 0.83)
LIPS	3.4	3.9 years	Fluvastatin 80 mg per day	–27%	+11%	–38%	0.69 (0.47 to 1.01)
CARE	3.6	5 years	Pravastatin 40 mg per day	–32%	NR	–28%	0.77 (0.65 to 0.91)
LIPID	3.9	5 years	Pravastatin 40 mg per day	NR	NR	–25%	0.78 (0.70 to 0.86)
PROSPER	3.8	3.2 years	Pravastatin 40 mg per day	NR	NR	–27% at 2 years	0.83 (0.71 to 0.96)
4S	4.9	5.4 years	Simvastatin 20–40 mg per day	–35%	+1%	–36%	0.69 (0.62 to 0.77)

In the absence of any direct evidence relating to the effect of treatment with rosuvastatin on clinical outcomes, some indication of the possible impact of treatment may perhaps be obtained by comparing the lipid-lowering effects of rosuvastatin with the lipid-lowering and clinical effects of statin therapy in the major placebo-controlled trials that report these outcomes. The effects of therapy on LDL-C and CHD death plus non-fatal MI are summarised in *Table 22*. It should be noted that the ASCOT-LLA study used atorvastatin at a fixed dose of 10 mg per day, rather than at either its maximum licensed dose of 80 mg per day or a dose designed to achieve a predetermined reduction in LDL-C.

These results suggest that studies that achieve a reduction in LDL-C relative to placebo of 25–29% achieve a 17–35% reduction in the risk of CHD death plus non-fatal MI, while studies which achieve a 36–38% reduction in LDL-C achieve a 31% reduction in the risk of CHD death plus non-fatal MI. The data summarised in *Table 21* indicate that rosuvastatin is capable of achieving a reduction in LDL-C of up to approximately 50% in patients with a mean baseline LDL-C of 4.9 mmol l⁻¹ (noticeably higher than in the studies summarised in *Table 22*, with the exception of 4S). However, it is not clear how this reduction in LDL-C would translate into a reduction in clinical events given that, in *Table 22*, the largest relative reduction in clinical events does not occur in the study with the largest relative reduction in LDL-C. In support of this, preliminary results from the 4D

study indicate that atorvastatin was associated with a mean reduction of 41% in LDL-C, but only with a non-significant reduction of 8% in the primary end-point, the combined incidence of cardiac death, non-fatal MI and stroke.[104]

Comparisons with 'usual care'
Quantity and quality of research available: comparisons with usual care
Four open-label studies compared a statin with usual care: ALLHAT-LLT,[127] ALLIANCE,[88] ESTABLISH[89] and GREACE.[128] Three of these studies (ALLIANCE, ESTABLISH and GREACE) used atorvastatin in patients with a history of CHD. The fourth study, ALLHAT-LLT, studied pravastatin in moderately hypercholesterolaemic patients aged over 55 years with well-controlled hypertension with and without CHD. (For further details, see Appendix 13.)

Assessment of effectiveness: comparisons with usual care
When meta-analysed, the results of these studies suggest that, in comparison with usual care, statins are associated with statistically significant reductions in the risk of non-fatal MI (RR 0.51, 95% CI 0.39 to 0.67), and of a composite of CHD death and non-fatal MI (RR 0.65, 95% CI 0.44 to 0.96); they were not associated with a significant reduction in the risk of any other event (for full details, see Appendix 14). These results should be treated with caution. The study whose results are most favourable to statin therapy, GREACE, is flawed. Patients who received atorvastatin also

received hospital-based structured care designed to achieve a specified target LDL-C level, while the control group only received community-based usual care. As a result, it is difficult to determine the extent to which the better outcomes seen in the atorvastatin arm are due to the use of atorvastatin, and the extent to which they are due to other components of the package of care which differed from those experienced by patients in the control arm. Certainly, although the use of both aspirin and β-blockers was virtually identical in both groups, only 14% of patients in the usual care arm are said to have received hypolipidaemic drug therapy of any sort throughout the study, compared with 98% in the atorvastatin arm.[128] By comparison, by the end of the ALLHAT-LLT study 26% of the usual care arm were receiving a statin and 2.4% another lipid-lowering drug, while only 70% of the pravastatin arm were receiving pravastatin at the planned dose of 40 mg per day (another 7% were taking pravastatin at a lower dose, 6% were taking a non-study statin, 0.6% were taking another lipid-lowering drug and 16% were not taking any lipid-lowering drug).[127] Similarly, in the ALLIANCE study, patients in the usual care arm were maintained on their original lipid-lowering therapy (which included diet, behaviour modification and antihyperlipidaemic medication, including atorvastatin), with adjustments made entirely at the discretion of their regular physicians: 66% were receiving lipid-lowering therapy at baseline.[88] It therefore seems plausible that the particularly favourable results seen in GREACE compared with ALLIANCE and ALLHAT-LLT are attributable to a lower standard of usual care in the former study. However, it should be noted that, despite substantial use of lipid-lowering therapies in the control arm, ALLIANCE also found that atorvastatin was associated with a statistically significant reduction in the risk of non-fatal MI and CHD death plus non-fatal MI.

Comparisons with 'no statin'
Quantity and quality of research available: comparisons with no statin
Three open-label studies compared a statin with no statin treatment in patients with CHD: Colivicchi 2002,[129] Sato 2001[87] and GISSI-P.[130] One of these was a very small study of the effect of adding atorvastatin to conventional medical treatment in patients with end-stage CAD who were already receiving conventional combination therapy.[129] Another studied the use of low-dose pravastatin in patients with a recent MI in a Mediterranean population.[130] The third used pravastatin in normocholesterolaemic Japanese patients with coronary atherosclerosis.[87] (For further details of these studies, see Appendix 15.)

Assessment of effectiveness: comparisons with no statin
Meta-analysis of the data from the studies that compared statins with no statin therapy yielded a statistically significant result only in relation to one end-point, CHD mortality (RR 0.64, 95% CI 0.42 to 0.98) (for full details, see Appendix 16). This general failure to demonstrate a treatment effect other than for this one outcome seems due in part to the small size of the Colivicchi and Sato studies, and in part to cross-over. In the Colivicchi study, all patients in the control arm who were already receiving statins or other lipid-lowering drugs before inclusion in the study continued to use these after randomisation, with the dosage titrated to reach LDL-C levels below 2.59 mmol l^{-1}. Any patients in the control arm who failed to achieve LDL-C levels lower than 2.59 mmol l^{-1} could receive atorvastatin (initiated at 20 mg per day). Thus, 83% of patients in the control arm received statins and 10% received fibrates, although no lipid-lowering drug other than atorvastatin was allowed in the intervention arm.[129] In the GISSI-P study, 19% of the control group started lipid-lowering treatment (mainly with pravastatin) during the course of the study, mainly as a result of a protocol modification following publication of the results of 4S, while 2% of patients in the pravastatin arm were prescribed an adjunctive cholesterol-lowering drug.[130] The third study did not provide any information on the use of non-study statins or other lipid-lowering drugs.[87]

Summary: comparisons with usual care and no statin
The results of the studies that compare a statin with usual care and no statin are difficult to interpret, largely because of a lack of clarity about the interventions used in the control groups. As a result, they appear to add little to our understanding of the benefits of statin therapy.

Dose comparisons
Quantity and quality of research available: dose comparisons
Two studies were identified that compared two doses of the same statin. The A-to-Z study compared the early use of an aggressive dose of simvastatin (40 mg per day for 30 days, then 80 mg per day) with 4 months' placebo treatment followed by a lower dose of simvastatin (20 mg per day) in patients with acute coronary syndrome and total cholesterol of 6.5 mmol l^{-1} or lower.[131] The PATE study compared low-dose pravastatin

(5 mg per day) with the standard Japanese dose of 10–20 mg per day in a population of elderly Japanese patients with hypercholesterolaemia with and without previous cardiovascular disease[132] (for details see Appendix 17).

Assessment of effectiveness: dose comparisons
In the A-to-Z study, the use of an aggressive dose of simvastatin was associated with a statistically significant reduction in the risk of cardiovascular mortality (RR 0.75, 95% CI 0.57 to 0.99), although not of any other clinical outcomes.[131] The PATE study did not show a statistically significant result in relation to any clinical endpoint, even when all fatal and non-fatal cardiovascular events were pooled[132] (for details see Appendix 18).

Subgroups
Particular interest has been expressed in the effectiveness of statins in specific subgroups, especially women, people with diabetes, the elderly (defined here as people aged 65 and over), cardiac and renal transplant recipients, people with familial hypercholesterolaemia and those with relatively low serum cholesterol. The evidence from placebo-controlled studies relating to each of these subgroups is discussed in turn below.

Women
Although several of the included placebo-controlled studies were carried out specifically in men,[82,115,133] none was carried out specifically in women. Consequently, the results for women are derived from subgroup analyses from studies carried out in mixed populations. This is problematic as none of those studies stratified randomisation by gender (with the possible exceptions of ASCOT-LLA and HPS, which randomised using minimisation and did not state which characteristics informed the minimisation algorithm). As a result, none of the data relating to women are known to represent true randomised comparisons, nor are those data relating to men that are not derived from the KAPS, REGRESS and WOSCOPS studies.

Such data as were available in suitable form were combined by meta-analysis. LIPID and LIPS presented data in a form that did not allow them to be included in the meta-analyses, and therefore their results are summarised separately. Although the results of the meta-analyses should be treated with caution, they suggest that statin treatment in women is associated with a statistically significant reduction in the relative risk of non-fatal MI, coronary revascularisation and CHD death plus

non-fatal MI. Failure to achieve significant results in relation to other outcomes is likely to be due to the small numbers involved. When the results are divided into primary and secondary prevention, statin therapy in women is associated with a significant reduction in the risk of CHD death plus non-fatal MI in secondary prevention (RR 0.75, 95% CI 0.61 to 0.92), but not in primary prevention (RR 1.10, 95% CI 0.57 to 2.10), whereas in men statin therapy was associated with a statistically significant reduction in risk in both secondary and primary prevention (RR 0.77, 95% CI 0.70 to 0.85, and 0.59, 95% CI 0.45 to 0.77, respectively); again, this failure to achieve a statistically significant result in primary prevention in women may be due to the small numbers involved. Thus, although the incidence of CHD is lower in women than in men, there is no evidence that the effectiveness of statins differs in women relative to men at the same level of cardiovascular risk as, for each outcome, although the point estimates of effect may vary, the confidence intervals overlap (for data, see Appendix 19).

People with diabetes
Two of the included placebo-controlled studies were carried out specifically in people with type 2 diabetes,[86,103] but none was carried out specifically in people without diabetes. Consequently, the results for people without diabetes presented below are derived entirely from subgroup analyses from studies carried out in mixed populations. As noted above in relation to women, this is problematic as randomisation was not stratified by diabetes status in any of the studies, with the possible exceptions of ASCOT-LLA and HPS, which randomised using minimisation, and did not state which characteristics were used. As a result, only those data relating to people without diabetes, and those data relating to people with diabetes derived from CARDS or DALI, definitely represent true randomised comparisons.

For comparability with CARDS and DALI, which recruited patients who had been diagnosed with type 2 diabetes at least 6 months[103] and a year,[86] respectively, before study entry, the data used from 4S and LIPID are those relating to patients with and without a clinical history of diabetes at study entry,[97,135] rather than those relating to patients who either had known diabetes at study entry or were found to have impaired fasting glucose.[136,137]

Where data were available in suitable form, they were combined by meta-analysis. As HPS presented data in a form that did allow them

to be included in the meta-analyses, its results are summarised separately (see Appendix 19). Although these results should again be treated with caution, statin therapy in people with diabetes appears to be associated with a statistically significant reduction in the relative risk of all-cause mortality, fatal and non-fatal MI, PTCA, and a composite of CHD death, non-fatal MI and coronary revascularisation. Failure to achieve significant results in relation to other outcomes is again probably due to the small numbers involved. There is no evidence that statins are either more or less effective in people with diabetes than in those without as, although for some outcomes the point estimates of effect may vary, in all cases the confidence intervals overlap. Although the incidence of CHD is higher in people with diabetes than in those without, the numbers of people with diabetes are too small to indicate any difference in the effect of statins when used for primary or secondary prevention in diabetic patients.

It is difficult to compare the effect of statins in people with and without diabetes in terms of absolute risk reduction and numbers needed to treat. The best evidence for people with diabetes comes from CARDS, a large study conducted entirely in people with diabetes who did not have either raised cholesterol levels or a clinical history of cardiovascular disease, even though many were hypertensive.[138] Not surprisingly, in this population the numbers needed to treat to avoid an event are relatively large (*Table 23*).

As most of the data relating to people without diabetes are derived from studies of secondary prevention (4S, CARE and LIPID), no direct comparison can be made with CARDS. It is possible to compare subgroup data for CHD death plus non-fatal MI from the ASCOT-LLA study of primary CHD prevention and the CARE study of secondary CHD prevention (*Table 24*) but, although in both primary and secondary prevention the risk of an event in the placebo arm

TABLE 23 People with diabetes: absolute risk reduction and NNT

CARDS	Risk of event in placebo arm	Absolute risk reduction (95% CI)	NNT for approximately 4 years to avoid an event (95% CI)
All-cause mortality	5.82%	1.70% (0.11 to 3.29)	59 (30.4 to 880.5)
CHD mortality	1.77%	0.36% (−0.56 to 1.27)	281[a]
Total stroke	2.77%	1.35% (0.30 to 2.40)	75 (41.7 to 330.5)
CHD mortality + non-fatal MI	NR		

[a] CI not calculated because the 95% CI for the absolute risk reduction extends from a negative number (indicating that treatment may be harmful) to a positive number (indicating that treatment may be beneficial).

TABLE 24 CHD death plus non-fatal MI: people with and without diabetes: absolute risk reduction and NNT

	Risk of event in placebo arm	Absolute risk reduction (95% CI)	NNT to avoid an event (95% CI)
Primary CHD prevention (ASCOT-LLA)			**Treatment period approximately 3.3 years**
People with diabetes	3.61%	0.59% (−0.80 to 1.98)	170[a]
People without diabetes	2.80%	1.21% (0.56 to 1.86)	83 (53.7 to 178.8)
Secondary CHD prevention (CARE)			**Treatment period approximately 5 years**
People with diabetes	20.39%	2.66% (−3.69 to 9.02)	38[a]
People without diabetes	11.95%	2.95% (0.94 to 4.95)	34 (20.2 to 106.6)

[a] CIs not calculated because the 95% CI for the absolute risk reduction extends from a negative number (indicating that treatment may be harmful) to a positive number (indicating that treatment may be beneficial).

TABLE 25 *CHD death plus non-fatal MI: people aged <65 and ≥65 years: secondary CHD prevention – absolute risk reduction and NNT*

CARE study	Risk of event in placebo arm	Absolute risk reduction (95% CI)	NNT for approximately 5 years to avoid an event (95% CI)
People aged <65	11.36%	1.44% (–0.82 to 3.69)	70[a]
People aged ≥65	17.26%	6.48% (2.70 to 10.26)	16 (9.7 to 37.0)

[a] CI not calculated because the 95% CI for the absolute risk reduction extends from a negative number (indicating that treatment may be harmful) to a positive number (indicating that treatment may be beneficial).

is higher in patients with diabetes than in those without, the studies are not able to demonstrate that, as a result, the number needed to treat to avoid an event is smaller in people with diabetes than in those without.

Elderly patients
One of the included placebo-controlled studies, PROSPER, was carried out specifically in elderly people (aged 70–82 years).[81] 4S and CARE presented subgroup data relating to people aged under 65, and those aged 65 and over, but in these studies randomisation was not stratified by age, and therefore such subgroup data do not represent true randomised comparisons.

Although the results should again be treated with caution, in people aged 65 and over statin treatment appears to be associated with a statistically significant reduction in the relative risk of CHD mortality, total stroke, non-fatal MI, coronary revascularisation, and CHD death plus non-fatal MI. Failure to achieve significant results in relation to other outcomes is again probably due to the small numbers involved. Again, there is no evidence that statins are more or less effective in older people and in those aged under 65 as, although the point estimates of effect vary, the confidence intervals overlap.

It is again difficult to compare the effect of statins in people aged under 65 and in those aged 65 and over in terms of absolute risk reduction and numbers needed to treat. As PROSPER was a mixture of primary and secondary prevention,[81] whereas 4S and CARE were both of secondary CHD prevention, they are not directly comparable; moreover, all were of different lengths. However, subgroup analysis of CARE indicates that, in secondary CHD prevention, the number needed to treat to prevent CHD death or non-fatal MI is substantially lower in patients aged 65 and over than in younger patients (*Table 25*).

Cardiac transplant recipients
Only one placebo-controlled statin study was identified in cardiac transplant patients. This was a small study of 40 mg per day fluvastatin in patients with hyperlipidaemia 3 months to 12 years after cardiac transplant.[139] In addition, one very small study directly compared two statins (pravastatin 20 mg per day and simvastatin 10 mg per day) in adults undergoing cardiac transplantation.[94] A further two studies compared statin therapy with no statin in patients who had received cardiac transplants either 1–2 weeks[140] or 4 days[141] previously (for further details, see Appendix 20).

None of these studies had statistically significant results in relation to clinical outcomes (for further details, see Appendix 21.)

Renal transplant recipients
Only one study was identified that studied the use of a statin (fluvastatin 40–80 mg per day) in renal transplant recipients. In this study, 15% of participants had previously experienced a cardiac, cerebrovascular or other vascular event[142] (for further details, see Appendix 22).

Treatment with fluvastatin reduced the risk of CHD death plus non-fatal MI (RR 0.67, 95% CI 0.50 to 0.90). None of the other clinical outcomes yielded statistically significant results (for further details, see Appendix 23). However, the power of the study will have been reduced by the fact that 14% of the placebo group took non-study lipid-lowering drugs (mainly statins), as did 7% of the fluvastatin group.

People with familial hypercholesterolaemia
No placebo-controlled studies were identified relating to this patient group. This is not surprising: these patients are at very high risk of cardiac events, and the current medical consensus is therefore that the benefits of statin therapy in this group are undeniable, making a placebo-controlled study unethical.

The only relevant study that was identified was therefore a direct statin–statin comparison.[85] This was carried out in patients with known heterozygous familial hypercholesterolaemia, 31% of whom had known cardiovascular disease at study entry (for details, see Appendix 24). The study compared atorvastatin 80 mg per day with simvastatin 40 mg per day. As its primary end-point was atherosclerosis progression as measured by carotid intima media thickness, it was underpowered to demonstrate an effect in terms of clinical outcomes. Moreover, the difference in outcomes between the two groups was potentially reduced as, in accordance with the study protocol, any participant whose serum cholesterol concentrations remained higher than 8.0 mmol l^{-1} on two consecutive visits was given a resin in addition to the study medication. This treatment was required by 15% of those in the simvastatin group, compared with only 2.5% of those in the atorvastatin group.

In this study, clinical outcomes were reported only as reasons for withdrawal from the study. In the case of non-fatal outcomes, it is not clear whether other participants with those outcomes might have remained in the study; as clarification on this point could not be obtained from the study investigators, only mortality data are reported here. No significant difference was demonstrated between the two interventions (for details, see Appendix 25).

Ethnic minorities

No studies were identified that provided information relating to populations from the Indian subcontinent, and the only study to present subgroup analyses of black and non-black ethnic groups was the ALLHAT-LLT study of pravastatin versus usual care, in which nearly 40% of participants were black. However, as the study was carried out in North America, Puerto Rico and the US Virgin Islands,[127] the ethnic mix of that black population would differ considerably from that of the black population of England and Wales.

The results of subgroup analyses for black and non-black participants are summarised in Appendix 26. Although there appears to be no difference between the subgroups in terms of all-cause mortality, pravastatin reduced the risk of CHD death plus non-fatal MI significantly in black but not in non-black populations. However, too much weight should not be put upon this finding, for two reasons. First, randomisation was not stratified by ethnic group, and therefore the subgroup findings are not true randomised

comparisons. Secondly, the comparator in this study was usual care, and it is possible that the usual care given to black ethnic groups may have differed from that given to non-black groups, and that this may have had the effect of enhancing the apparent efficacy of pravastatin in black patients.

Patients with different baseline LDL-C

Logically, one might expect the relative reduction in risk of CHD death and non-fatal MI associated with statin therapy to be greatest in those populations with the highest serum cholesterol levels at baseline. However, there is no clear evidence to support this suggestion. Only one study, PLAC I, stratified randomisation by baseline LDL-C; this reported the effect of statin therapy in patients with baseline LDL-C below 4.14 mmol l^{-1}, but did not provide the equivalent data for those with baseline LDL-C of 4.14 mmol l^{-1} or higher for comparison.[113] A further two placebo-controlled studies that had not stratified randomisation by baseline cholesterol nonetheless analysed the effects of statin therapy in subgroups with higher and lower baseline LDL-C levels; these are therefore not true randomised comparisons. In CARDS, the hazard ratio for a composite end-point of a major coronary event, revascularisation, unstable angina, resuscitated cardiac arrest or stroke was virtually identical in those with baseline LDL-C below and at least 3.1 mmol l^{-1}.[103] In WOSCOPS, the point estimate of the relative reduction in the risk of CHD death or non-fatal MI associated with statin therapy in fact appeared greater, at 37% (95% CI 15 to 53%), in patients whose baseline LDL-C was less than 4.9 mmol l^{-1} than in those with baseline LDL-C of 4.9 mmol l^{-1} or higher (risk reduction 27%, 95% CI 6 to 43%), although the confidence intervals overlapped.[82]

Table 26 summarises data from those placebo-controlled studies whose participants had the highest and lowest mean baseline LDL-C. Again, the confidence intervals overlap, and the point estimates are often very similar, suggesting that statins are no less effective in reducing the risk of CHD death and non-fatal MI in people with relatively low baseline LDL-C than in those with higher cholesterol levels.

Quality of life

Four studies were identified that reported results related to quality of life. These were the Aronow, Mohler and Mondillo studies in patients with intermittent claudication[21,105,118] and the Oxford Cholesterol Study in patients at increased risk of CHD because of a history of MI, angina pectoris,

TABLE 26 *Statin therapy: relative risk of CHD death and non-fatal MI with statin therapy compared with placebo, by mean baseline LDL-C*

Study	Mean baseline LDL-C	RR	95% CI
CARDS[103]	3.0	0.65	0.45 to 0.95
ASCOT-LLA[102]	3.4	0.65	0.50 to 0.83
HPS[74]	3.4	0.74	0.68 to 0.80
LIPS[110]	3.4	0.69	0.47 to 1.01
CARE[111]	3.6	0.77	0.65 to 0.91
CIS[98]	4.3	0.28	0.06 to 1.31
CAIUS[107]	4.7	1.02	0.15 to 7.15
4S[97]	4.9	0.69	0.62 to 0.77
KAPS[133]	4.9	0.62	0.21 to 1.87
WOSCOPS[82]	5.0	0.70	0.58 to 0.84
LiSA[93]	5.1	0.38	0.07 to 1.94

stroke, TIA, PAD, treated diabetes mellitus or treated hypertension.[101]

The Mohler study specifically measured quality of life, using the Short-Form 36 (SF-36); it did not find any significant difference between treatment groups.[21] This study also used the Walking Impairment Questionnaire (WIQ) and the Low Level Physical Activity Recall (LOPAR) questionnaire. Although no significant difference was seen in the WIQ, the LOPAR questionnaire indicated an improvement in physical activity compared with placebo in patients receiving both 10-mg ($p = 0.032$) and 80-mg atorvastatin ($p = 0.02$), and in the combined atorvastatin group ($p = 0.011$). The Mondillo study used a claudication self-assessment questionnaire, and found that patients receiving simvastatin displayed improvements in all four subjective parameters compared with those receiving placebo.[105]

All three studies in patients with intermittent claudication found that statin treatment was associated with an improvement in mean total walking time[21] or distance,[105] and in mean pain-free walking time[118] or distance.[105]

The Oxford Cholesterol Study found that simvastatin therapy did not affect either sleep[143] or mood.[144]

Adverse effects

Despite their potential benefits, most if not all drugs have the potential to cause adverse effects. It is vitally important to understand these risks. This is particularly true in the case of statins, because of the very large number of people who may take these drugs, the fact that many of these individuals do not have symptomatic disease, and the fact that they may take these drugs for life.

The most common adverse reactions caused by statins are relatively minor and transient: they include headache, dizziness, rash, diarrhoea, abdominal pain, constipation and flatulence.[145] However, some of the adverse effects associated with statins are potentially very serious. Rare but clinically important adverse effects are elevations in hepatic transaminases, peripheral neuropathy and myopathy. If statin therapy is not discontinued, myopathy [defined as creatine kinase (CK) increase to at least ten times the upper limit of normal accompanied by muscle pain or weakness] may result in rhabdomyolysis (severe muscle damage) and acute renal failure.[146] Although the exact mechanism by which statins cause rhabdomyolysis remains unclear, the risk appears to be dose related.[52]

There is increasing evidence that the different statins differ both in their potential for interacting with other drugs and in their rates of adverse events. In August 2001, cerivastatin, a synthetic statin, was withdrawn from the world market after the occurrence of 52 unexpected deaths from drug-related rhabdomyolysis (31 in the USA and a further 21 worldwide).[147,148] In addition, 385 non-fatal cases were reported among the estimated 700,000 cerivastatin users in the USA, and most of these required hospitalisation. Many of the fatalities either had received the full dose of cerivastatin (0.8 mg per day) or were using the drug concomitantly with gemfibrozil: this drug–drug interaction was implicated in 12 of the 31 US fatalities.[147]

Sources of evidence

A systematic literature review of the adverse effects of statins is beyond the scope of this review. Instead, the aim of this section is to provide a summary of the important adverse effects reported

by the clinical trials included in this review, and then discuss other important evidence; in particular, where available, postmarketing surveillance data.

RCTs

Serious adverse events (SAEs) are potentially the most important outcomes measured in RCTs. Regulatory bodies require all clinical trials to collect data on SAEs, including any adverse experiences that result in any of the following outcomes: death, a life-threatening experience, inpatient hospitalisation or prolongation of existing hospitalisation, or persistent or significant disability.[149] As many events that might generally be regarded as SAEs (all-cause mortality, cardiovascular events) have already been discussed as outcome measures in the review of clinical effectiveness, this section focuses on those events that have not already been reviewed.

Although RCTs are considered to provide the highest level of evidence for assessing the therapeutic efficacy of drugs, they can only provide limited data for assessing their safety. Premarketing trials are generally not powered reliably to detect rare adverse drug reactions, nor is their follow-up long enough to permit the detection either of adverse drug reactions that are widely separated in time from the original use of the drug, or of delayed consequences associated with long-term administration.[150] Moreover, trials often exclude special populations who may be at risk of unique adverse drug reactions or of an increased frequency of adverse drug reactions compared with the general population.[150] Participants in clinical trials are less likely than non-selected patients to be receiving potentially interacting medications; they may also be monitored more carefully than in real-life situations.

Postmarketing surveillance

By contrast with experimental studies, postmarketing surveillance monitors the safety of medicines under their usual conditions of use. Its aim is to identify any safety concerns that emerge when new products are in widespread use. However, postmarketing surveillance systems also have limitations, including under-reporting due to reliance on voluntary reporting, the poor quality of submitted reports, and the presence of confounders that prohibit the definitive establishment of causality to drug exposure.[151]

Trial evidence

Although the first statin became available in the mid-1980s, the effects of lifetime use are still unknown. In relation to the five statins included in this review, the best clinical trial evidence of long-term safety comes from large-scale, placebo-controlled trials of simvastatin and pravastatin. By comparison, the evidence for the long-term safety of atorvastatin and fluvastatin is weak, and comparable evidence for the safety of rosuvastatin is as yet unpublished.

The evidence from clinical trials with non-statin comparator arms suggests that the incidence of severe muscle problems with statin therapy is low (*Table 27*). Aggregation of data from all such RCTs included in the review of clinical effectiveness indicates that there were only six non-fatal cases of rhabdomyolysis among 47,637 patients randomly assigned to statin treatment versus three cases among 47,180 patients randomised to control (placebo, usual care or no statin treatment). Excluding data from the LIPID trial, which did not differentiate between myositis and myalgia, there were 22 cases of myositis in 43,125 patients randomised to statin treatment and 25 cases in 42,678 patients randomised to the control group. Not all studies reported the number of patients suffering myalgia. However, in the largest study, the HPS,[74] 20,536 patients were randomised to either 40 mg simvastatin per day or placebo, and CK levels were measured in patients who either reported unexplained muscle complaints or used a non-study statin in addition to study therapy. Over the mean 5 years of the study, similar numbers of patients in each group [3379 (32.9%) in the simvastatin group and 3409 (33.2%) in the placebo group] complained of unexplained muscle pain or weakness, and only 49 (0.48%) statin patients and 50 (0.49%) control patients discontinued because of muscle symptoms.

Although the RCT results indicate a low incidence of serious muscle problems in study participants who were followed up by researchers, these studies are likely to underestimate the incidence of such problems if statins are used in unselected populations.[152] In addition to the general issues relating to RCT evidence noted above, the generalisability of the findings of the RCTs included in this review is further limited by the fact that some of the large, long-term studies such as 4S,[97] ASCOT-LLA,[102] CARDS,[138] CARE,[111] ALLHAT-LLT[127] and the HPS[74] excluded patients known to be hypersensitive to, or intolerant of, statins.

Details of other clinical adverse events and withdrawals or discontinuation of study

TABLE 27 Summary of adverse events (rhabdomyolysis, myositis, CK elevation and myalgia) in RCTs which compared statin therapy with placebo, usual care or no statin therapy, and which met the review inclusion criteria

Study	Duration	Statin dosage (mg per day)	No. of patients		No. with rhabdomyolysis[a]		No. with myositis[b]		No. with CK elevation[c]		No. with myalgia[d]		Additional information reported by authors (no. with myopathy)[e]	
			Statin	Control	Statin	Control	Statin	Control	Statin	Control	Statin	Control	Statin	Control
Atorvastatin														
Control arm: placebo														
ASCOT-LLA[102]	3.3 years (median)	10	5,168	5,137	1	0	NR	NR	NR	NR	NR	NR	–	–
CARDS[138]	4 years (median)	10	1,428	1,410	0	0	2	10	2	10	61	72	1	1
DALI[86]	30 weeks	10	73	72	NR	NR	NR	NR	NR	NR	NR	NR	10	9
		80	72										7	
Mohler[21]	1 year	10	120	114	NR	NR	NR	NR	NR	NR	NR	NR	–	–
		80	120											
Control arm: usual care or no treatment														
ALLIANCE[153]	52 months (mean)	10–80 (median 40.5)	1,217	1,225	0	0	0	0	NR	NR	NR	NR	0	0
Colivicchi[129]	1 year	80	40	41	NR	NR	NR	NR	1	NR	NR	NR	–	–
ESTABLISH[89]	6 months	20	35	35	NR	NR	NR	NR	NR	–	NR	NR	–	–
GREACE[128]	3 years (mean)	10–80 (mean 24)	800	800	NR	NR	NR	NR	NR	NR	0	0	0	0
Subtotal	–	–	**9,073**	**8,834**	**1**	**0**	**2**	**10**	**3**	**10**	**61**	**72**	**18**	**10**
Fluvastatin														
Control arm: placebo														
ALERT[142]	5.4 years (median)	40–80	1,050	1,052	0	0	3	1	6	5	NR	NR	–	–
FLARE[108]	40 weeks	80	409	425	NR	NR	0	0	NR	NR	7	3	–	–
FLORIDA[109]	1 year	80	265	275	NR	NR	NR	NR	NR	NR	NR	NR	–	–
LIPS[110]	3.9 years (median)	80	844	833	0	0	0	3	NR	NR	NR	NR	–	–
LiSA[93]	1 year	40–80	187	178	NR	NR	NR	NR	0	1	NR	NR	–	–
O'Rourke[139]	1 year	40	52	27	0	0	NR	NR	7	–	6	2	–	–
Subtotal	–	–	**2,807**	**2,790**	**0**	**0**	**3**	**4**	**13**	**7**	**13**	**5**	**–**	**–**

TABLE 27 Summary of adverse events (rhabdomyolysis, myositis, CK elevation and myalgia) in RCTs which compared statin therapy with placebo, usual care or no statin therapy, and which met the review inclusion criteria (cont'd)

Study	Duration	Statin dosage (mg per day)	No. of patients		No. with rhabdomyolysis[a]		No. with myositis[b]		No. with CK elevation[c]		No. with myalgia[d]		Additional information reported by authors (no. with myopathy)[e]	
			Statin	Control	Statin	Control	Statin	Control	Statin	Control	Statin	Control	Statin	Control
Pravastatin														
Control arm: placebo														
CAIUS[107]	3 years	40	151	154	NR	NR	NR	NR	NR	NR	NR	NR	–	–
CARE[111]	5 years (median)	40	2,081	2,078	0	0	0	4	12	7	NR	NR	–	–
KAPS[133]	3 years	40	224	223	NR	NR	NR	NR	NR	NR	NR	NR	–	–
LIPID[112]	6.1 years (mean)	40	4,512	4,502	0	0	NR	NR	NR	NR	NR	NR	8	10
PLAC I[113]	3 years	40	206	202	NR	NR	(myositis or myalgias, n = 60)	(myositis or myalgias, n = 71)	NR	NR	(myositis or myalgias, n = 60)	(myositis or myalgias, n = 71)	0	0
PLAC II[95]	3 years	10–40	75	76	NR	NR	NR	NR	NR	NR	NR	NR	–	–
PMSG[96]	26 weeks	20–40	530	532	NR	NR	NR	NR	14	8	NR	NR	0	0
PREDICT[114]	6 months	40	347	348	NR	NR	NR	NR	NR	NR	NR	NR	–	–
PROSPER[81]	3.2 years (mean)	40	2,891	2,913	0	0	NR	NR	NR	NR	36	32	–	–
REGRESS[115]	2 years	40	450	434	NR	NR	NR	NR	NR	NR	1	0	–	–
WOSCOPS[82]	4.9 years (mean)	40	3,302	3,293	NR	NR	NR	NR	3	1	20	19	–	–
Control arm: usual care or no treatment														
ALLHAT-LLT[127]	4.8 years (mean)	40	5,170	5,185	NR	NR	NR	NR	NR	NR	NR		–	–
GISSI-P[130]	24.3 months (median)	20–40	2,138	2,133	0	0	NR	NR	NR	NR	NR		–	–
Kobashigawa[140]	1 year	20–40	47	50	0	0	0	0	0	0	0	0	–	–
Sato[87]	21.7 months (mean)	10	54	66	NR	NR	NR	NR	NR	NR	NR		–	–
Subtotal	–	–	**22,178**	**22,189**	**0**	**0**	**0**[f]	**4**[f]	**29**	**16**	**57**[f]	**51**[f]	**8**	**10**

Rosuvastatin (no placebo-controlled, treatment or usual care trials)

continued

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TABLE 27 Summary of adverse events (rhabdomyolysis, myositis, CK elevation and myalgia) in RCTs which compared statin therapy with placebo, usual care or no statin therapy, and which met the review inclusion criteria (cont'd)

Study	Duration	Statin dosage (mg per day)	No. of patients		No. with rhabdomyolysis[a]		No. with myositis[b]		No. with CK elevation[c]		No. with myalgia[d]		Additional information reported by authors (no. with myopathy)[e]	
			Statin	Control	Statin	Control	Statin	Control	Statin	Control	Statin	Control	Statin	Control
Simvastatin														
Control arm: placebo														
4S[97]	7.4 years (median)	20–40	2,221	2,223	0	0	6	1	NR	NR	NR	NR	1	0
Aronow[118]	1 year	40	34	35	NR	NR	NR	NR	NR	NR	NR	NR	–	–
CIS[98]	2.3 years (mean)	20–40	129	125	NR	NR	NR	NR	NR	NR	NR	NR	–	–
HPS[74]	5 years (mean)	40	10,269	10,267	5	3	11	6	30	19	3,379	3,409	10	4
MAAS[100]	4 years	20	204	200	NR	NR	NR	NR	NR	NR	NR	NR	0	–
Mondillo[105]	6 months	40	43	43	NR	NR	NR	NR	NR	NR	NR	NR	–	–
Oxford Cholesterol Study[101]	3.4 years (median)	20	206	207	NR	NR	NR	NR	7	8	2	2	–	–
		40	208						9		4			
SCAT[116]	47.8 months (mean)	20–40	230	230	NR	NR	NR	NR	NR	NR	NR	NR	–	–
Control arm: usual care or no treatment														
Wenke[141]	4 years	5–20	35	37	NR	NR	0	0	0	0	NR	NR	–	–
Subtotal		–	**13,579**	**13,367**	**5**	**3**	**17**	**7**	**46**	**27**	**3,385[f]**	**3,411**	**11**	**4**
Total for all statins		–	**47,637**	**47,180**	**6**	**3**	**22[f]**	**25[f]**	**91**	**60**	**3,516[f]**	**3,539[f]**	**37**	**24**

[a] Rhabdomyolysis defined by study investigators (fatal or non-fatal).
[b] Myositis defined by study investigators or as a CK elevation greater than ten times the upper limit of normal.
[c] Number with CK elevations defined by study investigators.
[d] Myalgia defined by study investigators or muscle complaints without serum CK elevations.
[e] Myopathy defined by study investigators.
[f] Data from the LIPID study not included as numbers with myositis or myalgias could not be differentiated.

TABLE 28 *Reported cases of fatal rhabdomyolysis and numbers of prescriptions for statins dispensed in the USA[155]*

Variable	Pravastatin	Simvastatin	Fluvastatin	Atorvastatin	Cerivastatin[d]	Total
Date approved in USA	31 October 1991	23 December 1991	31 December 1993	17 December 1996	26 June 1997	–
Cases of fatal rhabdomyolysis[a]	3	14	0	6	31	54
No. of prescriptions dispensed since marketing began[b]	81,364,000	116,145,000	37,392,000	140,360,000	9,815,000	385,076,000
Reporting rate (per 1 million prescriptions)[c]	0.04	0.12	0.00	0.04	3.16	0.14

[a] US cases reported to the Food and Drug Administration (FDA) before 26 June 2001 and which met the following criteria: the report included a clinical diagnosis of rhabdomyolysis, a temporal association between rhabdomyolysis and the use of a statin could be identified from the report, and death resulted either directly or indirectly from rhabdomyolysis.
[b] Data up to and including May 2001, derived from the US National Prescription Audit Plus, excluding the Long Term Care Channel.
[c] The FDA does not recommend rigorous comparisons between drugs based on these data since many factors can affect reporting and an unknown number of cases may not be attributed to the drug or reported to the FDA. They emphasise that reporting rates are not incidence rates.
[d] Withdrawn from the world market in August 2001.

medication due to adverse events from those clinical trials with non-statin comparator arms that met the review's inclusion criteria are summarised in Appendix 27.

As noted above, no long-term (>6 months) placebo-controlled trials of rosuvastatin have yet been published. Both studies included in this review that have 52-week follow-ups compared rosuvastatin with other statins. One reported that ten out of 268 patients receiving rosuvastatin (3.5%) withdrew because of adverse events that were considered to be related to trial medication, compared with eight out of 140 patients receiving atorvastatin (5.7%). Only two of the events associated with rosuvastatin were considered serious (rectal haemorrhage and serum creatinine elevation).[125] In the other study, no SAEs were reported in patients receiving rosuvastatin.[126]

Postmarketing surveillance data
Atorvastatin, fluvastatin, pravastatin and simvastatin
No published postmarketing surveillance data for the UK are available for atorvastatin, fluvastatin, pravastatin or simvastatin. An epidemiological study using data from the UK GPRD for the years 1991–1997 found that current statin therapy was associated with an eight-fold increase in the risk of myopathy. However, this equated to approximately one case per 10,000 person-years of statin therapy.[154]

The non-UK data suggest that, between product approval and 26 June 2001, fatal cases of rhabdomyolysis associated with statin therapy were rare, with reporting rates lower than one death per million prescriptions, with the exception of cerivastatin, which has since been withdrawn from world markets (*Table 28*).[155] However, these figures are likely to underestimate the risk both because they are based on voluntary reporting by healthcare professionals, and because they use as the denominator the number of prescriptions, not the number of individuals using the medication.[152]

Rates of fatal and non-fatal rhabdomyolysis reported to the US FDA's postmarketing database were also similar, at less than one case per million prescriptions, for all statins except for cerivastatin[156] (*Table 28*). More than 80% of cases reported for each drug when taken as monotherapy resulted in hospitalisation for renal failure and dialysis, and 10% resulted in death.[156] This demonstrates that, although rhabdomyolysis is a rare event, it presents a significant safety issue for statin drugs even when taken as monotherapy; the risk is increased when statins are used in combination with gemfibrozil (*Table 29*).

A more accurate estimate of the incidence of rhabdomyolysis attributed to statins, alone or in combination with fibrates, may be obtained from a recently published major analysis.[157] Prescription data were used to identify a cohort of 252,460 lipid-lowering drug users from 11 health plans

TABLE 29 *Reporting rates per million prescriptions for all US cases of rhabdomyolysis associated with statins until 31 July 2001*[156]

Variable	Pravastatin 1992–2001	Simvastatin 1992–2001	Fluvastatin 1994–2001	Atorvastatin 1997–2001	Cerivastatin[d] 1998–2001	Total
Monotherapy						
Cases of rhabdomyolysis[a]	17	99	1	45	200	482
Estimated prescriptions[b]	82,000,000	118,986,000	38,791,000	147,610,000	11,038,000	495,761,000
Crude rate per 1 million prescriptions	0.21	0.83	0.03	0.30	18.12	0.97
Combination therapy with gemfibrozil						
Cases of rhabdomyolysis[a]	2	37	0	6	279	324
Estimated prescriptions[c]	1,422,000	962,000	316,000	1,198,000	22,000	3,920,000
Crude rate per 1 million prescriptions	1.41	38.46	0.00	5.01	12,681.82	82.65

[a] Cases identified in the FDA Adverse Event Reporting System database with creatine phosphokinase >10,000 IU l^{-1}, signs and symptoms (myalgia, myopathy, gait disturbance) and clinical diagnosis of rhabdomyolysis.
[b] Estimates of prescriptions for statin therapy, with or without concomitant gemfibrozil therapy, based on percentage of mentions (IMS HEALTH NDTI™) summed across all years of marketing for each drug and applied to prescriptions for all years in which the drug was marketed (IMS HEALTH NPA*Plus*™).
[c] All dispensed prescriptions for all years the drug was marketed between 1988 and July 2001 (IMS HEALTH NPA*Plus*, excluding Long Term Care).
[d] Withdrawn from the world market in August 2001.
The analysis does not include concomitant therapy with fenofibrate, which was prevalent in 0–1% of mentions across statins. Few cases of rhabdomyolysis were reported for any statin plus fenofibrate or clofibrate; however, these were not included in the analysis.

across the USA between January 1998 and June 2001. Hospital data were then used to establish how many of that cohort were admitted to hospital with a diagnosis of rhabdomyolysis. There were 21 cases, all associated with statin intake (i.e. none occurred during non-exposed time); a further seven cases were excluded from the analysis because, according to automated claims data, they were not exposed to a lipid-lowering drug at the time when they developed rhabdomyolysis, although in each case their hospital record explicitly stated that they had been taking a statin at the time of the event. All patients with rhabdomyolysis were taking statins at half or less of the recommended maximum dose. The incidence rate of hospitalised rhabdomyolysis with monotherapy of atorvastatin, pravastatin and simvastatin was 0.44 (95% CI 0.20 to 0.84) cases per 10,000 person-years exposure; there was no statistically significant difference between those statins (average incidence of rhabdomyolysis for atorvastatin 0.54, 95% CI 0.22 to 1.12, for pravastatin 0.0, 95% CI 0 to 1.11, and for simvastatin 0.49, 95% CI 0.22 to 1.12). By comparison, the incidence rate for cerivastatin was 5.34 (95% CI 1.46 to 13.68). Inclusion of the seven excluded cases resulted in an incidence rate for atorvastatin, pravastatin and simvastatin of 0.68 (95% CI 0.38 to 1.15); again, the individual incidence rates remained indistinguishable.

However, when atorvastatin and simvastatin were used in combined statin–fibrate therapy, the risk increased considerably, to 5.98 (95% CI 0.72 to 216). The risk was also increased in patients aged 65 or older, and in those with diabetes mellitus.[157]

Rosuvastatin
On 12 August 2003, the FDA approved rosuvastatin for marketing at doses of 5–40 mg.[158] Although the sponsor had originally proposed to market rosuvastatin at daily doses ranging from 10 to 80 mg, the premarketing data indicated that the 80-mg dose was associated with a higher incidence of myopathy and rhabdomyolysis, and higher frequencies both of serum creatinine elevations unrelated to myotoxicity and of proteinuria with and without haematuria. The FDA therefore decided that the risks of treatment at that dose outweighed the benefits associated with the modest incremental reduction in cholesterol. Development of the 80-mg dose was subsequently discontinued.[159]

The premarketing data submitted to the FDA identified eight cases of rhabdomyolysis, one in 7727 patients receiving 10 mg (0.01%) and seven in 1574 patients receiving 80 mg (0.4%).[159] Eighteen further cases of rhabdomyolysis were reported between the beginning of marketing and 13 April 2004; these included 11 cases which

occurred in the space of 7 months in the USA. Two of the 18 patients were using a 40-mg dose, five were using 20 mg and 11 were using 10 mg. Rosuvastatin thus appears to have a higher rate of rhabdomyolysis than any other currently marketed statin,[160] and it is not, as had been hoped, limited to the 80-mg dose.

By mid-August 2004, approximately 3 million patients worldwide had received rosuvastatin. Indeed, following its licensing and launch in the UK in March 2003, by the end of July 2004 it had been used by over 190,000 UK patients. During this period, the most frequently reported adverse events were myalgia, headache, nausea, dizziness and arthralgia.[161] However, by 26 August 2004, the number of cases of rhabdomyolysis associated with rosuvastatin had risen to 65 in the USA alone,[162] and by October 2004 the UK Committee on Safety of Medicines had received ten reports of suspected rhabdomyolysis associated with rosuvastatin, the majority involving patients who had started on high doses of rosuvastatin, some of whom had pre-existing risk factors for myopathy.[52]

Rosuvastatin has also been associated with instances of acute renal failure and renal insufficiency, which were not secondary to rhabdomyolysis. As noted above, premarketing data indicated that a small proportion of patients taking rosuvastatin displayed persistent proteinuria and haematuria, in some cases associated with an increase in serum creatinine. This was dose related, affecting 1.3% of patients receiving 40-mg and 6.1% receiving 80-mg rosuvastatin. The FDA expressed concern that this might progress to renal failure in a small number of patients.[159] By 13 April 2004, postmarketing data recorded eight cases of acute renal failure and four of renal insufficiency in patients using rosuvastatin. Nine of these patients were taking 10 mg, one 40 mg and one 80 mg.[160]

AstraZeneca have claimed, on the basis of data from their clinical trial programme and ongoing pharmacovigilance assessments, that rosuvastatin is no more likely to cause adverse muscle effects than the other marketed statins. They consider rosuvastatin's safety profile to be similar to those of the marketed statins, and state that "This view of the benefit–risk profile of rosuvastatin is shared by regulatory authorities in the 64 countries where rosuvastatin is approved".[163] However, as a result of postmarketing reports of adverse events in patients receiving rosuvastatin, labelling changes have been made within the European Union, reflecting those already in use in the USA. These

changes highlight the patient populations who may be at increased risk of myopathy, particularly at the highest currently approved dose (40 mg). Patients at risk include those aged over 65, those with hypothyroidism and/or renal insufficiency, some Asian populations, and people concomitantly using ciclosporin and gemfibrozil.[164]

Other evidence
Concerns about the long-term safety of statins were originally raised by a review of the carcinogenicity of lipid-lowering drugs in animal studies.[51] However, laboratory experiments suggested that statins had an inhibitory effect on cancer cell proliferation.[165] Despite this, further concerns were raised because of evidence suggesting that low cholesterol concentrations were associated with increased cancer mortality. In particular, a Dutch cohort study found that, in people aged 85 and over, low plasma cholesterol was associated with significantly increased risks of both all-cause mortality and cancer mortality.[166] One of the aims of the large placebo-controlled PROSPER study was therefore to establish the balance of benefit and risk associated with the use of pravastatin in people aged between 70 and 82 years. The study found that pravastatin was associated with a statistically significant increase in incident cancer.[81] In view of this finding, the authors meta-analysed their results with those of other pravastatin trials, and found no significant effect of the drug on cancer rates. The authors concluded that the imbalance in cancer rates in the PROSPER study was a chance finding, which could in part have been driven by the recruitment of individuals with occult disease.[81] Subsequently, a meta-analysis of data from six large studies excluding PROSPER found no evidence to suggest that statin therapy affected the overall rates of fatal or non-fatal cancer (*Table 30*). However, most of the participants in these studies were under 70, and thus the question of whether cholesterol-lowering accelerates the development of cancer in the elderly remains open. Moreover, the authors of the meta-analysis cautioned that none of the trials reported all of the outcomes, that most reported cancer in different ways, and that reporting of site-specific cancers in the trials was incomplete; in addition, they note that it is not possible, on the basis of trials averaging 5 years' duration, to exclude the possibility of cancer risk resulting from longer exposure or after a longer latency period.[167]

Evidence from a case–control study conducted in Denmark suggests that statin use is associated with a four- to 14-fold increase in the risk of developing

TABLE 30 *Risk of fatal and non-fatal cancer with statin therapy*[167a]

Event	No. of trials	No. of patients	No. of events/total		Relative risk (95% CI)
			Statin	**Placebo**	
Non-fatal cancer					
Excluding non-melanoma skin cancer	3[b]	31,575	583/15,792	576/15,783	1.01 (0.90 to 1.13)
Including non-melanoma skin cancer	2[c]	13,173	374/6,593	374/6,580	1.00 (0.87 to 1.15)
Fatal cancer					
Excluding non-melanoma skin cancer	3[b]	31,575	436/15,792	429/15,783	1.02 (0.89 to 1.16)
Including non-melanoma skin cancer	2[c]	13,173	177/6,593	186/6,580	0.95 (0.78 to 1.16)
All cancers					
Excluding non-melanoma skin cancer	4[d]	38,198	1,271/19,114	1,264/19,084	1.00 (0.93 to 1.08)
Including non-melanoma skin cancer	4[e]	40,314	2,110/20,166	2,067/20,148	1.02 (0.96 to 1.08)

[a] WOSCOPS, CARE and LIPID used pravastatin, 4S and HPS used simvastatin, and AFCAPS used lovastatin (not reviewed in this appraisal).
[b] Data from 4S, WOSCOPS and HPS.
[c] Data from CARE and LIPID.
[d] Data from 4S, WOSCOPS, AFCAPS and HPS.
[e] Data from CARE, LIPID, AFCAPS and HPS.

idiopathic polyneuropathy, corresponding to one excess case for every 2200 (95% CI 880 to 7300) person-years of statin use. The risk increased in patients treated with statins for 2 or more years.[168] This evidence supports that of a cohort study undertaken by the same researchers in the UK, which found an elevated risk of idiopathic peripheral neuropathy in current statin users compared both with patients with hyperlipidaemia who had not been prescribed a lipid-lowering drug, and with an age- and gender-matched cohort drawn from the general population.[169]

Summary
Although concerns have been raised about rosuvastatin, statins are generally considered to be well tolerated and to have a good safety profile. This view is generally supported both by the evidence of the trials included in this review and by postmarketing surveillance data. Although increases in CK and myopathy have been reported, rhabdomyolysis and hepatotoxicity are rare. However, some patients may receive lipid-lowering therapy for as long as 50 years, and long-term safety over such a timespan remains unproven.

Continuance and compliance
The efficacy of an intervention is clearly related to the length of time for which it is taken and the extent to which it is taken in accordance with the intended dosing regimen. It has been claimed that a level of compliance of over 80%, with only trivial deviations, in relation to both the prescribed total dose and the prescribed timing of that dose will provide an adequate therapeutic effect in most

drugs.[69] Although most of the studies included in this review report continuance, in some studies it is not clear whether the authors are reporting continuance or compliance. Moreover, some do not report compliance with statin therapy even in terms of total dose, and none reports compliance in terms of timing. However, WOSCOPS found a significant reduction in risk of definite CHD death or non-fatal MI, relative to placebo, in patients who took 75% or more of the prescribed statin (RR 0.62, 95% CI 0.50 to 0.76), but not in those taking less than 75% (RR 1.01, 95% CI 0.66 to 1.55). This result should be treated with caution as analyses conditional on compliance are no longer truly randomised. However, the investigators recalculated this result in the high-compliance group using the Cox proportional-hazards model, adjusting for baseline risk factors that had previously been identified as being of prognostic value (smoking status, diabetes, taking nitrates, minor ECG abnormality, positive Rose questionnaire for angina, family history of CHD, age, history of hypertension, diastolic blood pressure, LDL-C/HDL-C ratio), and still found a 38% reduction (95% CI 23 to 50%) in the risk of definite CHD death or non-fatal MI in the high-compliance group relative to placebo, compared with a 31% reduction (95% CI 17 to 43%) in the entire cohort.[170] This result suggests that long-term compliance is probably required to achieve optimum benefits from statin therapy.

Because of the importance of continuance and compliance in relation to the effects of treatment, data drawn from the studies included in the review

TABLE 31 *Studies reporting continuance: percentage of patients in statin group still taking statin therapy*

Study	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Primary CHD prevention						
ASCOT-LLA[102]	NR	NR	87			
CARDS[138]	90	87	86	78		
WOSCOPS[170]	85	NR	NR	NR	70	
Secondary CHD prevention						
4S[97]	NR	NR	NR	NR	90	
CARE[111]	NR	NR	NR	NR	94	NR
LIPID[112]	94	NR	89	NR	NR	81
LIPS[91]	NR	NR	NR	73		
MAAS[100]	NR	NR	NR	75		
Mixed primary and secondary CHD prevention						
ALLHAT-LLT[127]	NR	87	NR	80	NR	77

will be supplemented with data from other relevant studies.

Evidence from included studies
Continuance
The evidence relating to continuance with statin therapy is summarised in *Table 31*. Where available, information is provided by year of treatment. WOSCOPS is included under primary CHD prevention as, although it was undertaken in a mixed population, only 5% of participants were reported as having CHD at baseline.

As would be expected, all studies that report continuance at more than one point in time demonstrate a gradual decrease in continuance over time (*Table 31*). As noted earlier, compliance with drug therapy is generally higher in patients with symptomatic disease than in those without. It is therefore perhaps not surprising that, at 1 year, the highest continuance is reported by a secondary prevention study, the LIPID study, or that, by year 5, continuance is substantially lower in WOSCOPS, which is predominantly of primary prevention, than in the 4S and CARE studies of secondary prevention. It is also perhaps not surprising that, of the primary prevention studies that present data at 1 year, continuance is lower in WOSCOPS than in CARDS, since the latter was carried out in diabetic patients, 80% of whom were already taking medication for their diabetes. However, the issue is not straightforward: within studies of statins in secondary prevention, it is not clear why LIPS and MAAS report much lower continuance rates at 4 years than 4S and CARE do at 5 years.

Most studies did not provide information on the reasons why participants specifically discontinued study medication rather than why they withdrew from the study. However, 4S stated that just over half of those who discontinued statin therapy did so because of adverse events; the reason given by the remainder was mainly patient reluctance to continue.[97]

Compliance
As noted above, very few studies report compliance, and not all of those that do specify how it was measured. In the only study of primary prevention that reported compliance, the DALI study in diabetic patients, compliance was said to be over 95% in all three treatment groups, but no indication was given as to how it was measured.[86]

There is more evidence relating to studies of statins in secondary prevention. The 3T study assessed compliance by questioning the patient and by counting tablets at each clinic visit; patients taking at least 85% of the correct doses were considered compliant. Eighty-eight per cent of patients in the atorvastatin group were at least 85% compliant throughout, as were 86% in the simvastatin group.[83] In PLAC I, mean compliance, assessed by pill count, was 95%.[113] SCAT also assessed compliance by pill count at each visit. As an attempt had been made to exclude potentially non-compliant patients during the placebo run-in phase, average compliance with statin therapy was approximately 95% throughout the trial.[116]

The fullest information on compliance with statin therapy comes from HPS, which was carried out in a mixed population. This study assessed compliance by reviewing the calendar-packed tablets remaining; compliance was defined as consumption of at least 80% of the study medication since the previous follow-up visit. On average, 85% of patients allocated to statin therapy were compliant with therapy throughout the study;

this figure fell from 89% at the end of the first year to 82% at 5 years. Most of the non-compliant patients appear to have discontinued therapy: only about 2% of patients overall were reported to be taking some, but less than 80%, of their allocated treatment.[74] In another mixed study, KAPS, compliance, assessed by tablet count, was 92% in the pravastatin group,[133] while another mixed study, PROSPER, achieved 94% compliance, again assessed by tablet count; however, in this study potential participants who were less than 75% compliant had been screened out in the placebo run-in phase.[171] In another mixed study, ALLHAT-LLT, which did not seem to screen participants for compliance, only 70–75% of patients reported taking 80% or more of their assigned pravastatin.[127]

In WOSCOPS, although continuance was relatively low, compliance was very high once patients were established on medication. At the first trial visit, mean compliance with statin therapy was approximately 85%, but it rose to approximately 95% at the end of the first year and remained stable until study end. A history of taking regular medication (for angina, diabetes or hypertension) increased the likelihood of being 100% compliant with study medication, while current smokers were less likely to be compliant.[170]

Evidence from other studies

It is generally accepted that continuance and compliance with medication are higher in RCTs than in general clinical practice. Several studies have explored continuance and compliance with lipid-lowering therapies in real life. However, because of the possibility that economic and cultural factors may influence continuance and compliance, only the evidence from UK studies is reviewed here.

A study carried out in Tayside, Scotland, studied patients who experienced their first MI between January 1990 and November 1995. Adherence with statin therapy was calculated on the basis of prescriptions dispensed after discharge from hospital, dividing the number of days with statin supply by the total number of days from the first prescription for a statin to the end of the study;[172] this may combine elements of continuance and compliance. Sixty-four per cent of patients had greater than 80% adherence, as did 69% of patients aged over 65 years. Adherence was not associated with deprivation. After adjusting for prior lipid-lowering therapy, dose and other risk factors, only patients with at least 80% adherence to statin therapy had significantly lower risks of further MI and of all-cause mortality.[172]

A retrospective cohort study was undertaken in a large general practice in Liverpool to investigate true patient compliance with statin therapy in primary care. Electronic medical records were used to identify any patient prescribed a statin between 31 December 1991 and 26 January 2003. Of the 869 patients meeting the study inclusion criteria, 74 (8.5%) had discontinued therapy; 44 did so within the first 6 months, and 27 did not take the statin for longer than a month. In 54 cases (73%), no reason for discontinuation was recorded, but ten patients (14%) were recorded as discontinuing because of side-effects (for comparison, 14% of compliant patients had their statin prescription changed because of side-effects). Compliance was defined as taking at least 80% of therapy: overall, 25% of patients were non-compliant. Cholesterol monitoring was found to be a significant predictor of patient compliance ($p < 0.001$).[73]

Tolmie and colleagues[173] undertook a study in an area of high social deprivation in the west of Scotland in patients prescribed statin therapy for at least 3 months. Eighty-six per cent of patients appeared to be good compliers, taking 70–100% of their statins, 8% were moderate compliers (taking 41–69%) and 6% were poor compliers (taking <41%). In-depth interviews with patients who were good, moderate and poor compliers indicated the importance, for compliance, of the credence that patients attached to the prescriber, and of their perceptions of the primary purpose of the consultation at which the drug was initiated.[173]

Continuance and compliance: summary

Not all patients who are prescribed statins will take them for any length of time. Between 5 and 15% are likely to discontinue therapy within the first year, and at the end of 5 years as many as 30% are likely to have discontinued. Although the proportion of people who discontinue treatment is likely to be higher in those receiving statins for primary prevention, the issue is complicated, with a likelihood of greater continuance in patients with conditions such as diabetes or hypertension, regardless of whether they have suffered a prior cardiovascular event. Compliance appears to be good in patients who do not discontinue therapy.

Summary of clinical effectiveness

There is evidence from placebo-controlled studies to suggest that statin therapy is associated with a statistically significant reduction in the risk of:

- all-cause mortality, non-fatal MI, and a composite end-point of CHD death plus

non-fatal MI, in both primary and secondary prevention

- stable angina in primary prevention
- cardiovascular mortality, CHD mortality, fatal MI, non-fatal stroke, PAD, unstable angina, and coronary revascularisation in secondary prevention.

As the confidence intervals for each outcome in each prevention category overlap, it is not possible to differentiate, in terms of relative risk, between the effectiveness of statins in primary and secondary prevention. However, the absolute risk of CHD death or non-fatal MI is higher, and the number needed to treat to avoid such an event is consequently lower, in secondary than in primary prevention.

There is no evidence that the effectiveness of statins differs in women relative to men at the same level of cardiovascular risk, in patients with diabetes compared with those without, or in older patients compared with those under 65 years of age, nor is there evidence that statins differ in effectiveness in patients with lower or higher cholesterol levels at baseline.

Because of poor study design, it is difficult to interpret the results of the studies that compare a statin with 'usual care', while those that compared a statin with no statin therapy very largely failed to achieve statistically significant results in relation to clinical outcomes.

On the evidence available from the placebo-controlled trials, it is barely possible to differentiate between the different statins in relation to any outcome: although the point estimates of their effect sizes may vary, the confidence intervals overlap in each case except for non-fatal MI, where simvastatin can just be differentiated from pravastatin. Only three head-to-head comparisons of one statin with another have reported clinical outcomes, and only one of these, the PROVE IT-TIMI trial, reported statistically significant results. These suggest that aggressive reduction in LDL-C with atorvastatin is more effective than moderate LDL-C reduction

using pravastatin in reducing the risk of hospitalisation for unstable angina, and of coronary revascularisation; however, these results cannot be considered conclusive as there was no statistically significant difference between the two statins in terms of the key composite end-point of CHD death or non-fatal MI.

It should, however, be noted that the different statins vary in terms of the volume of evidence available from placebo-controlled studies that report clinical outcomes. As noted earlier, there is no such evidence relating to rosuvastatin. Of the remaining four statins, there is least evidence for fluvastatin, with four studies of secondary CHD prevention in a total of 3416 patients (*Table 32*). There are five studies of atorvastatin, involving 14,969 patients; three of these studies were of primary prevention, but all of these were in patients who, because of their pre-existing medical conditions, were at relatively high risk of cardiovascular events. The eight studies of simvastatin, involving 26,851 patients, were all of secondary or mixed prevention. All of the 11 studies of pravastatin, involving 29,524 patients, were of secondary or mixed prevention, with the exception of CAIUS, which recruited patients with ultrasonographically identified early atherosclerosis but without symptomatic CVD.[107] Each statin is represented both by studies that appear to be of good quality, and by others whose quality cannot be assessed in that it is not clear from published sources whether the method used to assign participants to the treatment group was really random or the allocation of treatment was concealed (*Table 32*).

Statins are generally considered to be well tolerated and to have a good safety profile. This view is generally supported both by the evidence of the trials included in this review and by postmarketing surveillance data. Although increases in CK and myopathy have been reported, rhabdomyolysis and hepatotoxicity are rare. However, some patients may receive lipid-lowering therapy for as long as 50 years, and long-term safety over such a timespan remains unproven.

TABLE 32 *Strength of evidence from placebo-controlled studies reporting clinical outcomes for different statins (excluding studies in transplant patients)*

Statin/study	Prevention category	Patient group	No. randomised	Study quality[a]
Atorvastatin				
4D[84]	Mixed	Diabetic + renal failure	1,255	Good
ASCOT-LLA[102]	Primary CHD	Hypertensive	10,305	Good
CARDS[103]	Primary CVD	Diabetic	2,838	Good
DALI[86]	Primary CHD	Diabetic	217	?
Mohler 2003[21]	Secondary CVD	Intermittent claudication	354	?
Total			**14,969**	
Fluvastatin				
FLARE[108]	Secondary CHD	PTCA	834	?
FLORIDA[109]	Secondary CHD	Acute MI	540	?
LIPS[110]	Secondary CHD	Angina or silent ischaemia	1,677	Good
LiSA[93]	Secondary CHD	Stable symptomatic CHD	365	?
Total			**3,416**	
Pravastatin				
CAIUS[107]	Primary CVD	Ultrasonographically identified early atherosclerosis	305	Good
CARE[111]	Secondary CHD	MI	4,159	Good
KAPS[133]	Mixed	Hypercholesterolaemia, with and without CVD	447	Good
LIPID[112]	Secondary CHD	MI or unstable angina	9,014	?
PLAC I[113]	Secondary CHD	CHD	408	?
PLAC II[95]	Secondary CHD	CHD	151	?
PMSG[96]	Mixed	Primary hypercholesterolaemia and at least two additional CHD risk factors	1,062	?
PREDICT[114]	Secondary CHD	CHD (successful PTCA)	695	?
PROSPER[81]	Mixed	Elderly, with or at significant risk of CVD	5,804	Good
REGRESS[115]	Secondary CHD	CHD	884	?
WOSCOPS[82]	Mixed	Moderate hypercholesterolaemia	6,595	?
Total			**29,524**	
Simvastatin				
4S[97]	Secondary CHD	CHD	4,444	Good
Aronow 2003[118]	Secondary CVD	Intermittent claudication	69	?
CIS[98]	Secondary CHD	CHD	254	?
HPS[74]	Mixed	Substantial risk of death from CHD	20,536	Good
MAAS[100]	Secondary CHD	CHD	381	?
Mondillo 2003[105]	Secondary CVD	PAD	86	?
Oxford Cholesterol Study[101]	Mixed	Increased risk of CHD	621	Good
SCAT[116]	Secondary CHD	CHD	460	Good
Total			**26,851**	

[a] This is said to be good if it was clear from the report both that the method used to assign participants to the treatment group was really random and that the allocation of treatment was concealed.

Chapter 4
Economic analysis

Systematic review of existing economic literature

The primary objective of this review is to identify and evaluate studies exploring the cost-effectiveness of statins in primary and secondary prevention of CHD and CVD in the UK. The secondary objective is to evaluate methodologies used to inform the economic evaluation.

Search strategy
Studies were identified through searches of MEDLINE (1996 to present), EMBASE (from 1996), CDSR, and the NHS Centre for Reviews and Dissemination databases (DARE, NHS EED, HTA).

Inclusion and exclusion strategy
The titles and abstracts of papers identified through the searches outlined above were assessed for inclusion using the following criteria.

Inclusion criteria
- Cost-effectiveness analyses, as opposed to cost–benefit or cost minimisation
- UK setting
- statin therapy as one of the studied alternatives (possibly combined with other interventions such as lifestyle advice/diet)
- the benefits were estimated in terms of life-years saved (LYS) or quality-adjusted life-years (QALYs)
- adult populations
- the study was fully published in English.

Exclusion criteria
- Studies that adapted published evaluations for other settings
- studies not considered methodologically sound
- studies that did not report results in sufficient detail.

Reviews discussing cost-effectiveness studies of statin treatment were not included in this review, but were retained for use in discussion. Non-UK cost-effectiveness studies were retained and used to inform on possible modelling methodologies.

Quality assessment strategy
The quality of studies was assessed using a combination of key components of the British Medical Journal checklist for economic evaluations,[174] together with the Eddy checklist on mathematical models used in technology assessments.[175]

Results of review
Quantity and quality of research available
Electronic literature searches identified 206 potentially relevant publications. The inclusion and exclusion criteria were applied using the titles, abstracts and, when available online, full papers. Of these, 173 studies did not meet the inclusion criteria based on titles and abstracts only. Eight UK studies were identified at this stage. More detailed evaluations revealed that three of the potential UK studies did not fulfil all of the inclusion criteria. Two studies were excluded as the results were presented in terms of costs per events avoided.[176,177] A further study was excluded as the evaluation explored the cost-effectiveness of statins in several international settings including the UK.[178] The results presented for the UK were not detailed and were generated for comparison between the countries by using country-specific costings only. Five UK studies satisfied all inclusion and exclusion criteria (*Figure 25*) and form the basis of the review reported in this study.

Results: UK studies
Five UK studies satisfied all inclusion and exclusion criteria and form the basis of this review.[23,179–182] All scored well on modelling methodologies and presentation of results when assessed.

Three[179,180,182] of the five UK studies investigated the cost-effectiveness of statins in a male population only. Three[23,181,182] explored both primary and secondary prevention populations, whereas two[179,180] looked at primary prevention only. Three[23,179,180] defined their target population as being at risk of CVD, whereas two[181,182] used CHD risk levels. Three[23,181,182] used life-table approaches, one[179] used a Markov model and
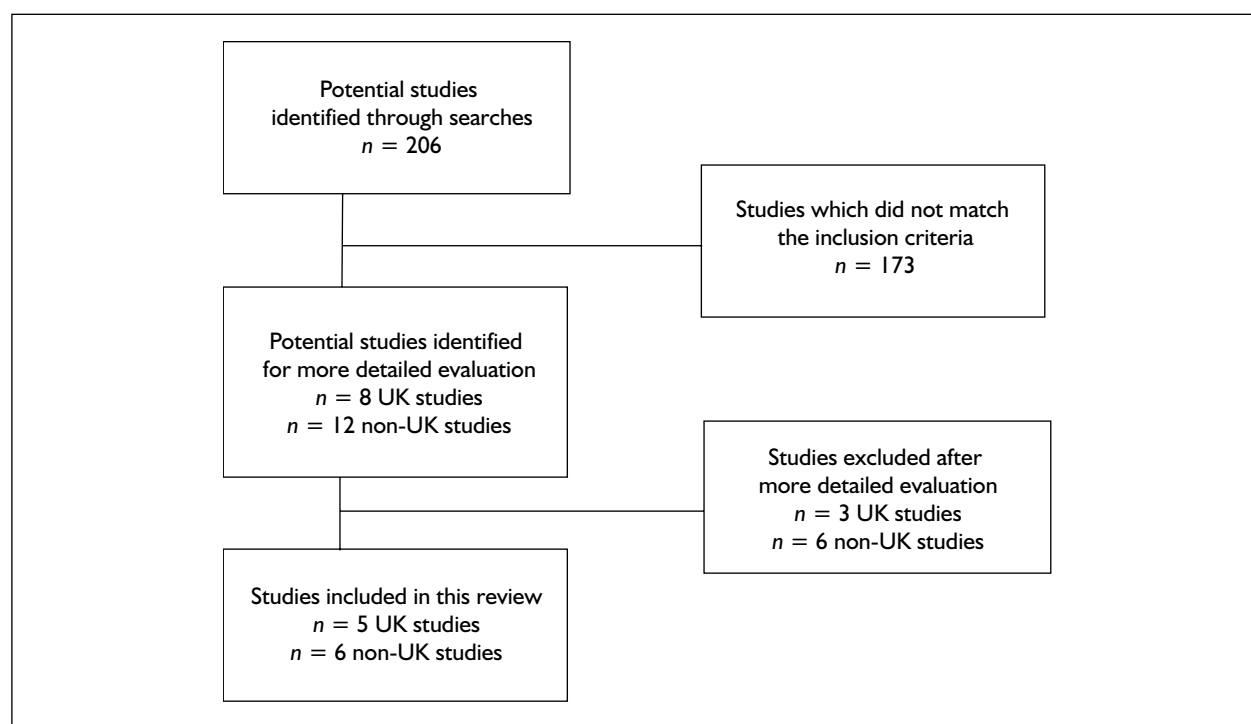
FIGURE 25 *Studies eliminated from or selected for the review after applying inclusion and exclusion criteria*

one[180] used a decision tree to compare the costs and benefits associated with statin treatment.

Synopses of the UK studies included in the review are given below.

Glick H, *et al*. A model for evaluating the cost-effectiveness of cholesterol-lowering treatment. *Int J Technol Assess Health Care* 1992;8:719–34[180]
Description
Glick and colleagues examine the cost-effectiveness of various cholesterol-lowering strategies in the USA and the UK. The costs and benefits associated with 20mg daily simvastatin were explored. A 28% reduction in cholesterol level was modelled based on data from the Lipid Research Clinics Primary Prevention Trial, while life expectancies, loss in life expectancy following onset of CHD and treatment costs were obtained from a UK study (referenced as unpublished data, Drummond and McGuire, 1989). The pattern of coronary risk for a 50-year-old man with a baseline cholesterol level of 7.5 mmol l^{-1} and varying risk factors – serum cholesterol level, systolic blood pressure, smoking habit and presence of left ventricular hypertrophy – was examined. The model uses a Framingham equation to calculate CHD risk before intervention and after intervention at 5-year intervals until the age of 75. The difference in CHD risk before and after intervention is therefore based on the surrogate end-point of cholesterol lowering. The

main results are presented in terms of the loss of expected years of life due to CHD, the loss in expected years of life that are free of CHD and cost per life-year gained (LYG). Costs and benefits are discounted at an annual rate of 5%. Depending on risk factors, simvastatin increases the number of expected years of life from between 0.41 and 0.83 years, with an associated cost per LYG of £22,900 and £9600 (1992 costs).

Comments
This appears to be a well-constructed model parameterised by relevant data available at the time. The main criticism of the model is that statin effectiveness is based on the surrogate end-point of cholesterol lowering. This may not have been out of choice, as the main clinical end-point trials were not published at the time. A full discussion of the issues surrounding the use of the surrogate end-point of cholesterol lowering as opposed to clinical end-points is discussed elsewhere in this report.

Pharoah P, Hollingworth W. Cost effectiveness of lowering cholesterol concentration with statins in patients with and without pre-existing coronary heart disease: life table method applied to health authority population. *BMJ* 1996; 312:1443–8[181]
Description
Pharoah and Hollingworth examine the cost-effectiveness of statins in lowering cholesterol

concentration in patients at varying risk of fatal CVD. The study examines the direct costs of statin treatment to a local health authority. A life-table approach was used to estimate the effect of statin treatment on survival by comparing direct costs of treatment offset by savings associated with reduction in coronary angiographies, non-fatal MI and revascularisation procedures. Effectiveness evidence for events avoided was taken from the Scandinavian 4S and Scottish WOSCOPS trials, while prevalence was based on evidence from White and colleagues.[106] The average annual cost of statin treatment was estimated to be £540 using two-thirds of patients on 20 mg daily and one-third on 40 mg daily, as in 4S. Costs for MI and revascularisation procedures were based on published evidence. All costs and life-years were discounted at 5%. Results were presented in terms of costs per lives saved and LYS for men and women. Using statin therapy for 10 years, the average cost-effectiveness for men aged 45–64 with no history of CHD and a cholesterol concentration greater than 6.5 mmol l^{-1} was £136,000 per LYS. The average cost-effectiveness for patients with pre-existing CHD and a cholesterol concentration greater than 5.4 mmol l^{-1} was £32,000.

Comments
This evaluation satisfied the majority of items used to assess the overall quality and appeared to be conducted well using the evidence available at the time. However, as the authors remark, the average figures hide enormous differences in cost-effectiveness between groups at different risk. Sensitivity analyses estimate figures ranging from £6000 per LYS in men aged 55–64 with cholesterol concentration above 7.2 mmol l^{-1} who have had an MI, to £361,000 per LYS in women aged 45–54 with a cholesterol concentration of 5.5–6.0 mmol l^{-1} and angina.

Caro J, *et al*. The West of Scotland Coronary Prevention Study: economic benefit analysis of primary prevention with pravastatin. *BMJ* 1997; 315:1577–82[179]
Description
Caro and colleagues estimate the economic efficiency of using pravastatin to prevent the transition from health to CVD in men with hypercholesterolaemia over a 5-year period. The study examines the direct costs of pravastatin treatment from an NHS perspective. Evidence from WOSCOPS is used to inform on benefits, average lengths of stay and cost data. Compliance was incorporated in the daily cost of using pravastatin (£1.66 per 40-mg tablet). Other costs

included monitoring, and costs for first hospital admission for management of events. All costs and benefits were discounted at 6%. A series of analyses explored the impact of varying discount rates, initial risk levels, efficacy of pravastatin and costs. Main outcomes are presented in terms of cost consequences, the number of transitions from health to CVD prevented, the number needed to start treatment and the cost per LYG. For men who have non-symptomatic hypercholesterolaemia, Caro and colleagues estimate that 31.4 patients need to start 5 years of pravastatin treatment to prevent one cardiovascular event, with 318 out of 100,000 men avoiding CVD. The events avoided equate to 2460 years of life with an associated drug cost of £23,340,984. Offsetting costs of events prevented gives an estimated net cost of £20,375 per LYG.

Comments
The approximate number of life-years gained during the treatment period is 225, while the majority of incremental life-years estimated are gained after treatment stops: 2235. As Caro assumes that patients who have received pravastatin for 5 years have the same life expectancy as the general population after treatment stops, the benefits are overestimated. In addition, WOSCOPS suggests that 9755 of 10,000 treated with pravastatin for 5 years would receive no benefit, but this is not discussed or analysed.

Pickin DM, *et al*. Cost effectiveness of HMG-CoA reductase inhibitor (statin) treatment related to the risk of coronary heart disease and cost of drug treatment. *Heart* 1999; 82:325–32[182]
Description
This study is based on a Trent Institute Working Group on Acute Purchasing study.[183] Pickin and colleagues estimate the cost-effectiveness of statin treatment in preventing CHD and examine the effect of the CHD risk level targeted and the cost of statins on the cost of effectiveness of treatment for men only. Published evidence from 23 RCTs was pooled to give an overall estimate of clinical effectiveness for the base case. A cohort life-table method uses data from outcome trials to estimate the cost per LYG from lifelong statin treatment at annual CHD event risks of 4.5% (secondary prevention) and 3.0%, 2.0% and 1.5% (all primary prevention). Evidence for effectiveness in patients at 4.5% risk was taken from the 4S trial, while evidence for patients at 1.5% risk was taken from the results of WOSCOPS. Owing to a lack of direct trial evidence, the effectiveness of reducing baseline risks of 2% and 3% was calculated by

interpolating between the WOSCOPS and 4S evidence. It was assumed that only half of the revascularisation procedures reported in 4S were avoided in the UK as the procedure rate is estimated to be 50% lower in the UK than in Sweden. A correction factor was used to adjust the mortality rate as the population in the trial was at higher risk of mortality than the general population. The baseline mortality risk was adjusted by 5% to take account of decline in CHD mortality in the years since the trial was reported. The annual cost of simvastatin and pravastatin was based on the dosage used in the trials, 27 and 40 mg, respectively. Events avoided included CABG (£5725), PTCA (£2436), admission for MI (£2306), and admission for stroke (8823). Cost and benefits were both discounted at 6%.

For gross discounted lifelong treatment for simvastatin the cost per LYG ranged from £5100 to £12,500 for risk levels between 4.5% and 1.5%, respectively. For pravastatin the results ranged from £7400 to £18,200. Sensitivity analyses included estimates of cost-effectiveness at varying annual costs of statin treatment. The results were sensitive to the cost of statins. The baseline annual cost of simvastatin and pravastatin was £555 and £811, respectively. This is high compared with current annual prices of around £250–350. At current prices the cost per LYG ranges from approximately £8000 to £2000 at CHD risk levels of 1.5% and 4.5%, respectively.

The study also estimates the proportion of the UK population that will be eligible for primary treatment at the levels of CHD risk evaluated in the modelling. The conclusion is that although statins are cost-effective at levels of risk as low as 1.5%, full implementation at this level would consume almost 90% of the current expenditure on drugs and is therefore unrealistic.

Comments
This study is unique among the UK cost-effectiveness studies in that the main objective was to estimate the cost-effectiveness of statin treatment in subgroups of the population at different levels of absolute CHD risk. The sensitivity analysis of varying the annual cost of statins allows an estimation of the cost-effectiveness of statin treatment at current prices. The results show that even at a low risk level of 1.5% the cost per LYG is well below acceptable willingness-to-pay thresholds. The estimation of the proportion of the population eligible for treatment, however, suggests that implementation at this level is not sustainable.

Ebrahim S, *et al*. What role for statins? A review and economic model. *Health Technol Assess* **1999;3:(19)**[23]
Description
This study is also based on the Trent Institute Working Group on Acute Purchasing study.[183] Ebrahim and colleagues use a life-table method to compare the cost-effectiveness of statins with other cholesterol-lowering treatments at varying levels of CHD mortality risk. Baseline risks of CHD mortality were used instead of the more commonly used combined fatal and non-fatal CHD event rates as these data are available for the other cholesterol-lowering treatments which are compared with statins. The study explains that a CHD event rate of 3% equates to a CHD mortality rate of between 1 and 1.5%. The study assumes that there has been a 5% annual decline in CHD mortality rates since the trials reported and has adjusted the baseline mortality rates accordingly. This rate is varied in a sensitivity analysis. Cost-effectiveness was calculated assuming that patients are treated for life. This was achieved by extrapolating the survival curves from the trials to a lifetime period. The effectiveness of statins is based on a meta-analysis of 23 trials. The trials that contributed most to the pooled estimates were WOSCOPS (8% weighting), 4S (21% weighting), CARE (16% weighting), LIPID (48% weighting) and AFCAPS/TexCAPS; (2% weighting). The costs of statins are based on the average dosage used in the RCTs. Costs and benefits are discounted at 6% per annum. Cost-effectiveness was estimated from the perspective of the NHS and included direct costs only. Results are presented for baseline annual CHD mortality rates of between 0.5 and 6%. The cost per LYG ranges between £4802 and £13,260 (6% and 0.5% annual mortality rate, respectively).

Comments
Although this study is based on the same spreadsheet model as the Pickin study, its aims and objectives were different and the results are therefore not directly comparable. However, after adjusting for the difference between baseline CHD mortality risk and baseline fatal and non-fatal CHD risk, the cost per LYG results from this study (£4802–13,260) are very similar to the Pickin results (£5100–12,500).

Overview of results from the five UK studies
Comparison of the results is not straightforward owing to the different objectives, populations and costings used. Caro's objective was to estimate the economic efficiency of using pravastatin to prevent the transition from health to CVD in men with

TABLE 33 *Summary of results from the UK cost-effectiveness studies used in the review*

Study	Model	Population (trial on which study is based)	Description	Central estimate cost/LYG (inflated to 2004 costs)
Caro, 1997[179]	Markov	Primary males (WOSCOPS)	CHD risk: 1.5% Drug: pravastatin Mean age: 55 years Discount rate: 6% Horizon: 5 years	£23,747
Glick, 1992[180]	Decision tree	Primary (Lipid Research Clinics Primary Prevention Trial)	High risk Low risk Drug: simvastatin Mean age: 50 years Discount rate: 5% Horizon: 25 years	£12,745 £30,402
Ebrahim, 1999[23]	Life table	Primary/secondary	CHD mortality risk: 6–0.5% Drug: composite from 23 trials Discount rate: 6% Horizon: lifetime	6–0.5% £5291–14,610
Pickin, 1999[182]	Life table	Primary (WOSCOPS), secondary (4S)	CHD risk: 4.5–1.5% Drug: pravastatin (primary) Drug: simvastatin (secondary) Mean age: 55 years (primary, male), 58 years (secondary, 80% male) Discount rate: 6% Horizon: life time	4.5–1.5% £8154–20,053 £5619–13,773
Phoroah, 1996[181]	Life table	Primary (WOSCOPS) Secondary (4S)	No history of CHD (primary), pre-existing CHD (secondary) Mean age: 55 years (primary, male) 58 years (secondary, 80% male) Discount rate: 5% Horizon: 10 years	£180,554 £42,483

hypercholesterolaemia, whereas Pickin estimated the cost-effectiveness of statin treatment in preventing CHD, the effect of the CHD risk level targeted and the cost of statins on the cost-effectiveness of treatment, and the cost-effectiveness in subgroups of the population at different levels of CHD risk. In comparison, Pharoah estimated the cost-effectiveness of statins in lowering serum cholesterol concentration on people at varying risk of fatal CVD, and explored the implications of changing the criteria for intervention on costs and cost-effectiveness for a purchasing authority.

Table 33 summarises the results from the five UK studies described above. The results have been adjusted to 2004 prices using inflation rates from the Office for National Statistics (ONS) for each year since study publication. For the majority of studies (except for Pharoah[181]), the results for primary treatment are of a similar magnitude. For primary patients at low baseline risk of CHD the results vary between £20,000 and £30,000. For primary patients at high baseline risk of CHD the results vary between £8000 and £13,000. It is generally accepted that statins are more cost-effective for patients at a higher baseline risk, as shown in these studies. As patients in secondary prevention are usually at high risk, the cost per LYG would be expected to be lower than in primary treatment, and this is demonstrated in the Pickin study. The results from the Pharoah study appear to be anomalously high compared with the other four studies. The reason for this is unclear. It would be expected that statins are more cost-effective over a longer time-horizon owing to the opportunity to accrue more benefits. The Pharoah study has a shorter time-frame than most of the other studies and this could partially account for some of the differences. However, the Caro study has a time-frame of 5 years with a cost per LYG of £23,000.

Results: non-UK cost-effectiveness studies

Twelve non-UK cost-effectiveness studies were retained to inform on methodological issues for use in the ScHARR cost-effectiveness study and as a rough comparison of the magnitude of cost-effectiveness results. These were reviewed with respect to:

- model design: life table, Markov, cohort, patient simulation, etc.
- techniques used for applying effectiveness evidence: cholesterol, events
- health states modelled.

Of the 12 cost-effectiveness studies originally retained, two[184,185] contained insufficient information to assess the model structure and methodology and one[186] was based on a previously published model[187] (already included in the review) with no further useful information. Three studies were based on trials that failed the inclusion criteria in the effectiveness review and therefore, although of interest methodologically, the results will not be included in this discussion.

Of the remaining six studies the settings were: two in primary prevention, three in secondary prevention and one in both settings.[188–193] The primary prevention models were all based on the WOSCOPS trial and the secondary prevention models were based on the LIPID (two), 4S (three) and CARE (one) trials. The studies were based on costs in Australia (two studies), Canada, Sweden, The Netherlands and the USA (one each). Only one study, Johannesson[194] included health state utilities and therefore reported results in terms of QALYs; the other studies reported cost per life-years gained. The aim of the Johannesson study was to estimate at what risk of CHD it is cost-effective to initiate cholesterol-lowering drug treatment in Sweden for men and women at various ages. Although this is a Swedish study and health transition rates and mortality are based on Swedish data, this aim is comparable to the aims of this assessment report.

Results

Johannesson[194] reports the optimal 5-year risk cut-off at QALY willingness-to-pay thresholds of US $40,000, $60,000 and $100,000 for men and women between the ages of 35 and 70 years. *Table 34* shows the results for the oldest and youngest age bands. For example, at a QALY threshold of $40,000 (the equivalent of a £21,000 threshold), it is cost-effective to treat a 35-year-old male at a CHD 5-year risk of 3.34% and higher.

From the other studies, in primary therapy the cost per LYG for pravastatin ranged from $32,000 to $51,000 and in secondary therapy from $10,000 to $13,000. Simvastatin estimates were all based on the 4S (secondary prevention trial) and ranged from $5,000 to $10,000.

Model design

Model design was described as Markov in two studies,[190,194] survival curve in one study,[192] life table in one study[193] and spreadsheet analysis in one study.[188] One study was an economic evaluation alongside a clinical trial.[191]

Health state utilities

The Johannesson study[194] derived the baseline health utility from a Swedish general population study based on the time trade-off method. The decrement in quality of life due to CHD was assumed to be 0.10 based on previous studies.

Health states used and methods for modelling risk reduction in UK and non-UK cost-effectiveness studies

Both UK and non-UK studies were examined for the type and frequency of health states modelled and risk reduction methods used. This was used as an information gathering exercise to inform the development of the ScHARR model. The health states modelled (not including death) are shown in *Table 35*. MI, revascularisation, angina, stroke and TIA were the most frequent. Revascularisation is high on the list as some studies were specifically exploring the use of statins following PCI.

TABLE 34 *Optimal risk cut-off for different willingness-to-pay thresholds*

Age (years)	$40,000		$60,000		$100,000	
	Men	**Women**	**Men**	**Women**	**Men**	**Women**
35	3.34	2.95	2.45	1.99	1.66	1.24
70	21.36	20.30	10.37	9.10	5.90	4.96

TABLE 35 *Health states modelled in UK and non-UK studies*

Health state modelled	Count
MI	8
Revascularisation	5
Stroke	4
Angina	3
TIA	2
Silent MI	1
Cardiac catheterisation	1
Coronary insufficiency	1
Coronary angiographies	1

TABLE 36 *Methods used in UK and non-UK studies for modelling the efficacy of statins*

Efficacy modelled by	No. of models
Relative risk (trial source)	4
4S	1
WOSCOPS	3
Cholesterol lowering via Framingham	1
Cholesterol lowering (non-Framingham equation)	1
Hazard ratios	1
Event rates from trial data	1
Survival curves from trial data	2
Life table	2

Of the models examined, four used a relative risk approach (three based on WOSCOPS and one based on 4S), two used a cholesterol-lowering methodology and six used other methods (*Table 36*).

Several modelling approaches were used in the published cost-effectiveness studies. The most frequently adopted technique was to model efficacy by applying relative risk evidence from RCTs. The appeal of this approach is due to several factors: the availability of relative risks in RCT publications, the ability to synthesise relative risks to provide pooled evidence and the potential for incorporating relative risk within a Markov-type model.

Cost-effectiveness evidence from industry submissions

As part of their industry submissions to NICE, Pfizer, Novartis, Bristol-Myers Squibb and AstraZeneca provided information about the cost-effectiveness models that they had produced. These were critiqued using the combined BMJ and Eddy frameworks and the results of this are shown in Appendix 28. This section describes the main aspects of these models.

Merck Sharp & Dohme provided details of a within-trial economic analysis for simvastatin. This is also discussed below.

Pfizer: cost-effectiveness model of atorvastatin
Model overview
This economic model evaluates the cost-effectiveness of atorvastatin compared with placebo (and simvastatin) in the primary and secondary prevention of CHD and CHD plus stroke. The cost-effectiveness of atorvastatin in particular subgroups of patients (e.g. men, women, diabetics, and by age) is explored. Cost-effectiveness in primary prevention populations at different baseline 10-year risk levels (15%, 20%, 25% and 30%) is considered.

The model was designed in Microsoft Excel$^{\text{TM}}$. A Markov modelling approach was adopted, using annual cycles. Health states in the model are: fatal MI, non-fatal MI, sudden death, stable angina, unstable angina, fatal stroke and non-fatal stroke. The annual likelihood of a patient experiencing a fatal or non-fatal coronary event is determined by one of two risk engines: the Framingham risk prediction model[195] and, for patients with diabetes, the UKPDS risk engine.[196]

The base-case analysis considers lifetime costs and benefits. Outputs are expressed as cost per QALY gained. The cost year is 2004. All costs are taken from the perspective of the UK NHS. Discounting of costs and effects is performed at rates of 6% and 1.5%, respectively.

Summary of effectiveness data
A cohort of patients of the same age and with a given set of risk factors, such as blood pressure level, lipid parameters and smoking status, enters the model. The annual likelihood of a CHD event is predicted using risk equations. The Framingham risk prediction model predicts the likelihood of initial (primary) and subsequent (secondary) CHD events for men and women separately, based on an accelerated life model; 'time to failure' is assumed to follow a Weibull distribution. The alternative risk equation, the UKPDS risk engine, is used for diabetic patients and is a first event equation only. Therefore, the Framingham second event equation is used to estimate the occurrence of subsequent events for diabetic patients.

For modelling of primary prevention, patients are assumed to begin without a history of CHD. Yearly transitions to a CHD event are predicted for a patient from the relevant risk equation. If a CHD

event is predicted to take place in a given year, it is assigned an expected cost according to the estimated probability distribution of event types. The source of these data is unclear and it was not possible to verify where they came from. Each event type is assigned a discounted lifetime cost. If the CHD event was non-fatal, a second risk equation predicts the yearly conditional probability of transition to a subsequent CHD event, and the expected cost of subsequent events is estimated as above. If a CHD event is not predicted to take place in a given year, the patient's age-specific mortality rate is estimated from national all-cause death rate tables. The cumulative transition probabilities to death allow life-years gained to be calculated. For secondary prevention analyses, the patient enters the model with a history of CHD, and the Framingham second event risk equation is used to predict the subsequent risk of further CHD events (patient is at higher risk of subsequent events). Data sources for risk factors used in the model are the Health Survey for England (HSE) 1998[197] and Health Survey for England Trends 2003. Baseline cholesterol (total and HDL) is taken from WOSCOPS and 4S.

Efficacy of interventions

The Framingham risk equations used in the model work on the ratio of plasma total cholesterol to HDL-C. The treatment effect of alternative statin therapies on this ratio drives the event rates in the model. These parameters are taken from a meta-analysis for all licensed doses. They are based on a weighted mean percentage reduction of each statin, derived by multiplying the efficacy of each dose of each statin by the proportion prescribed during the 6 months from December 2003 to May 2004.

The percentage mean decrease in total cholesterol and mean increase in HDL-C will play a key part in influencing the cost-effectiveness results. Long-term trials have shown that total cholesterol levels reduce in the short term, but increase slightly before levelling off at around 1 year. The

surrogate modelling in the ScHARR model uses a total cholesterol decrease of 25% and an HDL increase of –0.009 (i.e. an increase from baseline). This is based on the ASCOT-LLA and CARDS trials. These trials were chosen for reasons described in the effectiveness section of this report. The Pfizer estimates of a 33% decrease in total cholesterol and a 7% increase in HDL are mainly based on short-term trials (*Table 37*). For reasons not given, neither ASCOT-LLA nor CARDS is included in their meta-analysis.

No discussion of the potential limitations of the use of the Framingham equations is given. There is also no discussion of the relationship between cholesterol lowering and clinical end-points. No attempt has been made to use the results from the major outcomes trials for atorvastatin for validation purposes.

CVD events are modelled by increasing the number of coronary events predicted by the primary and secondary risk equations, using the ratio of non-haemorrhagic strokes to CHD events reported in cause-specific mortality tables for England and Wales in 2001: 0.32 for men and 0.68 for women.[198] The proportion of stroke events that are fatal/non-fatal is set in line with fatal/non-fatal CHD events, as determined by Framingham risk equations which vary with age, on average being 23% fatal for first events and 39% fatal for second events. When costing stroke events it is assumed that the proportion that is fatal (30%) or non-fatal (70%) is in line with proportion of fatal or non-fatal CHD events as determined by the Framingham risk equations. This varies with age, but averages approximately 23% fatal for first events and 39% fatal for second events.

It is assumed that the treatment effect of statins (lowering of total cholesterol and increases in HDL-C) does not occur until the end of the first full year of treatment. This is based on evidence from statin therapy trials indicating that risk reduction is typically delayed by around 12 months.

TABLE 37 *Efficacy of model interventions for all licensed doses, from meta-analysis*

Intervention	% mean change in TC (SD)	% mean change in HDL-C (SD)
Atorvastatin	–32.9 (1.8)	+7.1 (1.1)
Simvastatin	–24.6 (2)	+7.5 (2.6)
Placebo	0	0

SD, standard deviation; TC, total cholesterol.

TABLE 38 *Unit cost (£) of CHD and CVD events*

Event	Cost (£)
Sudden death	406
Angina	1959
Unstable angina	2221
Fatal MI	1152
Non-fatal MI	4070
Unstable MI	2926
Non-fatal stroke	2367
Fatal stroke	3383
Follow-on cost (CHD)	258
Follow-on cost (stroke)[a]	258

[a] Potential error in follow-on cost: estimates for each year subsequent to the year in which the event occurred given in Clarke *et al*. (2003)[200] were not the same for fatal stroke and fatal MI.

An annual continuation rate at which a patient is likely to continue taking medication can be set between 0 and 1, although in the base-case this is set to 1 and no sensitivity analysis is reported.

Cost and resource use
Therapy costs are based on drug costs. For atorvastatin this is based on 2004 prices as quoted in the BNF.[49] The price of generic simvastatin is based on the likely reimbursed prices as from 1 September 2004.[45]

Costs are assigned to each type of event (fatal or non-fatal MI, sudden death, stable or unstable angina and fatal or non-fatal stroke) (*Table 38*). Event costs have been taken from the UK Prospective Diabetes Study.[200] They are based on the hospital inpatient costs associated with these complications in diabetic patients in the year in which the complication occurred. The cost of ischaemic heart disease (£1959) is used as a proxy for angina and the cost of heart failure (£2221) as a proxy for unstable angina. The same source was used to obtain estimates of the subsequent increase in annual non-inpatient costs associated with a vascular event. These are diabetic patients and therefore these costs may be higher than the cost of these events for a non-diabetic population, owing to complications and co-morbidities in the diabetic population.

The weighted average for a coronary event is used. A reweighted average for coronary and stroke events is used if stroke is included as an outcome.

The stroke costs appear low, relative to other published papers on the cost of stroke in the

UK.[201,202] The cost of a fatal stroke is higher than the cost of non-fatal stroke, which is surprising given that stroke patients, particularly those who have experienced a major stroke, are likely to require substantial long-term care.

No adverse events are costed. This is not justified in the text, but is not likely to be a significant issue.

Utilities
The default utility values in the model are 0.83 QALYs for a person who has not had a CHD event, in line with population norms,[203] and 0.75 for individuals who have experienced a CHD event. This is a weighted decrement in line with estimates from Clarke and colleagues[204] suggesting permanent utility decrements of 0.055, 0.09 and 0.108 for patients as a result of an MI, ischaemic heart disease and heart failure, respectively. For stroke the decrement is taken from the same source and is set at 0.164.[204]

If only CHD events are being considered, the first CHD event is associated with a decrement to 0.75 and a second CHD event generates a subsequent multiplicative reduction. If CHD and stroke events are being considered, the CHD and stroke utility decrements are first weighted by the male or female proportion of CHD to stroke events, and the resulting weighted decrement is then applied to first and second CHD and stroke events multiplicatively.

Results
The results are presented for CHD and stroke combined, and not for CHD only. Only a very limited discussion of the results is provided.

In secondary prevention, for a non-diabetic population, incremental cost-effectiveness ratios (ICERs) are between £3200 and £5000 for men and £4500 and £5900 for women. For a diabetic population these fall to below £3000. The results indicate that atorvastatin is generally more cost-effective in men for non-diabetics, but slightly more cost-effective in women in a diabetic population. The ICERs are lower for younger patients (aged 50 years) than for older patients (aged 70 years).

In primary prevention, ICERs range between £1200 (female, aged 50 years at 30% 10-year risk) and £7300 (male, aged 70 years at 15% 10-year risk). Across all scenarios ICERs decline as baseline risk increases. The ICERs are lower in younger patients (50 years) than in older patients (70 years), given the same baseline risk. The

ICERs are generally lower in women (except for women aged 50 years at 10-year risks of 15% and 20%).

The reported ICERs in primary prevention for a man aged 50 years at 20–30% 10-year risk are lower than the ICER for a man aged 50 years with existing CHD (with a total cholesterol of 6 mmol l^{-1}). This is counter-intuitive. It seems more likely that a person who has already had a CHD event would, on average, be at significantly greater 10-year risk than 20% and it might therefore be expected to be more cost-effective to treat these patients. No comment or explanation is given in the results or discussion section.

Results are also reported for atorvastatin compared with simvastatin. The ICERs for secondary prevention all fall below £17,000 for non-diabetics and £11,000 for diabetics. In primary prevention the ICERs range between £4200 (female, smoker, diabetic, aged 50 years at 30% 10-year risk) and £23,100 (male, aged 70 years, non-diabetic, non-smoker at 15% 10-year risk).

Sensitivity analysis
Limited univariate sensitivity analysis was undertaken looking at changes to the discount rates for costs and benefits. The ICER for atorvastatin compared with placebo did not exceed £14,000.

Probabilistic sensitivity analysis (PSA) was undertaken. Each PSA was based on 1000 iterations. The distributions used were not detailed in the report. The PSA is reported for a willingness to pay of £20,000. The numbers given in Appendix E are the same as those reported in Table 17 of the main report. The acceptability curves for willingness to pay of £20,000 per QALY are shown for primary prevention, for CHD and stroke, for the comparison of atorvastatin with simvastatin, but not for atorvastatin with placebo. There is no discussion of how this curve may differ for other scenarios.

Summary
The model structure is reasonable and flexible. However, little justification is provided for the methods and data sources used, or how these may impact on results. For instance, there is no discussion of the use of cholesterol lowering to predict CHD events indirectly rather than the use of relative risks taken directly from trials.

Results are not shown for CHD outcomes alone, or for 10-year risk levels below 15%. Little discussion of results is given. This would have been helpful, particularly to explore in more depth the reasons for the results for primary prevention being lower than for secondary prevention.

Novartis: cost-effectiveness model of fluvastatin
Model overview
The Novartis model explores one specific application of statins in secondary prevention: for patients following PCI. The model is based on the LIPS trial.[110] LIPS was the first large RCT designed to determine the effect of statin treatment on clinical outcomes following a successful PCI. The primary outcome of LIPS was the survival time for which patients remain free of major adverse cardiac events (MACE), defined as cardiac death, non-fatal MI or an intervention procedure.

The trial involved 1677 patients (84% male), aged 18–80 years (mean age 60 years) with stable/unstable angina or silent ischaemia in Europe, Canada and Brazil. Baseline cholesterol was between 135 and 270 mg dl^{-1}. Follow-up was for 3–4 years. Exclusion criteria included hypertensives (trial mean blood pressure was 128/75), previous intervention, severe valvular disease, idiopathic cardiomyopathy, congenital heart disease and severe renal function. Patients were assessed at 6 weeks and thereafter at 6-monthly intervals.

The trial compared fluvastatin IR (see below) 40 mg twice daily plus diet and lifestyle counselling versus diet and lifestyle counselling alone. The results were favourable and particularly significant within a predefined subgroup of diabetics. The risk of MACE was lower in the subgroup of patients with diabetes in the fluvastatin arm compared with the placebo group (21.7% versus 37.8%, RR 0.53).[42]

Fluvastatin is available in two formulations: IR, an immediate-release formulation and XL, an extended-release formulation. Fluvastatin XL has been shown to be more effective than fluvastatin IR, 40 mg once daily, and equally as effective as fluvastatin IR, 40 mg twice daily. However, as the model is based on LIPS, efficacy relates to the IR formulation.

The model has a Markov structure programmed in Data 4.0 Treeage software. Cycle time is 1 month. Patients enter as 'healthy after first PCI'. Patients can remain healthy post-PCI or move to AMI or death (cardiac/other), or have a subsequent PCI/CABG. Patients cannot return to
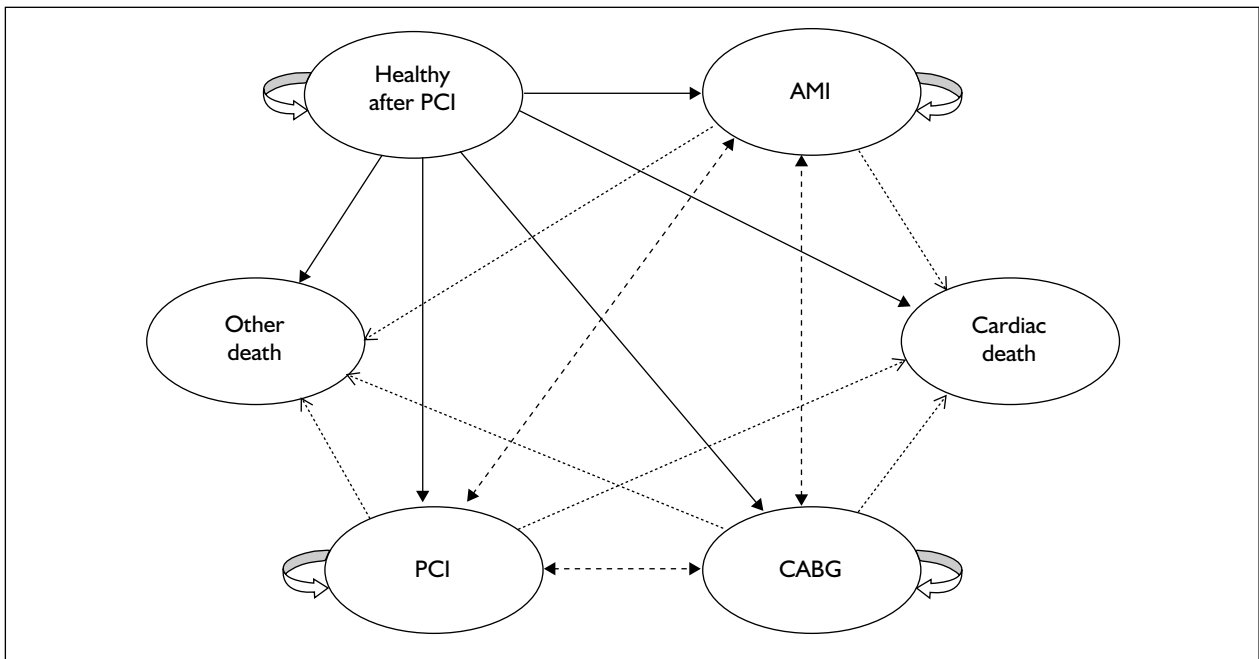
FIGURE 26 *Health states and disease progression*

the 'healthy after PCI' state. Patients in the AMI state can recover and remain healthy, suffer a further MI which incurs a decreased quality of life and increased costs, undergo PCI/CABG or die. Patients in the PCI/CABG state can undergo further interventions or have secondary fatal/non-fatal events. The time-horizon is 10 years.

Health states and disease progression are shown in *Figure 26*.

Summary of effectiveness data
The model uses the event rates which form the composite primary end-point (MACE index) in LIPS after converting them to monthly probabilities. The model uses the same rates for both arms until the time-point where the survival curves begin to separate in the trial. Event rates are therefore constant for both arms for all states except for AMI after 28 months, PCI

after 18 months and cardiac death after 3 months. The trial was insufficiently powered to detect differences in events subsequent to the first event and the assumption is made that subsequent events were the same for both arms. This is a conservative assumption. The model results are therefore driven by the difference in event rates for the states of AMI, PCI and cardiac death for first events and from the time-points listed above.

Costs and resource use
An NHS perspective is used. Sources for inpatient procedures and outpatients are NHS reference costs. All costs appear reasonable, except that Lescol XL is used instead of Lescol under the assumption that the efficacy is the same (this appears to be the case from the clinical effectiveness section of the report). The impact of the price difference between Lescol and Lescol XL is examined below.

TABLE 39 *Utility weights*

State	Health state utility weights (SD)	Distribution	Event/procedure (transition) utility weights (SD)	Distribution
Remain healthy	0.86			
AMI	0.78 (0.15)	Beta	0.083 (0.028)	Beta
PCI	0.86 (0.16)	Beta	0.042 (0.014)	Beta
CABG	0.86 (0.16)	Beta	0.059 (0.020)	Beta

Utilities

Several references are given for utility sources.[205–207] Subsequent AMI, PCI or CABG assigned disutility weights were subtracted from the utility score to take into account the decrease in their health status during that transition period (*Table 39*):

- healthy: 0.86[205]
- PCI and CABG patients, utility weights of 0.70 for 2 months before the intervention (to represent decreased quality of life from angina)
- 0.69 and 0.68 for PCI and CABG in the month of intervention
- 0.78 for 2.5 months post-CABG for recovery from surgery
- AMI patients were assigned disutility of 0.0825 over 3 months to account for a period of recovery and were assumed to have lower post-AMI utility (0.78), irrespective of subsequent interventions.

Model outputs

Outputs are costs and health outcomes of statin therapy following successful PCI (subgroup analysis of diabetics). Results are reported as costs per QALY.

Results

The base-case cost per QALY is £3200 for all patients and £1900 in the diabetic subgroup.

PSA

For a willingness-to-pay threshold of £10,000 per QALY, fluvastatin was cost-effective in 84.8% of cases, and for a threshold of £30,000 the probability of cost-effectiveness was 97.6%. Fluvastatin was cost-saving in 25% of cases.

One-way sensitivity analysis

Various one-way sensitivities were performed. The parameter with the greatest impact was the time-horizon. Over 25 years fluvastatin dominated; at 5 years the ICER increased to £21,000.

Summary

This is a reasonably well-constructed model. Efficacy is based on an international trial across Europe, with centres from Canada and Brazil included. PCI rates in these countries were not discussed and it is difficult to know how applicable the results are for the UK. It is unclear why Novartis decided to focus on post-PCI patients, as the justification for this is not given. It may be because the "prevention of coronary events after percutaneous coronary intervention" is specifically mentioned in the licensed indications. However,

the other statins are not necessarily excluded for this use.

A failing with the model is validation against trial data. Validation of this type would help to determine how accurate the model is in predicting event rates.

Although efficacy is based on Lescol, the cost of the cheaper Lescol XL is used in the model. If clinicians prescribe Lescol XL 80 mg post-PCI then this is not an issue. However, if they prescribe the more expensive Lescol at two 40-mg doses then this analysis will be biased in favour of fluvastatin. Using the cost of Lescol increases the ICER from £3000 to £13,000.

Bristol-Myers Squibb: cost-effectiveness model of pravastatin

Model overview

This is an individual patient-level simulation model comparing treatment with pravastatin 40 mg daily alongside diet and exercise compared with diet and exercise alone. The model has been previously published.[179] There are two submodels representing primary and secondary prevention. The health states modelled in primary prevention are non-CVD death, CVD death and non-fatal CVD event, and in secondary prevention are MI, CABG, PTCA, stroke, TIA, angina, angiography and CVD death. Efficacy is based on the WOSCOPS and LIPID trials, with compliance rates assumed from these trials. The time-horizon is 5 years maximum in both submodels based on the average follow-up in WOSCOPS. No health state utilities are used in the model and therefore the results are presented as cost per life-year gained. The model estimates costs from the perspective of the NHS. Discounting for both costs and health is at 3.5% per year. Various univariate and multivariate sensitivity analyses were performed.

Unit costs

Unit costs are not presented in the industrial submission report. The following unit costs are taken from an Excel spreadsheet in the submitted model (*Table 40*).

Validation

No model validation is reported either in the published study or the submission report.

Results

The results are applicable to the average age of the participants in the trials from which efficacy data are taken. Results for primary therapy are

TABLE 40 *Unit costs for the base scenario in the Bristol-Myers Squibb economic model*

Unit costs Scenario:	Base scenario		
Definition	**Acute event**	**1st year**	**Subsequent years**
Fatal MI	£2725.58		
Fatal stroke	£5552.25		
Fatal other CVD	£5335.90		
Angiography	£826.97	£213.78	£324.52
TIA	£2057.33	£154.23	£44.48
Stroke	£7661.14	£8986.08	£4720.22
PTCA	£2256.49	£213.78	£324.52
CABG	£8141.35	£213.78	£324.52
Angina	£2220.09	£231.04	£134.46
MI suspect	£3893.25	£261.09	£98.06
MI	£3893.25	£261.09	£98.06
	Units		
Monitoring frequency	2	Per year	
Serum cholesterol test	£5.00		
GP visit	£26.00		
Daily cost of drug	£1.06		

presented in 10-year CHD risk bands ranging from 4 to 30%.

In primary prevention the cost per LYG ranges from £61 to £120,000 (30–4% 10-year risk) for men and from £67 to £121,000 (30–4% 10-year risk) for women. In secondary treatment pravastatin dominates (costs less and is more effective) for both men and women. At approximately 15% 10-year risk (the approximate average 10-year baseline risk in WOSCOPS) the cost per LYG is around £5000–8000 for both men and women.

Sensitivity analysis

Extensive one-way sensitivity analysis was conducted, including discount rates, time-horizon, increased reduced treatment costs, and upper and lower 95% confidence intervals used for event rates. Best and worst case scenario results are presented. For primary prevention the best case scenario cost per LYG ranges from £0 to £49,000 and the worst case scenario ranges from £10,000 to infinity. In secondary prevention pravastatin dominates in all scenarios except with a 12-month horizon.

As the results have been presented at a range of risk levels in primary prevention, they have been summarised here in terms of a willingness-to-pay threshold. Three thresholds have been used:

TABLE 41 *Baseline scenario: risk cut-off point at which pravastatin is cost-effective at a given threshold*

	£15,000	£20,000	£30,000
Men	9%	7%	5%
Women	11%	8%	5%

TABLE 42 *Sensitivity analysis: risk cut-off point at which pravastatin is cost-effective at a given threshold*

		£15,000	£20,000	£30,000
Best case	Men	6%	5%	4.5%
	Women	7%	6%	4.5%
Worst case	Men	20%	16%	10%
	Women	17%	14%	11%

£15,000 £20,000 and £30,000. *Tables 41* and *42* show the approximate 10-year CHD risk level at which the cost per life-year estimates are cost-effective at a given threshold. For example, pravastatin is cost-effective in men at risk levels of 7% and higher at a willingness-to-pay threshold of £20,000. This falls to a 5% risk level in the best case scenario and rises to 16% in the worst case scenario.

Insufficient information was available in the industrial submission to critically appraise the

economic model. The model supplied is, in effect, a 'black box'. The only visible elements are the inputs and the results. Although the model has been published, without access to the calculations involved in generating the results the reviewers can provide no commentary as to the validity of the results generated.

AstraZeneca: cost-effectiveness model of rosuvastatin

Model overview
Two probabilistic models were developed to establish the cost-effectiveness of rosuvastatin and other available statins in the UK in treating newly diagnosed hypercholesterolaemic patients. The first (titration model), a 1-year model, estimates the short-term cost-effectiveness using 12-week cycles to titrate to higher statin doses if current National Service Framework (NSF) targets are not met. The second (CHD model) assesses the relative cost-effectiveness of available statins in comparison to no treatment, over a 20-year period. A UK NHS perspective is taken, with the majority of costs expressed at 2004 base prices.

Summary of effectiveness data
The effectiveness of statins in reducing cholesterol is based on US trials of 6 weeks' duration. The STELLAR[208] trial provides evidence for four of the five statins, while Ballantyne[209] is the source for the fifth one (fluvastatin). The authors identify that the use of US data is a potential weakness and UK-specific data (Wilson[210]) are used to generate baseline total cholesterol and LDL-C levels for a hypothetical cohort of 1000 patients. The implications and the uncertainty in how chemically induced reductions in cholesterol translate to actual reductions in cholesterol-related CHD risks over medium and longer terms are discussed. However, as long-term evidence on cardiac events avoided is not available for rosuvastatin, using evidence of effectiveness based on cholesterol reduction is reasonable. It is claimed that a 6-week trial is sufficient to establish percentage reduction in cholesterol as pooled analysis of Phase III studies demonstrates that the majority of the effect is evident within 2 weeks. However, as the predicted cholesterol reduction is used to generate the probabilities of events in the long-term model, the authors are assuming that the maximum reduction achieved at 6 weeks is held constant over the horizon modelled. Evidence for rosuvastatin is available from studies of 52 weeks' duration (Olsson[125] and Brown[126]), and a comparison of results with a discussion demonstrating the validity of using very short-term evidence to extrapolate over

20 years would increase the authenticity of the assumption made.

The effectiveness evidence used in the cost-effectiveness evaluation is presented in Appendix 29, *Table 148*.

The authors state that beta distributions are used to explore uncertainty in the effectiveness evidence, but the complementary log–log distribution has been used.[211] This is an obscure, rarely used distribution and the arguments used to support this choice are unclear. It is felt that a more transparent explanation for the choice of distribution, supported by examples of relevant use in published evidence, should have been provided in the text.

Difficulties were encountered in generating results from the Excel model provided; hence, it was impossible to examine what difference using an alternative distribution would have made to the results. However, it is not thought that the choice would have a huge impact on the results generated.

Framingham equations are applied using 4-year cycles to predict events using either the statin induced or sampled baseline cholesterol levels for the treatment and comparator cohorts, respectively. The authors refer to recent publications, which suggest that the Framingham equations overpredict events for a UK population. Based on this evidence, they conservatively recalibrate the number of initial events predicted.[212] As the source evidence does not provide details on possible overprediction on secondary events, the authors use the ratio from the reduction in initial events to adjust the number of secondary events. For secondary disease, again conservatively, they model first events only. However, as it is assumed that everyone commences in the stable angina state, the costs and benefits accrued through secondary events avoided are maximised. The time-horizon used is 21 years from a starting age of 55 years.

As discussed in the report, using Framingham equations to predict events is not ideal. However, conservative assumptions have been made throughout this part of the modelling and it is not thought that the number of events will have been overestimated.

Non-compliance, withdrawal and failure to titrate in accordance with guidelines are not modelled. It is acknowledged there is limited published evidence on long-term adherence to prescribed

TABLE 43 *Utility used in the AstraZeneca submission*

Health state	Rosuvastatin mean (SE)	Distribution	Source
CHD free	1.00	None	Assumption
Angina	0.78 (0.016)	Log-normal	Lacey[216]
MI year 1	0.683 (0.015)	Log-normal	Lacey[216]
Post-MI	0.718 (0.016)	Log-normal	Lacey[216]
Stroke mild	0.740 (0.026)	Log-normal	Sandercock[217]
Stroke moderate	0.740 (0.026)	Log-normal	Sandercock[217]
Stroke severe	0.380 (0.046)	Log-normal	Sandercock[217]
TIA	1.00	None	Assumption
CHF	0.683 (0.020)	Log-normal	Assumption
PAD	0.750 (0.022)	Log-normal	Bosch[218]

doses, and the impact this has on the reported effectiveness of statins. However, there is published evidence that suggests that the expected cholesterol reductions seen in trials are not observed in general clinical practice.[213] The evaluation would have been improved if this had been discussed in the text, together with a sensitivity analysis exploring its impact on the number of predicted events avoided and the resulting cost-effectiveness ratios.

Cost and resource use

Unit costs for acute coronary syndromes are based on a report by Palmer and colleagues,[214] using patient-level data from the PRAIS-UK study. Probability distributions are provided for both costs and resource use. Stable angina is differentiated from acute coronary syndrome by assuming a lower probability of undergoing a revasularisation procedure.

A weighted average of costs incurred through severity of stroke costs is taken from Youman and colleagues,[202] while a Derichlet distribution is used to model the proportions of stroke severity. The ratio of TIA to first ischaemic stroke excluding subarachnoid haemorrhage is 35:164 based on evidence from Mant and colleagues.[215]

The costs associated with adverse events are excluded based on the claim that there are no significant differences between adverse event rates among the statins modelled, which is reasonable.

The tables used for costs are given in Appendix 30, *Tables 150–154*.

Utilities

QALYs are calculated by applying utility values taken from published studies. Patients free of disease are assigned values of 1, or perfect health (*Table 43*). The utility values and reference sources

TABLE 44 *Percentage of patients achieving target at each dose of statin*

	10 mg	20 mg	40 mg	80 mg
Rosuvastatin	87.2%	8.5%	4.3%	
Atorvastatin	77.8%	12.2%	6.7%	3.3%
Simvastatin	36.6%	18.6%	8.7%	36.1%
Pravastatin	0.0%	35.0%	65.0%	
Fluvastatin		0.0%	37.5%	62.5%

seem reasonable given the lack of published evidence and the uncertainty surrounding the quality of life experienced by patients in the specific health states modelled.

Model outputs

Outcomes generated include the proportion of patients attaining NSF cholesterol targets, the cost per patient to achieve target, the incremental cost per life-year gained and the incremental cost per QALY for both primary and secondary disease.

Results

Results from the titration model are presented in *Table 44* in terms of the proportion of patients achieving NSF cholesterol targets. The figures estimated demonstrate that more patients taking rosuvastatin attain target cholesterol levels on lower doses than any of the other statins. However, it is felt that presenting evidence in this way is misleading. If a patient does not achieve a target level this does not mean that they do not gain benefits from treatment, but this is not stated overtly in the text.

Base-case results for the long-term CHD model are presented in terms of cost per QALY for men and women separately. The main results are presented in *Table 45*, and the model also compares atorvastatin, simvastatin and pravastatin with no treatment.

TABLE 45 *Summary of base-case cost-effectiveness ratios from AstraZeneca submission*

	Rosuvastatin vs no treatment		Fluvastatin vs no treatment		Rosuvastatin vs fluvastatin	
	Cost per LYG	**Cost per QALY**	**Cost per LYG**	**Cost per QALY**	**Cost per LYG**	**Cost per QALY**
Male base case (primary)	4,088	2,784	3,174	2,164	7,685	5,214
Female base case (primary)	7,367	4,730	5,725	3,668	14,156	9,165
Male base case (secondary)	7,611	13,373	6,596	11,520	11,001	19,728
Female base case (secondary)	10,775	31,373	9,021	25,903	17,550	54,023

TABLE 46 *Summary of high-risk cost-effectiveness ratios from AstraZeneca submission*

	Rosuvastatin vs no treatment		Fluvastatin vs no treatment		Rosuvastatin vs fluvastatin	
	Cost per LYG	**Cost per QALY**	**Cost per LYG**	**Cost per QALY**	**Cost per LYG**	**Cost per QALY**
Male high risk (primary)	3,140	2,023	2,441	1,573	5,632	3,631
Female base high risk (primary)	4,843	3,060	3,754	2,368	8,988	5,712
Male high risk (secondary)	10,515	19,001	9,208	16,579	14,796	27,061
Female base high risk (secondary)	9,751	24,412	8,231	20,279	15,169	40,280

An additional scenario explores the cost-effectiveness of statins in 'high-risk' patients, where patients are assumed to be drinkers and smokers (*Table 46*).

Probabilistic analysis

Monte Carlo simulations using 5000 iterations for each scenario are used to generate samples from the distributions. The results imply that rosuvastatin is the most optimum strategy in terms of life-years and QALY outcomes.

At a willingness to pay of £10,000 per life-year, secondary prevention in men with rosuvastatin has a 70% probability of being cost-effective, while for the cost per QALY analysis rosuvastatin is optimal at less than £15,000 per QALY and has a 70–80% probability of being cost-effective at around £20,000. In women, secondary prevention is likely to be cost-effective with rosuvastatin in terms of life-years with a probability of approximately 80% at a £20,000 willingness to pay, while in QALY terms rosuvastatin is optimal at approximately £30,000 per QALY.

Sensitivity analysis

A wide range of sensitivity analyses is presented, including different costs for simvastatin that reflect the predicted generic market, using different starting doses for each statin, higher and lower baseline cholesterol levels and lower target

cholesterol levels. However, it is felt that a more exhaustive list could have been provided to enable a full understanding of the implications of varying several of the assumptions and values used.

Summary

A comprehensive list of parameter values used in both the base-case and sensitivity analyses is provided, together with distributions used in the probabilistic analyses, although it is difficult to extract a figure that could be used to represent a unit cost for an avoided event. A discussion of how some of the modelling assumptions may affect the results is included, but this could have been expanded.

The results suggest that it is more cost-effective to treat primary than secondary patients. The authors suggest that this may or may not represent reality and is due to the conceptual approach adopted in their model. It is suggested that the anomaly is partially explained by the fact that the model allows a maximum of two events (one primary and one secondary) and thus represents a conservative approach.

Overall, the evaluation was thorough, and appears to have been conservative throughout. However, there are some concerns regarding several methodological issues. The results would have been more credible if they had been justified in

some way by a validation of the model structure or the number of events predicted and modelled in the primary and secondary analyses. Problems in using the Excel model provided have made a full exploration of the model difficult.

Merck Sharp & Dohme: within-trial analysis – cost-effectiveness of simvastatin in the HPS

The MSD submission presented results from within trial economic analyses of 4S (secondary prevention) and HPS (primary prevention). The submission did not include an economic model.

Cost-effectiveness of simvastatin in 4S

This is an updated analysis of the 4S analysis based on the methods used by Jonsson and colleagues.[219] Limited details are provided in the report. Cost-effectiveness results are presented as cost per life-year saved. The cost of simvastatin is based on the August 2004 drug tariff, and dosages from the trials (10 mg 0.1%, 20 mg 61.6% and 40 mg 31.6%).

Unit costs of hospitalisation, based on diagnosis related groups (DRGs), were combined with the number of hospitalisations for CVD events recorded in the trial. The incremental drug cost per patient randomised to simvastatin versus placebo was £1017. During the trial period the cost of hospitalisations was reduced by £483 per patient receiving simvastatin.

The total discounted gain in life expectancy was 0.240 years and the incremental cost per discounted life-year gained was estimated at £2011. No quality of life data are presented. Results of sensitivity analysis are presented, giving a range of £1280–2750 for variations in life expectancy, additional laboratory costs and varying discount rates.

Cost-effectiveness of simvastatin in HPS

Cost-effectiveness results are presented as the cost per major vascular event avoided and the cost per vascular death, and are therefore not directly comparable with other studies.

Estimates are based on resources used within the 5-year trial period. Treatment costs are based on 2001 UK prices for both simvastatin and hospital costs.

The difference in the cost of statin use was around £1500 per person over 5 years. Patients on simvastatin showed a significant 22% reduction in hospital costs. The vascular event costs were

reduced by £264–847 per patient, depending on the patient's risk. The cost of avoiding a major vascular event was £11,600 (95% CI £8500 to £16,300). The cost of the additional statin was offset by the cost of reductions in vascular events, which ranged from 56% in the highest risk group to 18% in the lowest risk group.

Summary of key issues arising from industry submissions

A comparison of the company submissions is complicated because of the different objectives and methodologies used. The time-horizon is one element that has a significant impact on cost-effectiveness results, and the horizons in the four models varied between 5 years and lifetime.

The main points from the company submissions are summarised in *Table 47*.

Issues arising

Of the four models submitted, two (Pfizer and AstraZeneca) used the surrogate end-point of cholesterol lowering and two (Novartis and Bristol-Myers Squibb) used clinical end-points. The issues relating to modelling the cost-effectiveness of statins by using surrogate end-points are discussed in the section 'Effectiveness of statin treatment' (p. 91). One of the issues that may impact on cost-effectiveness was highlighted in a study by Morris,[220] which found that Framingham equations substantially underestimated non-fatal MI, resulting in a lower incremental cost per life-year gained when effects due to cholesterol lowering were compared with the results of the WOSCOPS trial. The likelihood is that this difference will be exacerbated when utilities are applied to calculate QALYs. Another issue with cholesterol-lowering modelling is the choice of trials on which to base the estimate of the percentage change in cholesterol due to the effect of the drug. For instance, the Pfizer meta-analysis included all of the short-term trials and excluded two major long-term studies.

A problem with the Bristol-Myers Squibb model was the lack of transparency. The model provided did not allow an in-depth examination of the model structure. The published report and industry submission report did not provide enough information to compensate for this lack of transparency.

Comparison of results

Of the two submissions using clinical end-points, Novartis evaluated secondary treatment only, whereas Bristol-Myers Squibb evaluated primary

TABLE 47 *Summary of all industry submissions*

	Pfizer (atorvastatin)	Novartis (fluvastatin)	Bristol-Myers Squibb (pravastatin)	AstraZeneca (rosuvastatin)	Merck Sharp & Dohme (simvastatin)
Disease area	CHD and stroke	Prevention of cardiac events following PCI	CHD/CVD	CHD/CVD	CHD/CVD
Results: secondary[a]	£3.2–5.0 (men), £4.5–5.9 (women)	£3.2 (all patients)	Pravastatin dominated	£13–19 (men), £24–31 (women)	Cost per LYG: £1.2–2.7
Results: primary[a]	£1.9–7.3 (men), £1.2–5 (women)	NA	Cost per LYG: £0.061–120 (men), £0.067–121 (women)	£2–3 (men), £3–5 (women)	Cost per major vascular event avoided: £8.5–16
Method	Surrogate end-point (cholesterol lowering) using Framingham	Markov	Markov	Surrogate end-point (cholesterol lowering) using Framingham	Within-trial economic analysis: 4S (secondary), HPS (primary)
Model validation	None	None	None	None	NA
Time-horizon	Lifetime (maximum age 99 years)	10 years	5 years	20 years	5 years
Issues	Surrogate end-points used when clinical end-points are available TC and HDL taken from short-term trials; major long-term trials excluded Primary results are lower than secondary (counter-intuitive)	Very specific application, following PCI. No other analysis undertaken	Insufficient information was available within the industrial submission to critically appraise the economic model	Surrogate end-points used; however, clinical end-points are unavailable Primary results are lower than secondary (counter-intuitive)	None

[a] All company results are cost per QALY (£,000) compared with placebo unless otherwise stated.

and secondary treatment. Of the two models using surrogate outcomes, the results are similar in primary treatment, with costs per QALYs all being below £10,000. The results for men and women, however, are reversed in these submissions in that atorvastatin was found to be more cost-effective in women, whereas rosuvastatin was found to be more cost-effective in men. However, the numbers are of a similar magnitude for both drugs in either gender. When comparing results between primary and secondary prevention treatment in the Pfizer and AstraZeneca models, the message is conflicting. In the Pfizer model there is little difference in cost-effectiveness between primary and secondary treatment, whereas in the AstraZeneca model secondary prevention is less cost-effective than primary prevention.

The two submissions using clinical end-points had different objectives. Novartis evaluated fluvastatin for the prevention of cardiac events following PCI, whereas Bristol-Myers Squibb evaluated pravastatin in CHD/CVD prevention. In secondary treatment pravastatin dominates in the base case and in all sensitivity scenarios except for a 12-month horizon. Fluvastatin does not dominate, but the cost per QALY is very low at £3200. In primary prevention, the results vary significantly for pravastatin, between £61 (at 30% 10-year CHD risk) and £121,000 (at 4% 10-year CHD risk) per LYG. At the average baseline risk (15%) seen in WOSCOPS, the cost per LYG is around £5000–£8000 for both genders.

The within-trial economic analysis of simvastatin produced results in secondary prevention of a similar magnitude to the Novartis and Pfizer evaluations. The primary cost-effectiveness results are presented as the cost per major vascular event avoided and are therefore not directly comparable with the other studies.

Overall, considering the differences in techniques and objectives, the results could be considered to be of a similar magnitude in both primary and secondary treatment. The exception is perhaps the secondary prevention results from the AstraZeneca model, which are higher than the other evaluations and are also higher than the primary prevention results from the same model.

ScHARR economic analysis

Objectives
The primary aim of this evaluation is to appraise the cost-effectiveness of the use of statins for the

management of patients at increased risk of death or other cardiovascular events from CHD and to advise on any patient groups for which statins may be particularly appropriate. A secondary objective is to identify the appropriate level of risk of development of CHD at which to intervene with statins.

The analyses focus on the cost-effectiveness of statins as a group, taking into account the combined evidence base for all statins. Given that many statins are commonly used outside their licensed indications, the analyses are not restricted to the licensed indications.

Overview of modelling methodology and structure
A Markov model was developed to explore the costs and health outcomes associated with a lifetime of statin treatment, using a UK NHS perspective. Data from UK epidemiological studies are used to inform event rates, combined with results from a meta-analysis of statin RCT evidence to model the relative risk reductions of event rates for patients with and without statin therapy. Input parameters are assigned probability distributions to reflect their imprecision, and Monte Carlo simulations are performed to reproduce this uncertainty in the results. Results are presented in terms of QALYs for both primary and secondary prevention of CHD/CVD events.

Definitions of CHD, CVD, primary and secondary disease used in the analyses
For the purposes of this evaluation, a CHD event is defined as onset of stable angina, unstable angina, a non-fatal MI or death from CHD-related causes. A CVD event is defined as a CHD event plus a non-fatal stroke, TIA, or death from stroke or TIA-related causes. PAD is excluded from the model owing to a paucity of trial evidence.

Detailed methodology
To address the research question laid out in the objectives, the model uses a cohort of 1000 patients at a specified annual risk of a CHD event. The cohort represents patients with differing profiles such as baseline cholesterol levels, BMI, exercise levels and smoking and drinking habits, but with an equivalent selected annual risk. The model is run separately for each age group, gender and risk level. Patients progress through the model from the chosen starting age until they either die or reach the age of 100 years.

The model is used to perform three sets of analyses. The base case considers the impact of

statin treatment within CHD only. This complies with the scope specifically requested by the Department of Health. Two further scenarios were explored to take into account the evolving evidence on the impact of statins on reducing stroke events and because clinical and epidemiological advice to the project team made clear that the impact on stroke was an important consideration.

Base case: CHD analysis

The base-case analysis explores the costs and benefits associated with the effect that statin treatment has on reducing CHD events only. Hence, although all patients receive statin treatment, it is assumed that statin treatment has no impact on the probabilities of stroke or TIA events.

Scenario 1: CHD analysis with CVD outcomes

Scenario 1 is as the base case, but also takes into account the reduction in stroke events for patients with a history of CHD. The analysis is undertaken on patients with or at risk of CHD, but takes into account CVD outcomes.

Scenario 2: CVD analysis

Scenario 2 explores the costs and benefits associated with statin treatment in reducing CVD events. These analyses are undertaken on patients with or at risk of CVD. In these analyses all patients entering the treatment arm of the model are assumed to receive benefits associated with statin treatment.

Structure of the Markov model

A Markov model was used to explore the clinical pathway of patients at risk of CVD. This methodology is particularly useful for diseases involving risks that continue or increase over time, where events can occur more than once, and where the probability of an event occurring changes depending on the time since a previous event.[220–222] The methodology also offers flexibility for tracking costs and utilities over numerous health states.

In a Markov model the pathway followed by patients is divided into a finite number of mutually exclusive health states and at any point in time all patients within the model exist in one of these states. The proportion of patients in each of the health states is governed by age-dependent time-variant transition matrices which describe the annual probability of moving to an alternative health state. A list of health states and possible transitions modelled is provided in *Figure 27* and detailed in *Table 48*.

For the primary prevention analyses, all patients begin the evaluation in the event-free health state. During each annual cycle of the model, a proportion of patients enters one of the qualifying event-health states: MI, stable angina, unstable angina, CHD death, TIA, stroke, CVD death or death through other causes, while the remainder remains in the event-free state. For the secondary prevention analyses, all patients begin in the post-MI, post-stable angina, post-unstable angina, post-TIA or post-stroke health states. In each subsequent cycle, patients in a non-fatal health state may move to a subsequent event state listed in *Table 48*, die through CHD, CVD or other causes, or remain in the same state.

The probability of a patient moving between health states depends on both the current health state and age. The model cycles annually, with patients moving between health states until all patients have entered a fatal health state or reached 100 years, when it is assumed that all patients will die.

The effectiveness of statin treatment is applied by assigning the relative risk reduction of an event onto the transition between health states; hence, patients receiving statin treatment have a lower probability of a primary or secondary event. Half-cycle correction is used for both costs and benefits.

Treatment/comparator

The base-case evaluation compares the costs and benefits associated with statin treatment versus no treatment. Lipid-regulating drug therapy should be combined with advice on diet and lifestyle measures to reduce coronary risk including, if appropriate, reduction of blood pressure and use of statins.[43] It is assumed that all patients entering the model have been given standard advice regarding dietary control and other appropriate measures. It is also assumed that an equal proportion of patients in each cohort will receive medications such as aspirin, hypertensive treatments or alternative lipid-lowering treatments. As the costs and benefits of these would cancel out they have not been modelled.

Perspective

A UK NHS perspective has been used throughout; hence, productivity lost through illness or costs incurred directly by patients are not included. As per current NICE guidance, discount rates of 6% and 1.5% are applied to costs and health benefits, respectively.[223] However, to inform decision-makers fully, the base-case results are also reported undiscounted and an analysis is performed using

FIGURE 27 *Markov model structure. For primary analyses, all patients start in the event-free health state. For secondary analyses, patients are assigned to either post-stable angina, post-unstable angina, post-MI, post-TIA or post-stroke health states. History of CHD = history of either stable angina, unstable angina or MI. In the figure, history of CVD = history of other CVD such as TIA or stroke, but not a history of CHD.*

TABLE 48 *Transitions between health states and relative risk from statin treatment applied in the different scenarios explored by the ScHARR model*

From	To	Base case	Scenario 1	Scenario 2
Primary transitions:				
Event free	Remain in event free	–	–	–
	Stable angina	0.590	0.590	0.590
	Unstable angina	0.716	0.716	0.716
	Non-fatal MI	0.656	0.656	0.656
	Fatal CHD event	0.740	0.740	0.740
	TIA	–	–	0.790
	Non-fatal stroke	–	–	0.769
	Fatal CVD event	–	–	1.000
	Death other causes	0.656	0.656	0.656

continued

TABLE 48 *Transitions between health states and relative risk from statin treatment applied in the different scenarios explored by the ScHARR model (cont'd)*

From	To	Base case	Scenario 1	Scenario 2
First year secondary transitions				
Stable angina	Post-stable angina			
	Unstable angina	0.716	0.716	0.716
	Non-fatal MI	0.656	0.656	0.656
	Fatal CHD event	0.740	0.740	0.740
	Death other causes	–	–	–
Unstable angina	Post-unstable angina			
	Non-fatal MI	0.656	0.656	0.656
	Fatal CHD event	0.740	0.740	0.740
	Non-fatal stroke	–	0.769	0.769
	Fatal CVD event	–	1.000	1.000
	Death other causes	–	–	–
Non-fatal MI	Post-non-fatal MI			
	Non-fatal MI	0.656	0.656	0.656
	Fatal CHD event	0.740	0.740	0.740
	Non-fatal stroke/history CHD	–	0.769	0.769
	Fatal CVD event/history CHD	–	1.000	1.000
	Death other causes	–	–	–
TIA	Post TIA			
	Non-fatal MI/history CVD	0.656	0.656	0.656
	Fatal CHD event/history CVD	0.740	0.740	0.740
	Non fatal stroke	–	0.769	0.769
	Fatal CVD event	–	1.000	1.000
	Death other causes	–	–	–
Non-fatal stroke	Post-non-fatal stroke			
	Non-fatal stroke	–	0.769	0.769
	Fatal CVD event	–	1.000	1.000
	Non-fatal MI/history CVD	0.656	0.656	0.656
	Fatal CHD event/history CVD	0.740	0.740	0.740
	Death other causes	–	–	–
Subsequent year secondary transitions				
All first year secondary transitions plus:				
Post-stable angina	As stable angina			
Post-unstable angina	As unstable angina			
Post-non-fatal MI	As non-fatal MI			
Post-TIA	As TIA			
Post-non-fatal stroke	As non-fatal stroke			
Non-fatal MI/history CVD	Post-non-fatal MI/history CVD			
	Non-fatal MI/history CVD	0.656	0.656	0.656
	Fatal CHD event/history CVD	0.740	0.740	0.740
	Non-fatal stroke/history CHD	–	0.769	0.769
	Fatal CVD event/history CHD	–	1.000	1.000
	Death other causes	–	–	–
Post-non-fatal MI/history CVD	As non-fatal MI/history CVD			
Non-fatal stroke/history CHD	Post-non-fatal stroke/history CHD			
	Non-fatal stroke/history CHD	–	–	0.769
	Fatal CVD event/history CHD	–	–	1.000
	Non-fatal MI/history CVD	0.656	0.656	0.656
	Fatal CHD event/history CVD	0.740	0.740	0.740
	Death other causes	–	–	–
Post-non-fatal stroke/history CVD	As non-fatal stroke/history CHD			

RR, relative risk from statin treatment is applied to the probability of having an event. RR derived from RevMan meta-analysis for stable angina (0.590) and TIA (0.790), and from the Bayesian meta-analysis for unstable angina (0.716), non-fatal MI (0.656), fatal CHD (0.740), non-fatal stroke (0.769) and fatal CVD (1).

TABLE 49 *Distribution of patients to primary event health states in the ScHARR economic model*

Age (years)	Stable angina	Unstable angina	MI	Fatal CHD	TIA	Stroke	Fatal CVD	Total event rate per 1000 per annum
Men								
45	30.7%	10.7%	29.5%	7.1%	6.0%	12.9%	3.0%	4.2
55	32.8%	7.1%	17.2%	8.6%	8.9%	20.6%	4.8%	13.7
65	21.4%	8.3%	17.3%	9.7%	10.0%	27.0%	6.3%	24.3
75	19.1%	8.1%	16.1%	6.3%	8.0%	34.3%	8.0%	37.5
85	21.4%	9.6%	18.6%	5.5%	1.6%	35.1%	8.2%	42.6
Women								
45	32.5%	11.7%	8.0%	3.7%	16.0%	22.9%	5.4%	1.6
55	34.6%	7.3%	9.2%	3.9%	9.5%	28.8%	6.7%	6.6
65	20.2%	5.2%	12.1%	8.1%	7.3%	38.2%	9.0%	12.4
75	14.9%	3.4%	10.2%	4.3%	9.8%	46.4%	10.9%	23.4
85	13.6%	2.9%	10.0%	3.0%	8.7%	50.1%	11.7%	32.9

The total event rates are for all CVD events per 1000 population per annum.

the proposed rates for future evaluations of 3.5% for both costs and benefits.[224] Costs are at 2004 prices and are inflated where necessary.

Key modelling assumptions
The key modelling assumptions used are discussed in detail in the following subsections and a summary is provided in Appendix 31.

Event rates
Primary event rates
Previous economic evaluations of statins have used the Framingham study to ascertain the proportion of qualifying primary events, while others have used event rates in RCTs. However, neither methodology is ideal. The Framingham study is non-UK sourced and provides insufficient detail to apportion ratios by age. Similarly, the majority of primary prevention statin trials are non-UK sourced and the inclusion and exclusion criteria used for entry to the studies preclude generalisability of baseline event rates to wider populations. In the ScHARR model, UK-specific incidence rates have been used to ensure that patients entering the model match the likely distribution of events in the UK. Expert opinion (Yeo W, Royal Hallamshire Hospital, Sheffield: personal communication, November 2004) was sought for age-related event rates for stable angina and TIA which could not be fully populated using UK published evidence. (See Appendix 31 for further details.)

Primary incidence rates/ratios across health states modelled

Incident rates for primary CHD events are taken from the BCHDR,[7] and TIA and stroke from the Oxfordshire Community Stroke Project.[15,225] These are combined to derive the distribution across events by age and gender at the modelled risk level (*Table 49*).

In the absence of reported UK data for primary CHD events for older age groups, it is assumed that the rates for angina and non-fatal MI for the age groups 75–84 years and 85 years plus increase. The rate of increase is based on the ratio of increases reported for the age groups 55–64 and 65–74 years. The rates for fatal CHD events for patients over 74 years were held constant at the reported rate for 65–74 years of age. The published rates for first ever stroke by age were assumed to be distributed 81:19 for non-fatal:fatal events, based on the overall published figures from the Oxfordshire study. Uncertainty was explored using beta distributions.

Annual risk levels modelled
The cohort of patients in each primary prevention analysis starts at a selected annual CHD risk [the equivalent 10-year risk = $1 - (1 - \text{annual risk})^{10}$]. As the ratio of CHD to CVD risk changes with age and gender the corresponding annual CVD risk was calculated using published algorithms.[226] *Table 50* provides the initial ratios modelled by age and gender. The incidence rates were combined with the respective chosen CHD and corresponding calculated CVD annual risks to model the probability of a primary CHD or TIA/stroke event. Uncertainty in the ratio of CHD and CVD risk was

TABLE 50 *Initial annual CHD risk and corresponding annual CVD risk by age and gender used in the ScHARR cost-effectiveness model*

Age (years)	Men		Women	
	Annual CHD risk	**Annual CVD risk**	**Annual CHD risk**	**Annual CVD risk**
35–54	3.00%	3.83%	3.00%	4.00%
	2.50%	3.21%	2.50%	3.36%
	2.00%	2.58%	2.00%	2.73%
	1.50%	1.96%	1.50%	2.09%
	1.00%	1.33%	1.00%	1.46%
	0.50%	0.71%	0.50%	0.82%
≥55	3.00%	4.30%	3.00%	4.71%
	2.50%	3.67%	2.50%	3.99%
	2.00%	3.03%	2.00%	3.27%
	1.50%	2.40%	1.50%	2.55%
	1.00%	1.76%	1.00%	1.83%
	0.50%	1.13%	0.50%	1.11%

explored using log-normal distributions. The algorithms used to calculate the CVD risk and the parameters used in the probabilistic analyses are provided in Appendix 32.

In addition, as the risk of CHD and CVD increases naturally with age over time, for patients remaining in the event-free state it was assumed that their risk and thus the probability of a primary event increased during the analyses. To estimate the increase in risk with age, 1998 HSE[197] data were examined. For each of the modelling scenarios (all patients, non-diabetics, diabetics and gender), patients were grouped according to age and the average risk was calculated. These data were then examined for a mathematical relationship between age and risk increase. For all men and non-diabetic men a fairly robust linear relationship was found ($r^2 > 0.9$). For diabetic men a linear relationship was the best fitting mathematical model, although the model fit was less reliable than for all men and non-diabetic men ($r^2 = 0.3$). The slope of the linear relationship, 0.0003, was the same for all men, non-diabetic men and diabetic men. This represents an increase in the 1-year risk of 0.03% for a 1-year increase in age. For all women and non-diabetic women the best mathematical relationship was also found to be linear, but the model fit was not as good as for men ($r^2 = 0.25$, 0.4). No clear relationship between age and risk was found for diabetic women. Expert opinion was sought to verify the expected rate of risk increase in diabetic women (Yeo W, Royal Hallamshire Hospital, Sheffield: personal communication, November 2004). The rate of increase was assumed to be the same for diabetic women as for all women, in the same way that the rate of increase was the same for all three male groups.

The rate of increase used in the model is therefore 0.0003 for men, 0.00008 for all women and diabetic women, and 0.00007 for non-diabetic women.

Prevalence for secondary evaluations
Published UK prevalence data were used to distribute patients to initial health states for the secondary prevention evaluations (*Table 51*). For angina, MI and stroke these were taken from the British Heart Foundation Statistics Database,[227] while evidence from Bots and colleagues[228] was used to inform prevalence for TIA. It was assumed that the published angina figures included both stable and unstable angina patients, and prevalence for these health states was derived using the ratios for stable and unstable angina reported in the incidence data. As TIA prevalence was unavailable for the age group 45–54 years, this was scaled using the prevalence rates for stroke. Uncertainty in the initial distributions across the health states was explored using beta distributions.

Secondary event rates
UK-specific data are used wherever possible to ensure that event rates match the likely distribution in the UK. Two main sources have been used: with the exception of stable angina, for patients with a primary CHD event, the occurrence of further MIs, strokes and vascular deaths is derived from patients on the Nottingham Heart Attack Register (NHAR),[229] while the probabilities of subsequent strokes and vascular deaths for patients with a history of a stroke are derived from patients on the SLSR.[18]

Logistic and multivariate regression analyses were used to estimate the probability of experiencing

TABLE 51 *Distribution of patients in initial health states for secondary analyses by age and gender used in the ScHARR cost-effectiveness model*

Age (years)	Post-stable angina	Post-unstable angina	Post-MI	Post-TIA	Post-stroke	Total per 1000
Men						
45	28.7%	10.0%	37.4%	7.2%	16.6%	7.2
55	37.2%	8.0%	36.2%	4.3%	14.2%	23.2
65	31.2%	12.0%	32.1%	7.5%	17.2%	36.1
75	29.0%	12.4%	30.5%	4.8%	23.3%	44.2
Women						
45	34.1%	11.9%	26.3%	4.6%	23.0%	3.04
55	41.1%	8.9%	21.8%	8.2%	20.0%	11.00
65	33.4%	12.9%	25.7%	4.7%	23.4%	21.40
75	34.3%	14.6%	18.7%	6.9%	25.4%	34.70

Total per 1000 is the total number of patients with a history of CVD in a population of 1000.

secondary events within 1 year of a qualifying primary event (see Appendix 32). First, logistic regression was used to estimate the probability of experiencing a secondary event of any type; that is, the combined rate of non-fatal MI, non-fatal stroke and vascular death. Multivariate regression analysis was then used to determine the distribution of secondary events between each type, should an event occur. The results confirm the importance of accounting for age in the model. For patients experiencing an MI the probability of a secondary event within 1 year is strongly correlated with age (mean probability of 14.7% at 45 years, and 29.5% at age 85 years of age). Similarly, for patients experiencing a stroke the probability of a secondary event within 1 year increases with age (mean probability of 5.4% at 45 years, and 29.8% at 85 years of age), while patients with unstable angina have a mean probability of an event of 8.7% at the age of 45 compared with 31.3% at the age of 85 years.

Similar analyses were performed to estimate the probabilities of subsequent events in subsequent years. In the absence of data, these results are used to inform all subsequent events. This is a conservative approach as the application of these data implies that there is no additive effect on fatal or non-fatal event rates from previous events. Uncertainty in these event rates is explored using multivariate distributions.

TIA transitions are taken from a study by Rothwell and co-authors.[134] As this evidence provides a constant rate across all ages (TIA to non-fatal stroke = 0.042, non-fatal MI = 0.006, fatal CVD = 0.02 and fatal CHD = 0.019 at the age of 67 years), the data are combined with the corresponding changes

in incidence rates modelled to derive probabilities by age.[30] Again, uncertainty in these transitions is explored using beta distributions.

The economic model requires baseline transition probabilities for patients in the health state of stable angina for progression to MI, unstable angina or death, or to remain in the state. The stable angina health state presupposes that patients have no history of MI or unstable angina. The ideal source for these data is a registry database with the above health status recorded for each patient. As the comparator arm is defined as 'no treatment', the data relate to patients not receiving statins. Two registry databases with the potential to provide these data were identified from the evidence searches, the NHAR and MINAP. The NHAR was unable to provide the required data as stable angina was not specifically recorded, and the MINAP data are largely incomplete owing to a lack of hospital participation to fill in angina data, and include a large proportion of patients on statin treatment. As registry data were unavailable a MEDLINE search was conducted to identify clinical trials on stable angina patients in the pre-statin era. A total of 79 studies was found, four of which were identified as RCTs in stable angina patients. Of these four studies,[230–233] only one had a patient population with no history of MI or unstable angina.[230] The Juul-Mohler study[230] was a double-blind comparison of aspirin with placebo in patients with a history of chronic stable angina without a previous MI. The trial enrolled 2035 patients from a primary care setting in Sweden between 1985 and 1989. The primary end-point was the first occurrence of non-fatal or fatal MI or sudden death. Median follow-up time was

50 months. Number of events and thus probability of events at 1 year are estimated from the number of patients at risk at 1 year and the ratio of the number of events at trial end.

As Juul-Mohler and colleagues report a constant rate across all ages (stable angina to unstable angina = 0.006, non-fatal MI = 0.011, and fatal CHD = 0.007 at the age of 67 years), the data are combined with the corresponding changes in incidence rates to derive probabilities by age (*Table 52*). Again, uncertainty in these transitions is explored using beta distributions.

Mortality

To account for the proportion of patients dying from non-vascular causes, interim life tables published by the UK Government Actuary

TABLE 52 *Annual transition probabilities by age*

Population receiving no treatment	Unstable angina	Non-fatal MI	Non-fatal stroke	CHD death	CVD death
Markov model health state for age 45					
Stable angina	0.0013	0.0032	–	0.0009	–
Unstable angina (1st year)	–	0.0495	–	0.0362	0.0016
Unstable angina (subsequent year)	–	0.0186	–	0.0081	0.0004
MI (1st year)	–	0.1280	0.0015	0.0167	0.0007
MI (subsequent year)	–	0.0162	0.0004	0.0052	0.0002
TIA	–	0.0016	0.0035	0.0024	0.0013
Stroke (1st year)	–	0.0016	0.0431	0.0046	0.0046
Stroke (subsequent year)	–	0.0016	0.0144	0.0021	0.0021
Markov model health state for age 55					
Stable angina	0.0029	0.0062	–	0.0035	–
Unstable angina (1st year)	–	0.0497	–	0.0617	0.0027
Unstable angina (subsequent year)	–	0.0348	–	0.0100	0.0004
MI (1st year)	–	0.1152	0.0032	0.0319	0.0014
MI (subsequent year)	–	0.0179	0.0010	0.0091	0.0004
TIA	–	0.0031	0.0181	0.0092	0.0070
Stroke (1st year)	–	0.0031	0.0459	0.0111	0.0111
Stroke (subsequent year)	–	0.0031	0.0186	0.0049	0.0049
Markov model health state for age 65					
Stable angina	0.0060	0.0110	–	0.0070	–
Unstable angina (1st year)	–	0.0488	–	0.1031	0.0046
Unstable angina (subsequent year)	–	0.0632	–	0.0119	0.0005
MI (1st year)	–	0.1019	0.0068	0.0599	0.0027
MI (subsequent year)	–	0.0185	0.0022	0.0152	0.0007
TIA	–	0.0055	0.0423	0.0185	0.0163
Stroke (1st year)		0.0055	0.0481	0.0260	0.0260
Stroke (subsequent year)		0.0055	0.0223	0.0104	0.0104
Markov model health state for age 75					
Stable angina	0.0091	0.0158	–	0.0070	–
Unstable angina (1st year)	–	0.0466	–	0.1671	0.0074
Unstable angina (subsequent year)	–	0.1122	-	0.0139	0.0006
MI (1st year)	–	0.0874	0.0141	0.1088	0.0048
MI (subsequent year)	–	0.0178	0.0047	0.0235	0.0010
TIA	–	0.0080	0.0828	0.0185	0.0319
Stroke (1st year)		0.0080	0.0446	0.0586	0.0586
Stroke (subsequent year)		0.0080	0.0246	0.0206	0.0206
Markov model health state for age 85					
Stable angina	0.0122	0.0207	–	0.0070	–
Unstable angina (1st year)	–	0.0425	–	0.2587	0.0115
Unstable angina (subsequent year)	–	0.1955	–	0.0160	0.0007
MI (1st year)	–	0.0711	0.0278	0.1875	0.0083
MI (subsequent year)	–	0.0160	0.0091	0.0340	0.0015
TIA	–	0.0104	0.0961	0.0185	0.0370
Stroke (1st year)	–	0.0104	0.0446	0.1215	0.1215
Stroke (subsequent year)	–	0.0104	0.0252	0.0375	0.0375

Department were adjusted using the applicable deaths cited in the national mortality statistics for England and Wales.

Effectiveness of statin treatment
Effectiveness on clinical outcomes
The benefits associated with statin treatment are modelled by applying the relative risks observed in the RCTs to the events predicted in the model. Some previous evaluations have used the reductions in cholesterol levels observed in clinical trials in conjunction with the Framingham risk engine to predict reductions in cardiovascular events. However, as discussed in detail in the next section, evidence to support this methodology is subject to a number of uncertainties and therefore using relative risk reductions in clinical end-points is considered to be a more robust methodology. A Bayesian meta-analysis has been undertaken in addition to the standard meta-analysis reported (see the sections 'Placebo-controlled studies: summary of results'; and 'Results from Bayesian meta-analysis' (pp. 36 and 38). The Bayesian evidence synthesis provides the same inputs to the model as the traditional meta-analysis, namely the relative risks of the effect of statins for the event states in the model.

Since some of the five events are mutually exclusive, conditional relative risks were considered. From the Bayesian meta-analysis relative risks are for unstable angina, non-fatal MI, fatal CHD, non-fatal stroke and fatal CVD (see *Table 19*, p. 44). Relative risks for stable angina and TIA for use in the primary population analyses are taken from the standard meta-analysis (see *Table 16*, p. 43).

Estimating effectiveness from non-clinical end-points
The main outcomes of interest in assessing the cost-effectiveness of statins are morbidity and mortality. Cost-effectiveness assessments of statins should therefore, if possible, be based on the effect of statins on these end-points. However, trials of rosuvastatin to date report only on the intermediate end-point of cholesterol lowering and there is currently no direct trial evidence of the effect of rosuvastatin on morbidity and mortality. The ScHARR model has therefore been adapted to calculate the risk of CHD (morbidity and mortality) using a Framingham risk equation to assess the cost-effectiveness of rosuvastatin. There are, however, several general issues concerning the estimation of cost-effectiveness when using Framingham equations in modelling the link between cholesterol lowering and CHD risk.

Use of Framingham to predict the likely outcome of chemically induced reductions in cholesterol
The Framingham risk functions were derived to calculate baseline risk in patients before interventions are offered. Their use to predict the likely outcome of chemically induced reduction in cholesterol has not been validated. Validation against outcome studies is required to ensure that changes in the Framingham risk for a given reduction in cholesterol agree with the results of outcome studies. No published studies in this area were identified.

Use of Framingham to predict events in a UK population
The Framingham risk function has been validated for a population of UK and northern European men.[234] This study found close agreement among the Framingham, PROCAM and Dundee risk functions for average CHD risk, and moderate agreement for estimates within individuals. The authors concluded that when taking PROCAM as an external standard, the Framingham risk equation was able to separate high and low risk and was an acceptably accurate predictor of risk for northern European men.

Comparison of Framingham with clinical trials
A study by Morris[220] compared predicted CHD obtained using Framingham with actual incidence rates from WOSCOPS. Framingham equations were found to underestimate non-fatal MI substantially, which resulted in a lower incremental cost per life-year gained in the model compared with the trial. The likelihood is that this difference will be exacerbated when utilities are applied to calculate QALYs.

Other issues concerning the link between cholesterol lowering and CHD risk
The association between cholesterol levels and CHD risk levels has been well established by the major trials and secondary research. However, the nature of the relationship between the size of cholesterol-lowering reduction achieved with pharmacotherapy and the degree of CHD risk reduction is less certain.[235] Specifically, there is uncertainty about whether there is a common relationship between pharmacological cholesterol lowering and clinical benefit across the different statins.

A systematic review was therefore conducted for evidence of a common relationship that would enable a reliable predictive model of the relationship between cholesterol levels and clinical benefit to be constructed.

No publications were found to support a common relationship between cholesterol levels and clinical benefit across the different statins. There is, however, some evidence suggesting a degree of independence between statins in their cholesterol-lowering ability and subsequent clinical benefit. A study by Maron[235] found that although the cholesterol-lowering impact of treatment in the 4S trial (simvastatin lowered LDL by 35%) was much stronger than observed in the CARE trial (pravastatin lowered LDL by 28%), when a group of 500 CARE subjects was selected for enrolment characteristics similar to those of the 4S inclusion criteria (higher LDL and higher risk), the effect of pravastatin on clinical outcomes was similar to that of simvastatin. This effect was observed despite a 10 percentage point smaller reduction in LDL for pravastatin compared with simvastatin.

The lack of evidence to support a common relationship between statins may be due in part to the non-lipid effects of statins on clinical benefit. A recent study found that event-free survival was linked not only to cholesterol lowering, but also to C-reactive protein (CRP) lowering.[236] This finding was supported by the Nissen study.[237] The results of this study suggest that the statin-mediated reduction in CRP is potentially mediated by pathways independent of cholesterol lowering. This is part of the growing body of evidence suggesting that some of the clinical benefits of statin therapy may be attributed to mechanisms independent of their cholesterol-lowering effects.[238] These mechanisms increase the uncertainty around extrapolating the clinical benefit of rosuvastatin from its cholesterol-lowering ability based on the cholesterol-lowering and clinical benefits of the other statins.

In the event that evidence was found to support a common relationship across statins, there would still remain uncertainty around applying this model to rosuvastatin. The cholesterol-lowering ability of rosuvastatin of over 30% puts it outside the evidence base of the other statins. The clinical gain that may result from this additional cholesterol reduction is therefore unknown.

No evidence was found to support the theory that the high levels of cholesterol achieved in the rosuvastatin trials will translate to high levels of clinical benefit. Some evidence exists to suggest that there is some independence between levels of cholesterol lowering and levels of clinical benefit.

Rosuvastatin clinical outcomes trials are ongoing and are expected to report in 2007. Until there is published evidence on the clinical benefit of rosuvastatin treatment there remains uncertainty as to the magnitude of this benefit.

The ScHARR method for estimating the cost-effectiveness of rosuvastatin

Primary prevention: estimate of the relative risk reduction of CHD based on cholesterol lowering
The ScHARR model uses the 1998 HSE[197] data to estimate the likely CHD risk reduction achieved by a reduction in total cholesterol and the related increase in HDL-C in people without CHD. Annual CHD risk was calculated for each person using a Framingham equation.[239] The equation uses age, gender, blood pressure, total cholesterol, HDL-C, presence of diabetes and smoking as risk factors. CHD risk was calculated for each person at baseline and then recalculated taking into account changes to total cholesterol and HDL-C according to the percentage increase/decrease seen in the trial data for rosuvastatin. Patient data from the 1998 HSE were then grouped according to gender and baseline risk levels between 0.5 and 3% annual risk (in increments of 0.1%). The average CHD risk following cholesterol reduction was then calculated at each level of baseline risk. A relative risk reduction was then calculated from the proportionate difference between baseline CHD risk and cholesterol-altered CHD risk for men and women at each of the baseline risk levels.

The effect of rosuvastatin on cholesterol is based on two trials[125,126] identified from the literature review (see the section 'Assessment of effectiveness: direct statin–statin comparisons', p. 44) (*Table 53*). Both trials were of 12 months' duration, at which time it could reasonably be expected that cholesterol levels would be fairly stable. These trials investigated the effect of rosuvastatin at two dosages, 5 and 10 mg. Patients received a dose of either 5 or 10 mg for a fixed period of 12 weeks. Patients then entered a 40-week titration period in which a patient's dose could be titrated up to 80 mg. As a 5-mg dose is currently unlicensed in England and Wales this assessment has used the effect of the 10-mg dose. It should be noted that the 80-mg dose is not licensed in the UK; however, the proportion of patients who were titrated to 80-mg in these trials was very small (1.7%). The effect of this small proportion on the weighted cost (and efficacy) of rosuvastatin is therefore minimal. The mean dosage in the trials was 13.4 and 13.8 mg (Olsson[125] and Brown,[126] respectively). The ScHARR model is therefore simulating the efficacy and cost of around a 13.5-mg dose of rosuvastatin. This is within the licensed

TABLE 53 *Trials and values included in surrogate modelling*

	Treatment (*n*)	TC % reduction	HDL % increase	Time (months)	Dose (mg)
Rosuvastatin					
Brown[126]	116	0.342	0.08	12	10
Olsson[125]	132	0.38	0.03	12	10
Weighted mean		**0.362**	**0.051**		

TABLE 54 *Relative risk estimates predicted using cholesterol-lowering effect of rosuvastatin*

	RR	
	Men	**Women**
Secondary prevention	71.92%	67.07%
Primary prevention (annual CHD risk)		
0.5%	65.4%	65.3%
1.5%	58.8%	58.8%
3%	53.5%	53.3%

dose of 10–20 mg listed in the summary of product characteristics for rosuvastatin.

Secondary prevention: estimate of the relative risk reduction of CHD based on cholesterol lowering
A similar approach to the one used above in the primary prevention of CHD was used in the secondary prevention of CHD. In secondary prevention the predicted risk of a subsequent event is based on the equation by D'Agostino and colleagues.[195] The risk of a subsequent event is

calculated for each person in the HSE with a history of CHD. Risk is calculated at baseline and following the reduction in cholesterol. The relative risk of a subsequent event is calculated from the proportionate difference. Patients were grouped by gender and age. The relative risk varied insignificantly by age for rosuvastatin and therefore the average relative risk across all ages for each statin was calculated.

The relative risks estimated by this method can be seen in *Table 54*.

Costs
Costs of health states
A detailed review was undertaken to obtain the most recent and appropriate published evidence to populate costs. First year costs and subsequent year costs are assigned for each of the different health states modelled (*Table 55*).

Stable angina
It is assumed that patients with stable angina are typically not hospitalised. The annual cost of

TABLE 55 *Costs of health states in ScHARR cost-effectiveness model*

Health state		Cost (£, 2004)	Assumption/source
Stable angina	1st year	171	3 times 15 minutes' GP contact plus medication costs
	Subsequent year	171	3 times 15 minutes' GP contact plus medication costs
Unstable angina	1st year	440	As stable angina costs plus 60% of patients on clopidogrel
	Subsequent year	171	3 times 15 minutes' GP contact plus medication costs
MI	1st year	4448	Palmer[214] inflated to 2004 (£4118) plus primary care and medication costs as angina (£440)
	Subsequent year	171	3 times 15 minutes' GP contact plus medication costs
	Fatal event	1166	Clarke[200] inflated to 2004
TIA	1st year	1064	Assumed £264 for drug cost plus £800 for costs of test and surgery for appropriate patients (Stevenson MD, University of Sheffield: personal communication, November 2004)
	Subsequent year	264	Assumed £264 for drug cost only (Stevenson MD, University of Sheffield: personal communication, November 2004)
Stroke	1st year	8046	Youman[202] weighted by severity and inflated to 2004
	Subsequent year	2163	Youman[202] weighted by severity and inflated to 2004
	Fatal event	7041	Youman[202] inflated to 2004

stable angina is therefore assumed to relate to support within primary care: three GP visits per annum are assumed for monitoring and prescribing of medication. It is assumed that 90% of patients would receive, in addition to statins, glyceryl trinitrate spray, isosorbide mononitrate, one of verapamil, atenolol or dilitiazen, and aspirin, and in addition 20% of these patients would be on blood pressure-lowering therapy. The estimated total cost of medication is £171 (excluding statin cost) per patient per annum for the remainder of the patient's life.

Unstable angina

Medication costs for unstable angina are assumed to be the same as for stable angina, with the additional assumption that 60% of patients are also prescribed clopidogrel. In addition, a proportion of patients (50%) with unstable angina is assumed to be hospitalised in year 1 (Yeo W, Royal Hallamshire Hospital, Sheffield: personal communication), resulting in total year 1 costs of £440 per person. Subsequent costs for year 2 onwards are assumed to be the same as for stable angina.

Non-fatal MI

The cost of non-fatal MI in the first year is taken from Palmer.[214] The cost is based on data from the NHAR and is an annual average health state cost estimated by aggregating the resource consumed by each patient in the 1998 NHAR cohort. This cost includes revascularisation for a proportion of patients.

The cost of non-fatal MI in the subsequent year is based on the assumption that all patients receive primary care support. Primary care visits and medication costs in year 2 onwards are assumed to be the same as for angina.

Fatal MI

The cost of fatal MI is taken from Clarke.[200] The cost of non-fatal MI from the same source (£4070) was similar to that used in the model taken from Palmer.[214] It was therefore assumed that the relative difference in costs between fatal and non-fatal events from the two sources would be compatible.

Non-fatal stroke

The cost of stroke is taken from Youman,[202] based on the cost of acute events (mild stroke £5099, moderate stroke £4816 and severe stroke £10,555), weighted by the distribution of severity of strokes.

Fatal stroke

The cost of fatal stroke, £7041, is taken from Youman.[202]

TIA

It is assumed that a TIA has no costs associated with the event itself. However, following a TIA patients will undergo tests and remain on long-term medication. It is assumed that patients receive an outpatient visit, plus appropriate tests [computed tomographic (CT) scan, ultrasound, angiography] and a small proportion will require endarterectomy. The average cost per patient is estimated to be £800 (Stevenson MD, University of Sheffield: personal communication, November 2004). Patients are assumed to remain on long-term medication [a combination of aspirin, dipyridamole, an angiotensin-converting enzyme (ACE) inhibitor and a diuretic] at an estimated cost of £264 (Stevenson MD: personal communication, November 2004). Year 1 costs are therefore assumed to be £1064, with subsequent year costs of £264 per annum for the remainder of the patient's life.

Costs of statins

The relative risk effect of statins used in the model is taken from a meta-analysis of all trials and is therefore influenced by the number of patients in each arm of the trials. As the dosage used in the trials affects the relative risk and cost is related to dosage, the overall cost of statins should be linked to the trial dosages. The following describes the methodology used to estimate a combined weighted average cost for all statins used in the main analyses and also an average cost for each statin. As simvastatin is available as a generic product, the cost was based on a weighted average cost of proprietary and generic products. Prescribing data from the Department of Health is available for the number of items prescribed for each of these products in 2003 (*Table 56*).[41] These were the latest available data at the time of the report. A combined cost for simvastatin products was estimated by weighting the cost at each dosage by the number of items prescribed for each product at each dosage. This cost of simvastatin is based on 2003 prescribing shares and it is almost certain that generic prescribing has increased since then. Higher levels of generic prescribing would give more weight to the lower generic prices, resulting in a lower combined cost of simvastatin.

To weight cost by trial evidence, data on dosage and number of patients in the treatment arm were extracted from all the trials that were used to estimate relative risks. The cost of each statin at each dosage was weighted by the number of patients in the treatment arm of the trials at the same dose level (*Table 57*). Where trials allowed

TABLE 56 *Simvastatin proprietary and generic prescribing in 2003*

Proprietary and generic products	Items dispensed in 2003[41] (thousands)
Simvador_Tab 10 mg	3.2
Simvador_Tab 20 mg	4.9
Simvador_Tab 40 mg	7.4
Simvastatin_Tab 10 mg	1949.7
Simvastatin_Tab 20 mg	2776.3
Simvastatin_Tab 40 mg	1688.6
Simvastatin_Tab 80 mg	110.8
Zocor_Tab 10 mg	983.8
Zocor_Tab 20 mg	1237.1
Zocor_Tab 40 mg	566.7
Zocor_Tab 80 mg	42.9

titration and data were available on the proportion of patients at each dose, the number in the treatment arm was proportioned out to the correct dosage. The cost of statins has therefore been weighted by the numbers in the treatment arms of the trials at each dosage level, to estimate an overall statin cost.

As no rosuvastatin trials contributed to the estimation of relative risks, the cost of rosuvastatin is not included in this estimate. However, a cost of rosuvastatin is required for the surrogate end-point modelling. Two rosuvastatin trials[125,126] were used to inform the cholesterol-lowering modelling. These trials had two rosuvastatin arms with starting doses of 5 and 10 mg per day and allowed titration up to 80 mg per day. The 5-mg arm was not included in the analysis as it is not currently licensed in the UK. The 80-mg dose is not licensed in the UK; however, as titration will influence the efficacy of the drug in these trials it has been taken into account in the estimation of

the cost of rosuvastatin. The proportion of patients titrated to 80 mg in both trials was very low (Brown 1.3%; Olsson 2.0%). As the cost of rosuvastatin was derived by weighting the cost of 10 mg and 80 mg by this proportion, the effect of the 80-mg dose on the weighted cost of rosuvastatin is minimal.

All statin costs were obtained from the September 2004 BNF.[49]

Table 58 shows the weighted cost of statins used in the economic modelling. The cost of individual statins is weighted by the trial evidence. The relatively low cost of atorvastatin compared with simvastatin, in *Table 57*, is due to the high weighting given to the 10-mg cost of atorvastatin (*Table 58*). Ninety-five per cent of trial patients were in this category, resulting in a large weight being attributed to the low 10-mg cost of £18.03. For simvastatin, all patients were in either the 20- or 40-mg category and 86% were in the more expensive 40-mg category. A higher weight is therefore placed on these costs, resulting in an annual cost for simvastatin of £297 compared with £243 for atorvastatin. The high annual cost of pravastatin is due to 99% of trial patients being in the more expensive 20- or 40-mg categories.

TABLE 58 *Weighted cost of statins used in analysis*

Statin	Annual cost
Atorvastatin	£243.10
Fluvastatin	£204.00
Pravastatin	£387.30
Rosuvastatin	£244.10
Simvastatin	£296.90
Combined[a]	£316.80
a Rosuvastatin not included.	

TABLE 57 *Statin cost and numbers in treatment arm of RCTs*

Statin	10 mg		20 mg		40 mg		80 mg	
	Cost (28 tabs)	No. in treatment arm	Cost (28 tabs)	No. in treatment arm	Cost (28 tabs)	No. in treatment arm	Cost (28 tabs)	No. in treatment arm
Simvastatin[a]	14.01		20.21	1865	23.18	11438	29.03	
Atorvastatin	18.03	6981	29.69		29.69		29.69	385
Fluvastatin			12.72		12.72	187	16.00	1518
Pravastatin	16.18	3	29.69	18	29.69	14218		
Rosuvastatin	18.03	245	29.69		29.69			4
a Combined proprietory and generic cost based on 2004 prices and 2003 prescribing data.								

The majority of analyses are based on the costs and effectiveness of statins collectively.

Pravastatin became available as a generic product in August 2004. It is anticipated that this will reduce the cost of the proprietory pravastatin and this may also influence the cost of other statins. A list of generic pravastatin prices and a discussion concerning potential changes to statin prices are presented in the section 'Price of statins' (p. 127) It is anticipated that the cost of statins will fall over the next few years.

Annual cost of statins weighted by prescribing

The methods described above link the cost of statins to the trial effectiveness of statins, but may not reflect the actual prescribing cost of statins to the NHS. An annual cost of statins weighted by prescribing data has been estimated, based on 2003 prescribing data from the Department of Health. The weighted cost is based on the cost and number of prescriptions of each statin at each dosage. This is then combined to give an overall prescribing weighted annual cost. The total number of prescription items (thousands) for each statin was:

- atorvastatin (Lipitor): 7724
- fluvastatin (Lescol): 774
- pravastatin (Lipostat): 2582
- rosuvastatin (Crestor): 277
- simvastatin (Zocor): 2830
- simvastatin (Simvador): 15
- simvastatin (Simvastatin): 6525.

The annual cost of statins estimated from this method is £273; this represents a 14% decrease from the trial weighted cost of £317. Use of this cost in the model would not, however, take into account any potential change in efficacy resulting from using a different mix of statins to that on which the trial evidence is based.

Costs of monitoring

Guidelines indicate that patients taking statin treatment should have the following tests at the start of treatment: cholesterol measurement, liver function tests, renal function tests and a CK test. The liver function tests should be repeated at 4–6 weeks and thereafter at intervals of 6–12 months. Cholesterol should be checked at intervals of 6–12 months. The first test is generally conducted by the GP and thereafter by the general practice nurse and the relevant pathologist.

However, these guidelines are rarely adhered to strictly in general clinical practice and, based on

expert opinion (Cooper R, Staffa Health, Alfreton, and Yeo W, Royal Hallamshire Hospital, Sheffield: personal communications, October 2004), the following tests are costed: liver function test (£10.63) at baseline, 3, 6 and 12 months, then annually thereafter; cholesterol test (£10.63) at baseline, 6 and 12 months, then annually thereafter. In addition, it is assumed that all patients receive a baseline CK test, with 10% of patients having additional annual tests. It is assumed that tests are conducted by the practice nurse (£12 per visit). Based on the above, monitoring costs are £124 for the first year [(7 × £10.63) + (4 × £12) + £1.59] and £33.42 [(2 × £10.63) + £12 + (0.1 × £1.59)] for subsequent years. All costs are taken from Curtis and Netten.[240]

Costs of adverse events

Statins are generally well tolerated and have a good safety profile. This view is generally supported both by the evidence of the trials included in this review and by postmarketing surveillance data. (See *Table 27*, pp. 54–6, for a summary of adverse events in RCTs). Although increases in CK and myopathy have been reported, rhabdomyolysis and hepatotoxicity are rare. Hence, the associated costs of managing adverse events are expected to be small and are not modelled.

Utility
Utility by age

As CHD risk increases with age, and events occur more frequently in older populations, the baseline utility assigned to patients, as well as the disutility associated with health states, could potentially have an impact on the estimated ICERs. In addition, the HRQoL in the general population decreases with age, so it is important to consider these values when assigning disutilities associated with CHD events.

A study by Kind and colleagues[241] valued the utility by age in the UK general population (*n* = 3395) using the EuroQol 5 Dimensions (EQ-5D) questionnaire, and significant differences in HRQoL were found between age groups. The patient-level data were reanalysed and a linear relationship was established between baseline utility and age. The values used in the ScHARR model are provided in *Tables 59* and *60* and the results of the regression are provided in Appendix 32. Uncertainty is explored in the probabilistic analyses, and scenarios have been explored using an event-free utility of 1 across all ages.

TABLE 59 *Parameters values modelled for baseline utility by age*

	Coefficient	SE
Intercept	1.060	0.029
Age	–0.004	0.000

TABLE 60 *Utility values by age used in the ScHARR cost-effectiveness model*

Age (years)	Utility	Age (years)	Utility
45	0.869	75	0.741
50	0.848	80	0.720
55	0.826	85	0.699
60	0.805	90	0.678
65	0.784	95	0.656
70	0.763	100	0.635

Utility by health state

A literature review was undertaken to identify the best available utility estimates for inclusion in the model. The health state utility values included in the economic model are stable angina, unstable angina, stroke and MI. Studies were identified through searches of electronic databases, handsearching, citation searching and reference list checking. Other sources examined were existing cost-effectiveness studies, the Cochrane Library and the Harvard catalogue of preference scores. At this stage no exclusion criteria were applied with regard to the type of instrument used, the valuation technique, whose values were used or the population type.

A total of 1625 studies was identified from electronic databases. Titles and abstracts were reviewed and 58 hard copies of papers were retrieved for closer inspection. Of the studies retrieved, nine had utility values for the health states listed above for a general population and two for a diabetic population. Preference was given to studies reporting mean values rather than median values, as means incorporate the strength of people's preferences.[242]

These studies were then evaluated based on the following criteria:

- the population setting: UK studies were preferred to non-UK studies
- the type of instrument: the recommendation for economic evaluations is that health state utilities should be obtained using a choice-based technique such as standard gamble or time

trade-off, rather than a rating scale. There is no consensus as to which of these two should be used.[243]

Results of systematic review of utility
Stroke
Two studies were found that provided mean utility estimates. One study was based on data collected in the Evaluation of Dutch Integrated Stroke Service Experiment study.[244] Patients with consecutive stroke from eight hospitals in six regions of The Netherlands were included. The study was conducted between 1999 and 2000. In total, 598 stroke patients were included. The mean age was 73.5 years and 54% were women. Patient interviews were conducted at 2 and 6 months after stroke using the EQ-5D instrument. The other study was a meta-analysis of quality of life estimates for stroke.[245] Studies were identified by searching through NHS EED and MEDLINE, as well as examining bibliographies of review articles and citation searching. In total, 20 articles were found, reporting 53 quality of life estimates. A metaregression was used to find the best pooled estimates for stroke and also to assess the impact of study design characteristics on the pooled quality of life estimate. Only severity of stroke and the bounds of the scale used were predictive of quality of life. The scale of death to perfect health was found to be the best predictor of quality of life estimates, compared with the scales of death to normal health, death to excellent health and worse possible health to perfect health. The elicitation method and respondents were not found to be statistically significant predictors of quality of life. As this study was based on a meta-analysis of all known utilities and because elicitation methods and respondents were not predictive of outcomes, the estimates are considered to reflect more accurately quality of life for stroke patients than the estimates from van Exel and colleagues.[244] The values from this study are therefore used in the ScHARR cost-effectiveness model, and are: mild stroke 0.87, moderate stroke 0.68 and severe stroke 0.52.

The ScHARR model uses an overall non-fatal stroke health state that does not distinguish between severities. The above utilities were therefore combined. A study by Youman and colleagues[202] estimated the proportion of patients experiencing strokes of differing severity from the data set of a UK trial investigating stroke outcomes in 290,000 newly diagnosed patients. The proportion of stroke survivors experiencing a mild, moderate or severe stroke was 0.19, 0.27 and 0.54, respectively. The above utilities at each

severity were weighted by the proportion of stroke patients in the respective severity, and a combined utility for stroke of 0.63 was thus estimated.

Stable angina

Only one study was found that reported mean quality of life specifically in stable angina patients.[207] This was an economic and quality of life substudy of the Bypass Angioplasty Revascularization Investigation,[246] a US study that enrolled 553 patients with multivessel CAD and angina or documented ischaemia. Quality of life was assessed in 387 patients using the time trade-off method. Patients with angina had a mean time trade-off score of 7.03 compared with a mean score of 8.7 in patients without angina. The difference between these scores represents the decrement due to stable angina that is used in the ScHARR model. However, the baseline in this study (patients with CAD) is not comparable to the baseline in the ScHARR model (general population). The score for patients without angina was therefore scaled up to a score of 1 and the score for stable angina was scaled up by the same multiplier. The value for stable angina used in the ScHARR model is therefore 0.81.

Unstable angina

Only one study was identified that provided a mean utility value for unstable angina.[247] This was an RCT comparing care in a chest pain clinic observation unit with routine care in the emergency department of the Northern General Hospital in Sheffield, UK. As part of a cost-effectiveness analysis, EQ-5D questionnaires were administered to 676 patients at 6 months following treatment. A record of patient diagnosis at entry included MI and unstable angina. For unstable angina the mean utility score at 6 months was 0.77 based on questionnaires from 209 patients (Goodacres S, University of Sheffield: personal communication, November 2004).

MI

Two studies were identified that reported mean utility values for MI: the above study by Goodacre[247] and a study by Bradley and colleagues.[248] The Bradley study used the Health and Activities Limitations Index (HALex) to evaluate the quality of life of 176 patients enrolled in the Michigan State University Inter-Institutional Collaborative Heart Study (MICH study), a registry of AMI patients. As the Goodacre study meets the criteria for the population setting and also uses a more validated quality of life instrument, this study was chosen to provide the utility for MI (0.76) (*Table 61*).

TABLE 61 *Utilities for health states*

Health state	Utility mean (SE)	Source
CHD		
Stable angina	0.808[a]	Meslop[207]
Unstable angina	0.770 (0.038)	Goodacre[247]
MI	0.760 (0.018)	Goodacre[247]
CVD		
TIA	1	Population norm by age and gender[241]
Stroke	0.629 (0.04)	Tengs[245]

[a] Uncertainty in stable angina is correlated to unstable angina for probabilistic analyses.

TIA

It was assumed that the utility score for patients following TIA is the same as the population norm.[241]

These utilities are used as a multiplier in the model to adjust the utility of patients following an event.

Disutility due to statin treatment

Results from some studies have suggested that patients with very low serum cholesterol levels have a higher risk of suicide and mortality,[249–251] and that patients receiving medication to reduce serum cholesterol levels have a higher risk of death from trauma, suicide and homicide.[252–254] However, 4-year follow-up results from 559 patients receiving pravastatin and 571 receiving placebo concluded that there is no association between long-term statin-induced reductions in serum cholesterol level and measures of anxiety, depression or anger. A subsequent 12-month study ($n = 41$) designed to determine the effects of pravastatin on HRQoL in older adults concluded that pravastatin was well tolerated and did not adversely affect HRQoL.[255] In addition, as adverse events and side-effects are rare, patients receiving statin treatment in the model do not receive a penalty utility due to their medication. As statins are prescribed for life, there may be a disutility associated with this, but it is assumed that this is small in comparison to the benefits received and as such is not modelled.

Cost-effectiveness analysis

ICERs determine the additional cost of using statin per QALY gained compared with no treatment, where:

$$ICERs = \frac{(Cost_{statin} - Cost_{no\ treatment})}{(Utility_{statin} - Utility_{no\ treatment})}$$

Subgroups

Patients with diabetes

Patients with diabetes are at increased risk of CHD, and incidence rates are thought to be twice as high as in non-diabetic populations. However, the distribution of patients throughout CHD health states and the ratio of fatal and non-fatal events is likely to be similar to a non-diabetic population. Hence, the diabetic analysis has no adjustments made for the primary event rate, as the model is examining the cost-effectiveness of patients at an assigned risk level.

As data in the published diabetic trials provided insufficient evidence to be used for the transitions modelled, subsequent event rates are assumed to be twice those of non-diabetic patients (Yeo W, Royal Hallamshire Hospital, Sheffield: personal communication, September 2004). The relative risk used in the diabetes analysis remains unchanged from the base case, as the current evidence base suggests that there is no statistically significant difference between the results from the diabetic and non-diabetic trials.

Costs for the health state events were taken from the UKPDS study by Clarke and colleagues.[200] Where insufficient detail is provided and to retain internal consistency, the costs were adjusted in proportion to the base-case costs. Similarly, the UKPDS data were used to assign health state utilities and again missing values were adjusted according to the base-case values modelled, taken from Clarke.[200] Full details are provided in Appendix 33 (*Tables 157* and *158*).

Patients with familial hypercholesterolaemia

Patients with familial hypercholesterolaemia who have a history of premature CHD form a high-risk subgroup. It is estimated that these patients have an incidence rate that has the same effect as being 6 years older than in the base case, although it is thought the ratio of events in the CHD health states, and the ratio of fatal to total events, are similar to the base case. The probability of subsequent events is also likely to be similar to that of the base case (Yeo W: personal communication, September 2004). It is not thought that health state costs or utilities will differ from the base-case analyses.

The effectiveness evidence is limited. Results from the one 2-year statin study on 330 patients with familial hypercholesterolaemia do not suggest that statins have a greater impact on reducing their CHD events than that seen in other trials. In modelling terms this suggests that although a patient with familial history of premature CHD is at a higher baseline risk level than the general population at the same age, as incident distributions and subsequent event rates remain unchanged, results from the base-case analyses are generalisable to this subgroup.

Non-European groups

Patients of non-European descent and in particular British Asians have an incidence rate that is approximately 1.5% higher than the base case. However, it is thought that transitions between health states will be similar to those modelled for the base case, and utilities and costs are unlikely to differ (Yeo W: personal communication, September 2004). Non-European groups are not modelled explicitly as there is no direct evidence of effectiveness for this population from the statin trials.

Compliance

Although published figures of compliance and continuance are contradictory and inconclusive, it is generally accepted that a proportion of patients is non-compliant with statin treatment and a proportion of patients will withdraw completely. Compliance and continuance rates impact on the costs associated with treatment, the effectiveness of the treatment, and thus the benefits accrued through events and deaths saved. In addition to compliance and continuance, it is acknowledged that in general clinical practice some patients collect prescriptions at the designated intervals but fail to take the medication, incurring full costs with few or no benefits.

These issues are particularly pertinent when addressing asymptomatic patients in primary prevention. As non-compliant patients represent a significant cost and burden on healthcare resources, it is important to explore the impact of adjusting the proportions assumed to be fully compliant with treatment in any cost-effectiveness evaluation.

Techniques used to model compliance in existing economic analyses

Of the 40 cost-effectiveness papers reviewed to inform on modelling techniques, very few addressed long-term compliance with statin treatment and the methodologies used varied enormously. Two papers adjusted statin costs based on the compliance rates in the trials used for evidence of effectiveness,[179,256] while a third model[257] assumed a compliance rate of 95% based on evidence pooled from statin effectiveness studies. Berto and colleagues assumed that

effectiveness data were based on 100% compliance in the RCT, and reduced this value in proportion with a 30% non-compliance rate based on expert opinion.[258] Lim and colleagues used an exponential decline in compliance which levelled off at 50% after 3 years, based on published evidence.[193] Two evaluations modelled health states on and off therapy, allowing non-compliant patients to resume therapy following an event.[259,260]

Compliance and continuance in the ScHARR model
Based on the evidence reported from the statin trials, and published evidence in general clinical practice, patients who are likely to withdraw typically do so in the first few years of treatment, with the majority of withdrawals in the first 12 months. Evidence also suggests that non-compliance is greater in the early treatment period, with patients' adherence to correct dosages remaining fairly constant in the long term. Compliance and continuance rates differ between secondary and primary prevention cohorts, with secondary patients generally having a higher compliance rate and a smaller rate of non-continuance over time.

Effectiveness data from the major outcome trials are based on ITT analysis over a typical duration of 3–5 years. This encompasses the period during which the largest proportion of patients withdraw and reduce compliance. Hence, the results of the ITT analysis could be considered conservative as they are not derived from a full sample of patients who are fully compliant.

As robust data on true compliance and continuance rates are not available from patients in either RCTs or general clinical practice, a series of assumptions was required to model the effectiveness of statin treatment.

The base case assumes that the relative risks derived from the ITT analyses can be generalised to patients taking statin treatment in general clinical practice. This assumption is based on the ITT analysis and the evidence that suggests that after the first few years compliance and continuance stabilise and remain fairly constant in the long term. It is acknowledged that this assumption is based on poor-quality evidence and is subject to significant uncertainty, although it should be noted that several of the largest trials may reflect clinical practice.

A series of sensitivity analyses was performed to establish the impact on the results when

adjustments are made to the relative risks, and statin and monitoring costs. The variations in these parameters are based on the data available from RCTs and studies conducted in general clinical practice. The proportion of patients who are assumed to be fully compliant to treatment and the adjustments to statin and monitoring costs that are used in the different scenarios are provided in *Table 62*. The implications and conclusions that can be drawn from the results of these analyses are discussed in detail later in this chapter in the 'Discussion of results' section, 'Key issues' on p. 117.

It is assumed that the ITT relative risks from statin trials are derived from samples of 100% compliant patients who do not withdraw from treatment. The proportion of patients who are assumed to remain fully compliant with treatment over the first 5 years in each scenario explored is provided in *Table 62*. After 5 years the proportion is assumed to remain unchanged from the year 5 value. These values are based on collated published evidence, supported by expert opinion (Yeo W, Royal Hallamshire Hospital, Sheffield: personal communication, December, 2004). The associated statin and monitoring costs are decreased in proportion.

An additional extreme case analysis is performed to examine the impact of reducing the benefits in proportion to the percentage of compliant patients, while retaining the full treatment costs.

Results of ScHARR analysis

To inform both policy decision-makers and clinicians in general practice, three sets of analyses are reported. The base case considers the impact of statin treatment within CHD only. This complies with the scope specifically requested by the Department of Health. Base-case results are reported in the next section. Two further scenarios are explored to take into account the evolving evidence on the impact of statins on reducing stroke events. Scenario 1 is as the base case, but also takes into account the reduction in stroke events for patients with a history of CHD, again complying with the remit from the Department of Health. Scenario 2 explores the costs and benefits associated with statin treatment in reducing all CVD events. Results for scenarios 1 and 2 are reported in the section 'Results: alternative scenarios' (p. 110).

Owing to the large number of results presented, only base-case results are tabulated and discussed

TABLE 62 *Proportion of patients assumed to be compliant with treatment, used in sensitivity analyses in the ScHARR cost-effectiveness model*

Compliance evidence			Scenarios explored		
Year	RCT[a]	General clinical practice[b]	A[c]	B[c]	C[c]
			% compliant	% compliant	% compliant
Primary prevention					
1	0.88	0.8	0.8	0.7	0.7
2	0.87	0.7	0.7	0.65	0.65
3	0.87	0.68	0.68	0.6	0.6
4	0.79	0.65	0.65	0.55	0.55
5	0.8	0.65	0.65	0.5	0.5
Secondary prevention					
1	0.94	0.9	0.9	0.85	0.8
2	0.87	0.8	0.8	0.78	0.75
3	0.89	0.78	0.78	0.7	0.65
4	0.77	0.75	0.75	0.65	0.6
5	0.79	0.75	0.75	0.65	0.55

[a] Proportion of patients fully compliant with treatment by year of treatment duration based on RCT evidence from statin trials.
[b] Proportion of patients fully compliant with treatment by year based on evidence from general clinical practice.
[c] Proportion of patients fully compliant with treatment and the proportion of costs modelled.

TABLE 63 *CHD analysis: secondary prevention results for a cohort of 1000 patients: cost per QALYs (£,000)*

	Age (years)	Undiscounted			Discounted		
		Incremental costs	Incremental QALYs	Incremental cost per QALY	Incremental costs	Incremental QALYs	Incremental cost per QALY
Men	45	£10,684	700	£15.3	£4,732	462	£10.2
	55	£7,863	565	£13.9	£4,109	410	£10.0
	65	£5,394	397	£13.6	£3,310	314	£10.5
	75	£3,433	227	£15.1	£2,455	193	£12.7
	85	£1,976	115	£17.2	£1,615	103	£15.7
Women	45	£11,905	776	£15.3	£4,966	493	£10.1
	55	£9,033	644	£14.0	£4,432	452	£9.8
	65	£6,327	499	£12.7	£3,660	387	£9.5
	75	£4,119	297	£13.9	£2,799	248	£11.3
	85	£2,343	148	£15.8	£1,853	132	£14.0

in the following section of the report. Results of the different scenarios and sensitivity analyses are summarised and full tables are provided in Appendix 34. Unless otherwise stated, evidence and costs are based on all statins licensed for use in the UK in August 2004 for which evidence on clinical end-points is available.

Results: base case (CHD analyses)
For the base-case analyses the main results are presented, followed by results for diabetics, results from the surrogate end-point analysis and sensitivity analysis for the base case.

Base-case results
Cost-effectiveness results are presented for secondary and primary prevention by age and gender.

Secondary prevention
The costs per QALY estimated for the use of statin treatment in secondary CHD prevention are well within limits generally accepted as cost-effective, as can be seen in *Table 63*. The discounted results range from approximately £10,000 to £15,700. There is little difference between cost-effectiveness results in men and women.

TABLE 64 *CHD analysis: primary prevention results for a cohort of 1000 patients at varying annual CHD risk – undiscounted cost per QALY (£,000)*

	Age (years)	Annual CHD risk					
		3.00%	**2.50%**	**2.00%**	**1.50%**	**1.00%**	**0.50%**
Men	45	£15.7	£16.3	£17.3	£19.3	£23.1	£31.8
	55	£18.5	£19.6	£21.5	£24.6	£30.4	£43.4
	65	£22.0	£24.1	£27.3	£32.5	£41.8	£62.9
	75	£30.9	£34.6	£40.0	£48.6	£63.8	£97.8
	85	£39.9	£44.9	£52.0	£62.4	£79.3	£111.5
Women	45	£23.2	£23.4	£24.4	£26.8	£32.3	£47.7
	55	£24.2	£25.0	£26.9	£30.5	£38.0	£58.1
	65	£26.4	£28.6	£32.1	£38.0	£49.5	£78.6
	75	£38.4	£42.6	£48.7	£58.6	£76.4	£117.4
	85	£52.3	£57.7	£65.0	£75.5	£91.6	£119.0

TABLE 65 *CHD analysis: primary prevention results for a cohort of 1000 patients at varying annual CHD risk – discounted cost per QALY (£,000)*

	Age (years)	Annual CHD risk					
		3.00%	**2.50%**	**2.00%**	**1.50%**	**1.00%**	**0.50%**
Men	45	£9.5	£10.0	£10.8	£12.2	£14.9	£20.9
	55	£12.6	£13.5	£14.9	£17.2	£21.5	£31.1
	65	£16.8	£18.5	£21.0	£25.1	£32.5	£49.5
	75	£26.2	£29.4	£34.1	£41.5	£54.7	£84.8
	85	£36.8	£41.5	£48.1	£58.0	£74.1	£105.2
Women	45	£13.7	£14.0	£14.9	£16.6	£20.3	£30.5
	55	£15.9	£16.6	£18.0	£20.6	£25.9	£40.0
	65	£19.3	£21.0	£23.7	£28.2	£37.0	£59.3
	75	£31.5	£35.0	£40.2	£48.5	£63.7	£98.9
	85	£47.4	£52.4	£59.3	£69.1	£84.3	£110.6

The ICERs increase slightly beyond the age of 65, but are under £16,000 at the age of 85 for both men and women.

Primary prevention
The undiscounted and discounted cost per QALY estimates for primary prevention are presented in *Tables 64* and *65*. Incremental cost and incremental QALYs for these results are given in Appendix 34.

These results suggest that it is more cost-effective to commence treating patients at younger ages than at older ages. At 45 years of age the estimated discounted costs per QALY range from approximately £9000 to £21,000 for men between 3% and 0.5% annual risk of a CHD event, and from £14,000 to £30,000 for women between the same risk levels. At 85 years of age the corresponding values are £37,000–105,000 for men and £47,000–111,000 for women.

The estimated ICERs increase sharply with age, and the differences with age observed in primary prevention are much larger than seen in the secondary analyses. This is to be expected as the potential to save events and therefore the utility and cost benefits accrued from remaining in the event-free health state decrease in older cohorts.

If the natural increase in CHD risk due to age is taken into account, then a male patient at 0.5% annual CHD risk at the age of 45 would be at over 1.7% risk at the age of 85 years. If statin treatment were delayed until the age of 85 years the ICER would increase to £58,000 per QALY from £20,000 per QALY, suggesting that the maximum benefit in primary prevention could be achieved by offering statin treatment at early ages.

Figures 28 and *29* compare the ICERs estimated for the secondary and primary prevention of CHD events across the age groups. As can be seen, while secondary prevention is more cost-effective than primary prevention across all ages, for patients commencing statin treatment at a young age to prevent the onset of CHD, the costs per QALY are
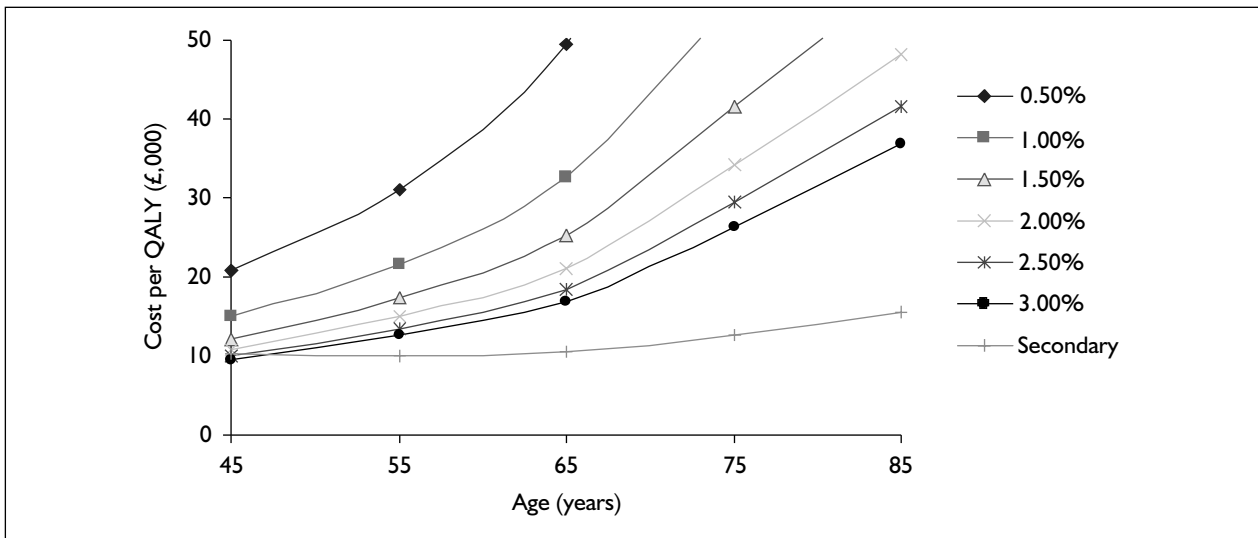
FIGURE 28 *CHD analysis: estimated cost per QALY for primary prevention at various CHD risk levels compared with secondary prevention – men*
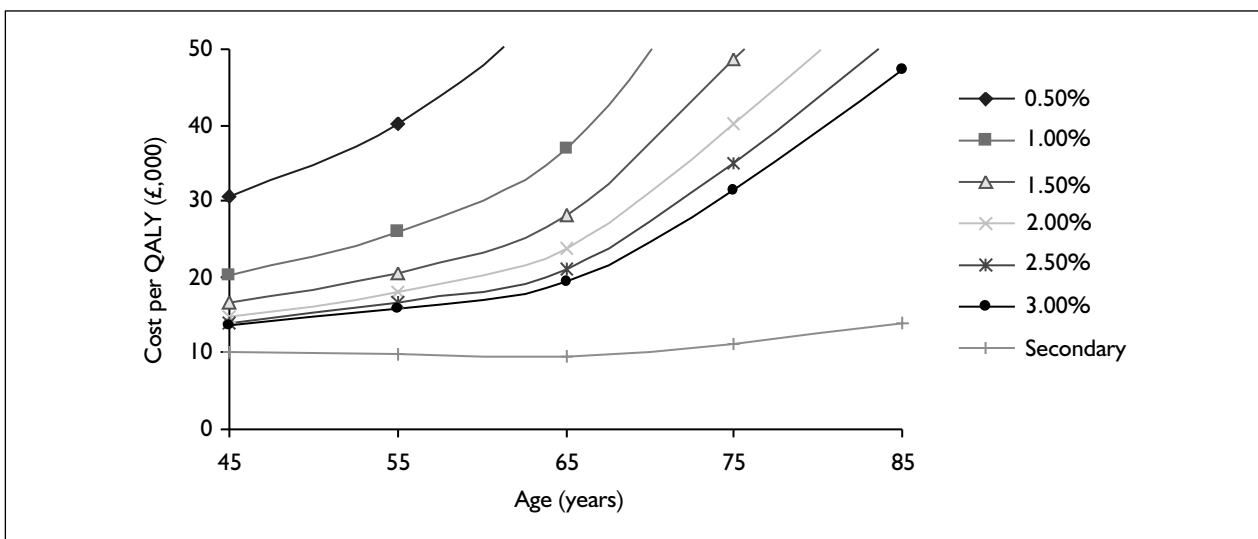
FIGURE 29 *CHD analysis: estimated cost per QALY for primary CHD prevention at various CHD risk levels compared with secondary prevention – women*

still well within the ranges considered cost-effective.

Results for primary prevention should be considered in the context of typical risk levels at different ages in the population of England and Wales. To estimate the percentage of people (primary prevention) in the general population who are at risk of CHD, data from the 1998 HSE[197] were aggregated by annual CHD risk level and age group. *Table 66* shows the results from the HSE data. The table is presented as the cumulative (from the bottom up) percentage of people at varying levels of annual CHD risk. For example, 7% of people aged between 45 and

54 years are at 1.5% risk or higher and 15% are at 1.0% risk or higher.

The table illustrates that the percentage of people at high risk reduces significantly in lower age groups. The numbers in *Table 66* must be viewed with some caution owing to limitations of both the Framingham risk equation and the HSE data set. Framingham risk equations cannot be used reliably for age ranges outside the Framingham population on which the equations are based. In addition, the risk level predicted by Framingham equations becomes increasingly less reliable as patient parameters reach the limits of the original Framingham subjects. Therefore, data in the older

TABLE 66 *Cumulative (bottom-up) percentage of men and women at risk by age group and risk level*

	Annual CHD risk (%)	Age range (years)					
		18–44	45–54	55–64	65–74	75–84	≥85
Men	<0.5	100%	100%	100%	100%	100%	100%
	0.5	8%	61%	91%	99%	100%	100%
	1.0	2%	27%	63%	90%	97%	98%
	1.5	1%	12%	40%	75%	88%	95%
	2.0	0%	6%	27%	57%	76%	86%
	2.5	0%	2%	18%	42%	58%	75%
	3.0	0%	1%	11%	31%	49%	64%
	>3.0	0%	1%	8%	22%	39%	45%
Women	<0.5	100%	100%	100%	100%	100%	100%
	0.5	1%	16%	49%	72%	71%	57%
	1.0	0%	5%	19%	34%	32%	27%
	1.5	0%	2%	8%	18%	14%	2%
	2.0	0%	1%	4%	11%	8%	2%
	2.5	0%	1%	2%	7%	4%	2%
	3.0	0%	1%	1%	4%	2%	2%
	>3	0%	0%	0%	3%	1%	2%

Data from the Health Survey for England 1998.[197]

TABLE 67 *CHD analysis: estimated cost per QALY for primary prevention at various CHD risk levels – weighted average by risk levels (£,000)*

	Annual CHD risk					
	3.00%	2.50%	2.00%	1.50%	1.00%	0.50%
Men	£20.0	£18.8	£21.0	£21.9	£23.0	£27.5
Women	£21.3	£21.7	£26.6	£28.1	£40.5	£56.8

age groups, 75–85 and 85 years and above, are considered to be less reliable than the younger age groups. This level of uncertainty is compounded by the fact that there are smaller volumes of patients at older ages in the HSE data set and therefore the available data may well be less representative of the general population.

To provide an estimate of primary prevention ICERs by risk level alone the distribution by age across risk levels from *Table 66* was used to provide a weighted average ICER for each risk level (*Table 67*).

The weighted average ICERs by risk level take account of the age distribution within the risk group. Younger patients are predominantly at lower risk levels. However, these averages should be treated with caution owing to concerns regarding the robustness of the HSE data and the limitations of Framingham risk equations, particular for older patients, as discussed above.

Discussion of base-case results

The cost-effectiveness of statins depends on the level of CHD risk in the population treated, and the age and gender of the population under consideration. In secondary prevention the cost per QALY is estimated to vary between approximately £10,000 and £15,700 between the ages of 45 and 85, with ICERs increasing slightly with age, but with little difference between men and women. In primary prevention the discounted cost per QALY estimates for primary prevention at the age of 45 range between £9500 and £30,500 for men and women as annual CHD risk levels fall from 3% to 0.5%. By the age of 85 years the corresponding values are £36,800 and £110,600.

However, it should be noted that there is greater uncertainty in the ICERs at younger ages. This is partly because the modelling is undertaken over the lifetime of the patients. Therefore, for younger patients the length of extrapolation required is significant as the modelling time-frame goes well

TABLE 68 *CHD analysis for diabetic patients: discounted cost per QALY for a cohort of 1000 diabetic patients (£,000)*

	Age (years)	Secondary prevention	Primary prevention: annual CHD risk					
			3.0%	**2.5%**	**2.0%**	**1.5%**	**1.0%**	**0.5%**
Men	45	£6.1	£6.2	£6.6	£7.3	£8.4	£10.4	£14.9
	55	£5.8	£8.6	£9.3	£10.3	£12.1	£15.3	£22.5
	65	£6.2	£11.9	£13.2	£15.1	£18.2	£23.7	£36.5
	75	£7.3	£18.5	£20.9	£24.4	£29.9	£39.9	£63.1
	85	£8.8	£26.8	£30.5	£35.8	£43.8	£57.4	£85.4
Women	45	£6.2	£8.6	£9.0	£9.8	£11.1	£14.0	£21.6
	55	£6.0	£10.4	£11.0	£12.2	£14.2	£18.3	£29.0
	65	£5.8	£13.8	£15.2	£17.3	£20.8	£27.6	£45.0
	75	£6.8	£23.1	£25.8	£29.9	£36.4	£48.5	£77.6
	85	£8.1	£36.7	£41.0	£47.0	£55.8	£69.9	£96.2

beyond the duration of major outcome trials to date. In addition, there is greater uncertainty in the baseline data at younger ages; for instance, transition probabilities taken from data sets such at the NHAR and SLSR have much smaller numbers of patients at younger ages and therefore the uncertainty in the estimated transition rates is greater.

Subgroups
Diabetic patients
As diabetic patients are at an increased risk of CHD events, a sensitivity analysis was performed to explore the cost-effectiveness of statin treatment in both primary and secondary prevention of CHD events for diabetic patients. The conclusions of the section 'People with diabetes' (p. 48) are that any difference in the effectiveness of statin treatment on diabetic and non-diabetic patients is insignificant. Hence, the relative risk due to statin treatment is as the base case. However, in addition to being at increased risk of a primary CHD event, diabetic patients are at a higher risk of having a subsequent event.

The estimated ICERs for diabetic patients with a history of CHD range from approximately £5800 to £8800 per QALY, approximately 50% lower than the estimated ICERs in the base case. Statin treatment is more cost-effective in secondary prevention than in primary prevention, with the costs per QALY in primary prevention ranging from £6200 for men aged 45 years at 3% annual risk of a CHD event to £96,200 for women aged 85 years at 0.5% risk (*Table 68*).

If Framingham risk assessment tools are used to predict CHD risk for patients with diabetes these results can be considered conservative as evidence suggests that Framingham underpredicts both CHD event rates and CHD mortality rates, by 40%

and 80%, respectively.[261] Hence, a patient with a predicted risk of 1.5% (based on the Framingham risk assessment tool) will, in reality, have a higher risk level and a corresponding lower cost per QALY.

It is estimated that 27% of UK diabetics aged between 35 and 74 years have established CVD, with a further 30% at an annual CHD risk of 1.5% or higher.[262] If a threshold of 1.5% or over annual risk was taken as the risk value to offer statin treatment, two-thirds of the UK diabetic population would require treatment. Based on the evidence that suggests that Framingham underpredicts risk in diabetics, and hence the corresponding reduction in cost per QALY, the results suggest that statin treatment should be considered cost-effective for the vast majority of diabetics in the UK.

Surrogate end-point analysis
In the surrogate end-point analysis the benefits associated with statin treatment are modelled by applying the relative risks estimated indirectly from the cholesterol-lowering effects of statins [see the section 'Estimating effectiveness from non-clinical end-points' (p. 91)].

Secondary prevention
Using Framingham to predict the reduction in events based on cholesterol lowering of individual statins, the costs per QALY estimated are shown in *Table 69*. These ICERs are comparable with the base-case results generated using the relative risk reductions of events.

Primary prevention
The results estimated for primary prevention analyses by CHD risk levels and ages are shown in *Tables 70* and *71*. These ICERs are again comparable with the base-case results generated using the relative risk reductions of events.

TABLE 69 *CHD analysis: secondary prevention – using Framingham/cholesterol links to predict the reduction in events for cohorts of 1000 patients; discounted cost per QALY (£,000)*

	Age (years)	Rosuvastatin
Men	45	£7.8
	55	£7.7
	65	£8.2
Women	45	£6.6
	55	£6.5
	65	£6.4

TABLE 70 *CHD analysis: primary prevention – using Framingham to predict events avoided for cohorts of 1000 patients at 0.5% annual CHD risk; discounted cost per QALY (£,000)*

	Age (years)	Rosuvastatin 0.5%
Men	45	£9.8
	55	£15.0
	65	£23.9
Women	45	£14.8
	55	£19.7
	65	£28.9

TABLE 71 *CHD analysis: primary prevention – using Framingham to predict events avoided for cohorts of 1000 patients at 3% annual CHD risk; discounted cost per QALY (£,000)*

	Age (years)	Rosuvastatin 3.00%
Men	45	£5.0
	55	£6.8
	65	£9.0
Women	45	£7.6
	55	£9.0
	65	£10.6

The results of the surrogate modelling must be viewed with several caveats as the link between cholesterol lowering and clinical end-points is not robust. It is accepted that Framingham equations do not perform well when patient parameters such as blood pressure and age reach the limits of those found in the Framingham population and this will certainly be the case for a proportion of the HSE subjects. The coefficients within the Framingham equations are also subject to uncertainty and this uncertainty has not been captured in the above results. There is also an issue of the ability of Framingham to predict risk when cholesterol is reduced chemically. The Framingham risk

functions were derived to calculate baseline risk in patients before interventions are offered. Their use to predict the likely outcome of chemically induced reduction in cholesterol has not been validated. The cholesterol-lowering trial evidence on which the model is based is also limited. Only two trials over the 6-month exclusion criteria applied in this assessment were identified and these were specifically cholesterol-lowering trials. Cholesterol-lowering trials have consistently performed better than clinical end-point trials in terms of cholesterol-lowering.

Until clinical end-points are available, the cost-effectiveness results for rosuvastatin must be treated with caution.

Sensitivity analysis
A range of sensitivity analyses was undertaken on the base-case results. First, univariate sensitivity analyses were undertaken to assess the impact of a range of input parameters, including costs, utilities, relative risks, compliance and time-frame of the model. A risk threshold analysis was undertaken to demonstrate the annual CHD risk at which statin treatment is cost-effective for male and female patients, using age bands of 5 years. PSA was undertaken to determine the impact of the imprecision of input values on decision uncertainty.

Univariate sensitivity analyses
A number of univariate sensitivity analyses was conducted to explore the impact of varying key parameters and assumptions required to populate the model. Key results are presented in *Table 72* for secondary and primary prevention. Minimum and maximum values are presented for each scenario. A full range of results and a full description of the parameters varied in each analysis are presented in Appendix 34.

Results of additional sensitivity analyses requested after the first appraisal committee meeting are provided in Appendix 35. These explore the impact of using different time-horizons and discount rates, and the effect of weighting the ICERs by the population in the UK at each risk level.

Discussion of univariate sensitivity results
The sensitivity analysis shows that results are most sensitive to assumptions on the cost of statins, discount rates and the time-frame of the model. The model is robust to changes in other parameters, including relative risks, cost of health states, health state utilities, and assumptions on incidence, prevalence and compliance.

TABLE 72 *Summary of the cost per QALY results of the univariate sensitivity analyses: discounted cost per QALY (£,000)*

	Secondary prevention		Primary prevention	
	Min.	Max.	Min.	Max.
Gender	**F**	**M**	**M**	**F**
Age (unless otherwise stated) (years)	65	85	45	85
Annual CHD risk	–	–	3.00%	0.50%
Base case	**£9.5**	**£15.7**	**£9.5**	**£111**
Sensitivity analysis				
a Using 3.5% discount rate for costs and benefits	£15.9[c]	£23.7[d]	£19.4	£152[e]
b Relative risk[a]	£9.4	£15.7	£12.4[f]	£69.1[g]
c Health state costs: +20%	£9.5	£15.5	£9.5	£110.7
d Average cost of statins: –20%	£7.8	£12.7	£7.8	£91.5
Average cost of statins: –40%	£6.1	£9.8	£6.1	£72.4
e Utility: holding baseline utility constant at 1 for all ages	£6.7	£10.5	£7.3	£72.3
f Utility: +10% on health state utilities with baseline utility as basecase (varying by age)	£8.3	£14.2	£14.4	£117.4
Utility: –10% on health state utilities with baseline utility as basecase (varying by age)	£10.9	£17.4	£7.3	£105.5
g Utility: combining baseline utility constant at 1 for all ages and +10% on health state utilities	£5.9	£9.5	£10.9	£77.1[h]
Utility: combining baseline utility constant at 1 for all ages and –10% on health state utilities	£7.8	£11.6	£5.7	£69.0
h Higher (150%) incidence and prevalence by age for health states[b]				
Increase proportion to non-fatal MI health state	£9.2	£15.5	£8.9	£106.5
Increase proportion to non-fatal stroke health state	£10.1	£16.6	£10.3	£114.7
i Upper CI for natural increase by age in CHD risk and corresponding CVD risk	NA	NA	£9.9	£108.9
Lower CI for natural increase by age in CHD risk and corresponding CVD risk	NA	NA	£9.1	£112.4
j 10-year time-frame	£18.6[i]	£124.5[j]	£35.7	£367
k Compliance falls to 55% in secondary and 50% in primary prevention by year 5 with full treatment costs	£13.9	£21.5	£16.1	£133

[a] 1000 Monte Carlo samples generated on relative risks from statin treatment while holding all other parameters constant at mean value.
[b] For each analysis the incidence (prevalence) rate for an individual health state is increased by 150% while holding the rates constant for the other health states.
[c] Women aged 45, secondary.
[d] Men aged 65, secondary.
[e] Women aged 75 at 0.5% annual CHD risk.
[f] Men aged 45 years at 1.5% annual CHD risk.
[g] Women aged 85 years at 1.5% annual CHD risk.
[h] Men aged 85 at 0.5% annual CHD risk.
[i] Women aged 85, secondary.
[j] Men aged 85, secondary.

The impact of a reduction in the cost of statins is shown in more detail in *Tables 73* and *74*. The cost of statins used in the economic modelling is a weighted average of statins with clinical outcome data, based on the quantity of trial evidence available. The cost of statins is likely to vary according to local prescribing patterns and over time. A reduction of 20% and 40% from the base-case level of £317 per annum was assessed. An estimate of the overall cost of statins weighted by current prescribing data was found to be 14% lower than the cost of statins used in the modelling [see the section 'Costs of health states' (p. 93)]. Current average prescribing costs may be higher or lower than this depending on the local prescribing policy. This indicates that, in reality, the cost-effectiveness of statins may lie somewhere between the base-case estimates and the estimates based on a 20% decrease in cost shown above.

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TABLE 73 *Sensitivity analysis: secondary prevention results for a cohort of 1000 patients using a 20% and 40% reduction in the weighted statin cost used in the basecase; discounted cost per QALY (£,000)*

	Age (years)	Incremental cost per QALY		
		Base case	Statin cost –40%	Statin cost –20%
Men	45	£10.2	£6.5	£8.4
	55	£10.0	£6.3	£8.2
	65	£10.5	£6.7	£8.6
	75	£12.7	£8.1	£10.4
	85	£15.7	£9.8	£12.7
Women	45	£10.1	£6.4	£8.2
	55	£9.8	£6.3	£8.0
	65	£9.4	£6.1	£7.8
	75	£11.3	£7.2	£9.3
	85	£14.0	£8.9	£11.4

TABLE 74 *Sensitivity analysis: primary prevention results for a cohort of 1000 patients using a 40% reduction in the weighted statin cost used in the basecase; discounted cost per QALY (£,000)*

	Age (years)	Annual CHD risk					
		3.0%	2.5%	2.0%	1.5%	1.0%	0.5%
Men	45	£6.1	£6.4	£6.9	£7.8	£9.5	£13.4
	55	£8.2	£8.8	£9.6	£11.1	£13.9	£20.1
	65	£10.9	£12.0	£13.6	£16.3	£21.0	£32.0
	75	£17.0	£19.1	£22.1	£26.9	£35.5	£55.1
	85	£23.9	£27.0	£31.3	£37.8	£48.4	£68.8
Women	45	£9.0	£9.2	£9.7	£10.7	£13.1	£19.7
	55	£10.5	£10.9	£11.8	£13.4	£16.8	£25.9
	65	£12.7	£13.8	£15.5	£18.4	£24.0	£38.5
	75	£20.8	£23.0	£26.3	£31.7	£41.5	£64.4
	85	£31.2	£34.5	£38.9	£45.3	£55.2	£72.4

A reduction in the assumed cost of statins by 20% results in ICERs of below £13,000 for all ages in secondary prevention. A reduction in the assumed cost of statins by 40% results in ICERs of below £10,000 for all ages in secondary prevention and ICERs between £20,000 and £25,000 for men and women at the age of 65 at 1% CHD risk, compared with levels of £33,000–37,000 for this population in the base-case analysis.

The discount rate selected for analysis makes a significant impact on the cost-effectiveness results. This is shown in greater detail in *Tables 75* and *76*.

Shortening the time-frame of the model to 10 years of statin treatment increases the estimated cost per QALY across all age groups. The discounted ICERs using the 10-year horizon range from approximately £24,000 to £125,000 per QALY for women and from £20,000 to £100,000 per QALY for men. Using a 10-year horizon as opposed to lifetime has a greater

impact on the results for the younger ages, and these results suggest that it is less cost-effective to treat younger patients than older patients. Younger patients are less likely to benefit from statins in the first 10 years of treatment as the risk of subsequent and fatal events is lower in younger patients. However, if treatment is started at earlier ages and continued over the patient's lifetime the costs avoided and health benefits gained accrue to reduce the cost per QALY. The 10-year results for older patients (£20,000 and £19,000 for men and women aged 85 years) are comparable to those estimated for a lifetime of treatment (£16,000 and £14,000 for men and women aged 85 years). It should be noted, however, that given that statin therapy has costs and benefits that extend over the lifetime of a patient, a lifetime time-horizon for analysing cost-effectiveness is appropriate.

The use of a shorter time-frame reverses the age gradient in primary prevention results (*Tables 64* and *65*). If reality lies somewhere in between, then

TABLE 75 *Sensitivity analysis: secondary prevention results for a cohort of 1000 patients 3.5% discount rates; discounted cost per QALY (£,000)*

	Age (years)	Undiscounted			Discounted		
		Incremental costs	Incremental QALYs	Incremental cost per QALY	Incremental costs	Incremental QALYs	Incremental cost per QALY
Men	45	£10,684	700	£15.3	£6,299	279	£22.6
	55	£7,863	565	£13.9	£5,196	276	£18.8
	65	£5,394	397	£13.6	£3,969	235	£16.9
	75	£3,436	227	£15.1	£2,789	157	£17.8
	85	£1,976	115	£17.2	£1,747	90	£19.4
Women	45	£11,905	776	£15.3	£6,730	284	£23.7
	55	£9,033	644	£14.0	£5,720	293	£19.5
	65	£6,327	499	£12.7	£4,480	281	£15.9
	75	£4,119	297	£13.9	£3,241	198	£16.4
	85	£2,343	148	£15.8	£2,030	114	£17.8

TABLE 76 *Sensitivity analysis: primary prevention results for a cohort of 1000 patients using 3.5% discount rates; discounted cost per QALY (£,000)*

	Age (years)	Annual CHD risk					
		3.0%	2.5%	2.0%	1.5%	1.0%	0.5%
Men	45	£19.4	£20.6	£22.6	£25.9	£32.2	£46.5
	55	£22.9	£24.7	£27.5	£32.1	£40.6	£60.1
	65	£26.7	£29.6	£33.9	£40.8	£53.4	£82.5
	75	£36.8	£41.5	£48.4	£59.2	£78.8	£124.0
	85	£46.0	£52.1	£60.7	£73.6	£94.9	£136.9
Women	45	£29.6	£30.8	£33.1	£37.5	£46.8	£72.4
	55	£30.4	£32.1	£35.1	£40.6	£51.8	£81.8
	65	£32.1	£35.2	£40.0	£48.1	£63.7	£103.9
	75	£46.3	£51.6	£59.6	£72.5	£96.1	£152.2
	85	£61.3	£68.1	£77.4	£90.9	£111.9	£149.0

the age/cost-effectiveness relationship may become cancelled out, which would be a useful simplifying conclusion.

As CHD risk increases with age, and events occur more frequently in older populations, the baseline utility assigned to patients, as well as the disutility associated with health states, could potentially have an impact on the estimated ICERs. In addition, the HRQoL in the general population decreases with age, so it is important to consider these values when assigning disutilities associated with CHD events.

Utility of the general population free of CHD and CVD is assumed to vary with age in the ScHARR model, based on the study by Kind and colleagues.[241] It is acknowledged that when using utility data from this study there is a small element of double-counting in the model as a proportion of the patients in the sample will have a history of CHD. However, using an alternative assumption, that of constant baseline utility of 1 across all ages, would bias the results in favour of statin treatment. The overestimation of benefits would come from two main sources. If a constant utility value of 1 was used, all patients remaining in the event-free health state would potentially accrue a larger health benefit than was appropriate. In addition, few older patients would have a utility of 1 irrespective of CHD history. Consequently, any benefits achieved by events avoided in these patients should reflect their probable baseline utility. The results of the sensitivity analysis show that using a constant baseline utility of 1 reduced the ICER by around 20% in secondary prevention and up to 35% in primary prevention. A baseline utility that varies with age is considered to be a more conservative alternative.

TABLE 77 *CHD analysis: threshold analysis for the basecase CHD evaluation – annual CHD risk level at which it is cost-effective to prescribe statin treatment based on thresholds of £20,000 and £30,000 per QALY*

	Threshold			
	£30,000	£30,000	£20,000	£20,000
Age (years)	M	F	M	F
45	0.18%	0.52%	0.55%	1.02%
50	0.34%	0.63%	0.79%	1.26%
55	0.54%	0.79%	1.14%	1.59%
60	0.78%	1.02%	1.55%	2.05%
65	1.13%	1.36%	2.19%	4.40%
70	1.62%	1.96%	3.10%	
75	2.42%	3.29%		
80	3.27%			

TABLE 78 *CHD analysis: probabilistic sensitivity analysis – discounted cost per QALY results for cohorts of 1000 patients using 5000 simulations for each evaluation (£,000)*

	Age (years)	Secondary prevention	Primary prevention: 1.5% annual CHD risk
Men	45	£10.3	£12.5
	55	£10.1	£17.3
	65	£10.6	£25.2
	75	£12.8	£41.5
	85	£15.7	£57.9
Women	45	£10.1	£17.8
	55	£9.9	£20.7
	65	£9.6	£28.4
	75	£11.4	£48.5
	85	£14.1	£68.9

Threshold analysis
A threshold analysis based on risk levels was carried out for primary prevention results. Using the base-case scenario and thresholds of £30,000 and £20,000, a series of additional evaluations was explored to obtain the annual CHD risk at which statin treatment is cost-effective for male and female patients, using age bands of 5 years (*Table 77*).

Based on a threshold of £30,000, the risk level at which statins would be perceived as cost-effective would be around 1.2% for men and women at aged 65 years, but as low as 0.2–0.5% at the age of 45 years.

Probabilistic sensitivity analysis
Probability distributions for key input parameters were used to determine the impact of the

imprecision of input values on decision uncertainty (*Table 78*). The 1.5% CHD risk level was chosen for primary prevention for illustrative purposes. Results for other risk levels were derived and shown to be similarly close to the base-case results, and so have not been presented.

The results from the probabilistic analysis are close to the results from the base-case analysis for both secondary and primary prevention.

Figures 30–33 illustrate the results of the PSA represented as a cumulative distribution function of cost–utility. These cost-effectiveness acceptability curves (CEACs) show the risk that the use of statins may exceed a certain threshold of acceptable affordability.

Using a threshold of £30,000 per QALY, the results of the probabilistic analyses for the base-case CHD analyses in secondary prevention demonstrate that statin therapy is cost-effective for all patients with a history of CHD. At the age of 85 years 91% and 84% of secondary prevention ICERs are below £20,000 per QALY for women and men, respectively, while almost all other ICERs across all ages are cost-effective using a threshold of £20,000.

Secondary prevention
As can be seen from the results presented in the CEACs, there is very little difference in the results for the age bands 45, 55 and 65 years.

Primary prevention
The 1.5% annual CHD risk level was chosen for illustrative purposes.

For patients aged 45 years at 1.5% annual risk of a CHD event, 60% and 92% of ICERs are cost-effective using thresholds of £20,000 and £30,000, respectively. However, when examining the costs and benefits associated with cohorts aged 65 years, the proportion of results that are cost-effective reduces to 6% and 9% using the £20,000 threshold, and 55% and 80% using the £30,000 threshold for women and men, respectively.

Results: alternative scenarios
Scenario 1: CHD analysis with CVD outcomes
Secondary prevention
When exploring the impact of statin treatment in reducing secondary CHD events and associated subsequent fatal CVD and stroke events in patients with a history of a CHD event, the estimated costs per QALY range from approximately £9000 for women aged 65 years to £14,000 for men aged
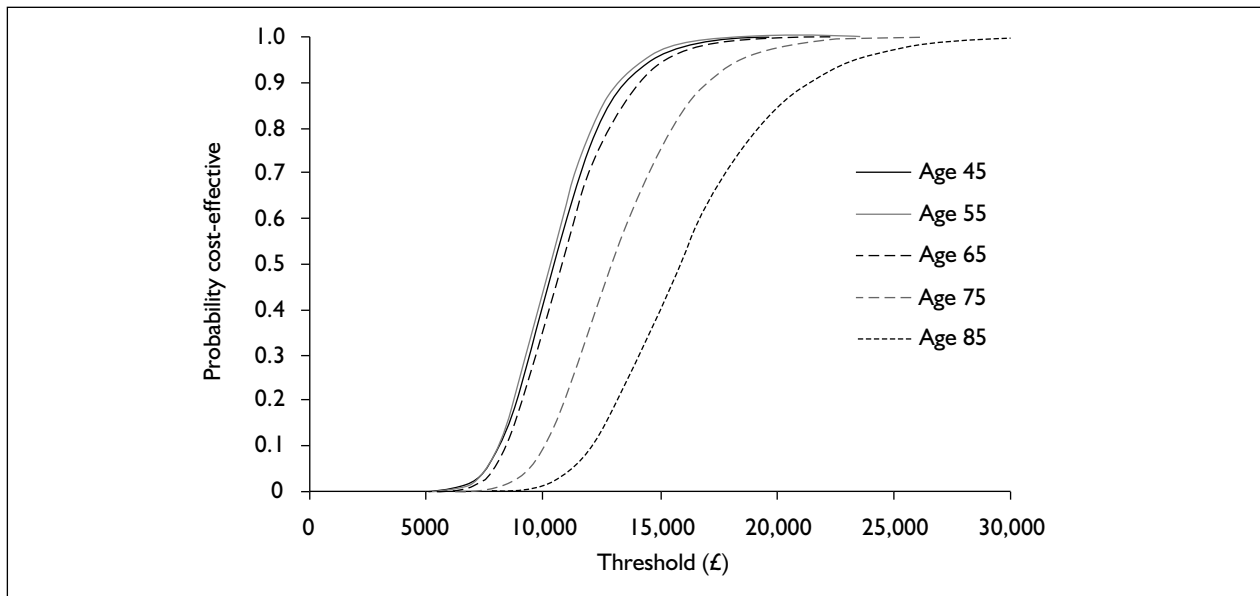
FIGURE 30 *CHD analysis: secondary prevention CEAC – men*
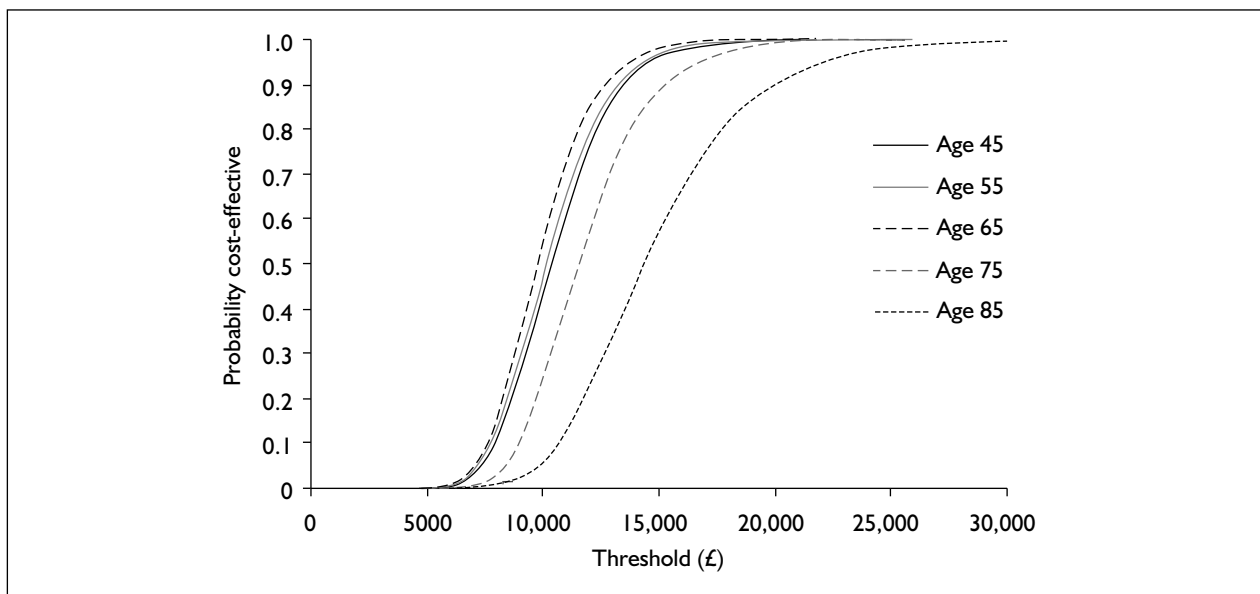
FIGURE 31 *CHD analysis: secondary prevention CEAC – women*

85 years (*Table 79*). These are comparable with the base-case results (CHD only), which ranged from £9000 to £16,000 for similar cohorts.

Primary prevention
The estimated ICERs for the scenarios exploring the cost-effectiveness of statins in primary prevention for patients at risk of a CHD event with stroke as an outcome do not differ from the base-case results, with costs per QALY ranging from approximately £9000 for men aged 45 years at 3% risk of an annual CHD event to £110,000 for women aged 85 years at 0.5% risk of an event

(*Table 80*). This is not an unexpected result as the only difference between the scenarios is the non-fatal strokes experienced by patients with a history of a primary CHD event.

Scenario 2: CVD analysis
Secondary prevention
When exploring the effect of statin treatment in reducing CHD and other cardiovascular outcomes (including TIA and stroke), the impact is to reduce the cost per QALY for a given age and risk level, relative to the base case (*Table 81*). The cost per QALY ranges from approximately £8400 for

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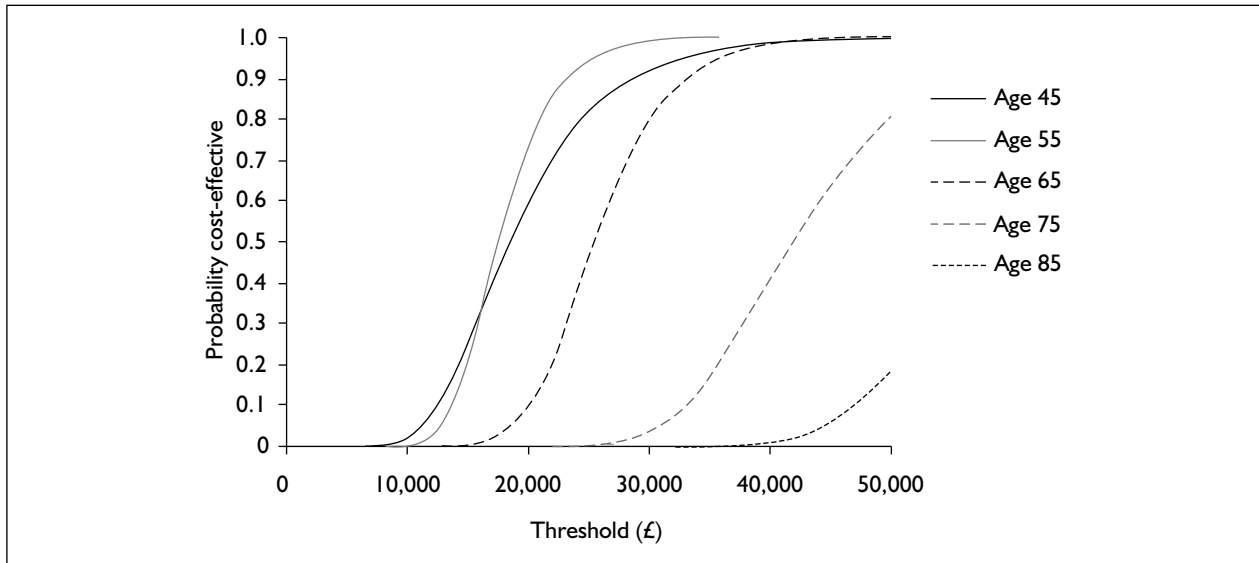
FIGURE 32 *CHD analysis: primary prevention CEAC, 1.5% CHD risk – men*
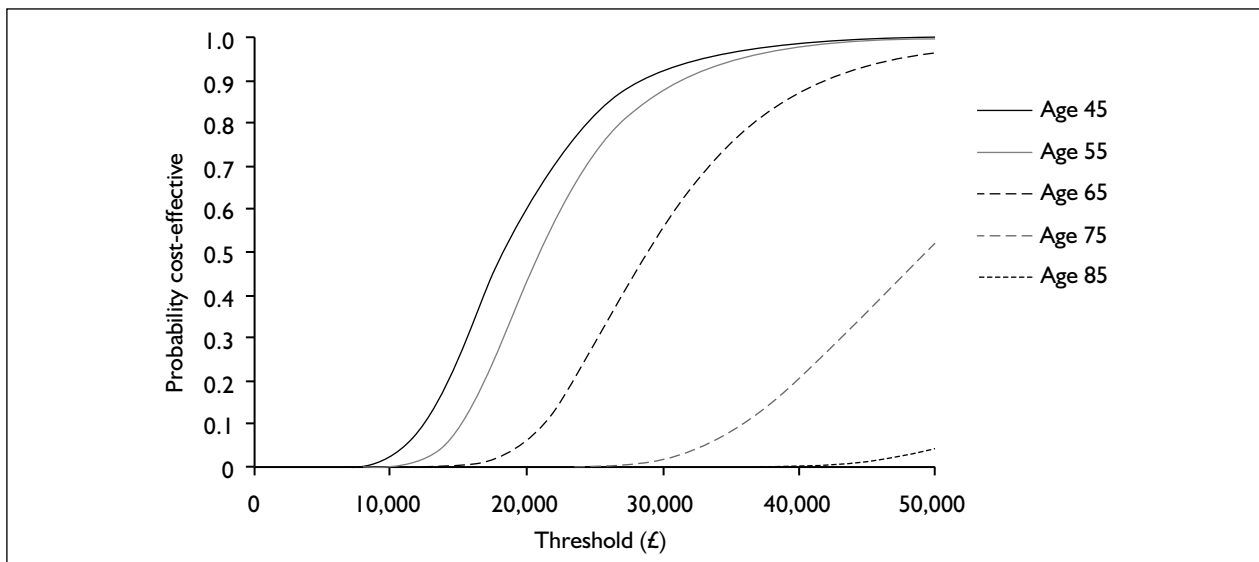
FIGURE 33 *CHD analysis: primary prevention CEAC, 1.5% CHD risk – women*

TABLE 79 *Secondary prevention: cost-effectiveness results for a cohort of 1000 patients for scenario 1 (CHD analysis with CVD outcomes) (£,000)*

	Age (years)	Undiscounted			Discounted		
		Incremental costs	**Incremental QALYs**	**Incremental cost per QALY**	**Incremental costs**	**Incremental QALYs**	**Incremental cost per QALY**
Men	45	£10,695	745	£14.4	£4,737	491	£9.6
	55	£7,869	603	£13.1	£4,113	437	£9.4
	65	£5,393	425	£12.7	£3,311	337	£9.8
	75	£3,424	245	£13.9	£2,451	208	£11.8
	85	£1,963	125	£15.7	£1,606	113	£14.3
Women	45	£11,911	822	£14.5	£4,969	521	£9.5
	55	£9,034	679	£13.3	£4,434	477	£9.3
	65	£6,322	533	£11.9	£3,660	412	£8.9
	75	£4,108	317	£13.0	£2,795	265	£10.6
	85	£2,328	159	£14.6	£1,843	142	£13.0

TABLE 80 *Primary prevention cost-effectiveness results for a cohort of 1000 patients at varying annual risks for scenario 1 (CHD analysis with CVD outcomes); discounted cost per QALY (£,000)*

| | Age (years) | Annual CHD risk | | | | | |
		3.0%	2.5%	2.0%	1.5%	1.0%	0.5%
Men	45	£9.3	£9.8	£10.7	£12.1	£14.7	£20.7
	55	£12.5	£13.4	£14.8	£17.1	£21.3	£30.9
	65	£16.6	£18.3	£20.8	£24.9	£32.2	£49.0
	75	£25.9	£29.0	£33.7	£41.0	£54.2	£84.0
	85	£36.3	£41.0	£47.6	£57.4	£73.5	£104.5
Women	45	£13.5	£13.9	£14.7	£16.4	£20.1	£30.2
	55	£15.7	£16.4	£17.8	£20.4	£25.7	£39.7
	65	£19.0	£20.8	£23.4	£27.9	£36.6	£58.7
	75	£31.1	£34.6	£39.7	£48.0	£63.0	£98.1
	85	£46.9	£51.9	£58.8	£68.6	£83.8	£110.1

TABLE 81 *Secondary prevention: cost-effectiveness results for a cohort of 1000 patients for scenario 2 (CVD analysis) (£,000)*

| | Age (years) | Undiscounted | | | Discounted | | |
		Incremental costs	Incremental QALYs	Incremental cost per QALY	Incremental costs	Incremental QALYs	Incremental cost per QALY
Men	45	£10,452	700	£13.6	£4,651	462	£9.2
	55	£7,722	565	£12.5	£4,041	410	£9.0
	65	£5,238	397	£11.8	£3,218	314	£9.1
	75	£3,332	227	£13.0	£2,382	193	£10.9
	85	£1,911	115	£14.5	£1,563	103	£13.1
Women	45	£11,650	776	£13.8	£4,871	493	£9.1
	55	£8,768	644	£12.4	£4,312	452	£8.6
	65	£6,163	499	£11.2	£3,562	387	£8.4
	75	£3,979	297	£11.9	£2,701	248	£9.6
	85	£2,257	148	£13.2	£1,784	132	£11.7

women aged 65 years to £13,100 for men aged 85 years, in comparison to the base-case results of £9500 and £15,700, respectively.

Primary prevention
For primary prevention analyses, a cohort of patients with a defined CHD risk enters the model The defined CHD risk has a corresponding CVD risk depending on both age and gender. The scenario 2 analyses use the same selected baseline annual CHD risks as the baseline evaluations and the corresponding annual CVD risks used in each evaluations are provided for information in *Table 82*.

The results for the CVD analysis in primary prevention show lower ICERs than for the CHD analysis. In the CHD analysis men aged 45 years at 3% CHD risk have an estimated ICER of £10,200. In the CVD analysis the corresponding ICER is £5200. The most marked difference

between the results is for older age groups. For instance, in the base-case CHD analysis a female cohort aged 85 years at 0.5% annual CHD risk produced an estimated cost per QALY of £110,600, compared with £45,600 in the CVD analysis.

To provide an estimate of primary prevention ICERs by CHD risk level alone, the distribution by age across risk levels from *Table 66* was used to provide a weighted average ICER for each risk level (*Table 83*).

The weighted average ICERs by risk level take into account the age distribution within the risk group. Younger patients are predominantly at lower risk levels. However, these averages should be treated with caution owing to concerns regarding the robustness of the HSE data, particular for older patients.

TABLE 82 *Primary prevention: cost-effectiveness results for a cohort of 1000 patients at varying annual risks for the scenario CVD; discounted cost per QALY (£,000)*

Age (years)				Annual risk				
CHD risk		3.0%	2.5%	2.0%	1.5%	1.0%	0.5%
CVD risk <54 years		3.8%	3.2%	2.6%	2.0%	1.3%	0.7%
CVD risk >54 years		4.3%	3.7%	3.0%	2.4%	1.8%	1.1%
Men	45	£5.2	£5.5	£6.0	£6.8	£8.2	£11.0
	55	£5.9	£6.4	£7.1	£8.1	£9.9	£13.4
	65	£7.5	£8.3	£9.4	£11.2	£14.1	£19.9
	75	£10.9	£12.3	£14.3	£17.4	£22.4	£32.4
	85	£17.1	£19.5	£22.7	£27.6	£35.3	£49.8
CHD risk		3.0%	2.5%	2.0%	1.5%	1.0%	0.5%
CVD risk <54 years		4.0%	3.4%	2.7%	2.1%	1.5%	0.8%
CVD risk >54 years		4.7%	4.0%	3.3%	2.5%	1.8%	1.1%
Women	45	£5.4	£5.6	£6.0	£6.8	£8.3	£11.9
	55	£5.5	£5.8	£6.4	£7.4	£9.4	£13.7
	65	£6.4	£7.0	£8.0	£9.6	£12.6	£19.2
	75	£9.1	£10.2	£12.0	£14.7	£19.5	£30.0
	85	£14.5	£16.5	£19.5	£23.8	£31.1	£45.6

TABLE 83 *CVD analysis: estimated cost per QALY for primary prevention at various CHD risk levels – weighted average by risk levels (£,000)*

	Annual risk					
CHD risk	3.0%	2.5%	2.0%	1.5%	1.0%	0.5%
CVD risk <54 years	3.8%	3.2%	2.6%	2.0%	1.3%	0.7%
CVD risk >54 years	4.3%	3.7%	3.0%	2.4%	1.8%	1.1%
Men	£8.9	£8.5	£9.5	£10.1	£10.8	£12.8
CHD risk	3.0%	2.5%	2.0%	1.5%	1.0%	0.5%
CVD risk <54 years	4.0%	3.4%	2.7%	2.1%	1.5%	0.8%
CVD risk >54 years	4.7%	4.0%	3.3%	2.5%	1.8%	1.1%
Women	£6.8	£7.2	£8.6	£9.5	£13.7	£18.8

When results for the primary and secondary analyses of CVD are compared using *Figures 34 and 35*, it can be seen that in almost every analysis presented, for younger age groups it is slightly more cost-effective to provide statin treatment for primary prevention than for secondary prevention. In the secondary prevention analyses all patients commence in a health state and thus incur health state costs and have a lower utility than the patients in the event-free health state. In primary prevention, patients start in a 'well' state with the highest possible utility. Avoiding primary events prevents a large reduction in utility for the patient and also the costs associated with events, which include both the first year cost of the event itself and follow-on costs in subsequent years. When exploring the benefits associated with CVD, as the relative risk of statin treatment is applied to primary stroke and TIA events in addition to the

CHD events, a larger proportion of patients will accrue benefits from remaining in the event-free health state, enhancing the benefits from secondary strokes avoided following a CHD event. Although it becomes less cost-effective to treat patients with no history of CVD when commencing treatment at older ages, the results suggest that the costs and benefits associated with treating these patients are not prohibitive.

Probabilistic sensitivity analysis for CVD analysis
The results from the probabilistic analysis in *Table 84* are very close to the deterministic CVD analysis for both secondary and primary prevention, suggesting that the results are robust to changes in the key modelling assumptions.

The results of both the primary and secondary evaluations indicate that taking into account stroke
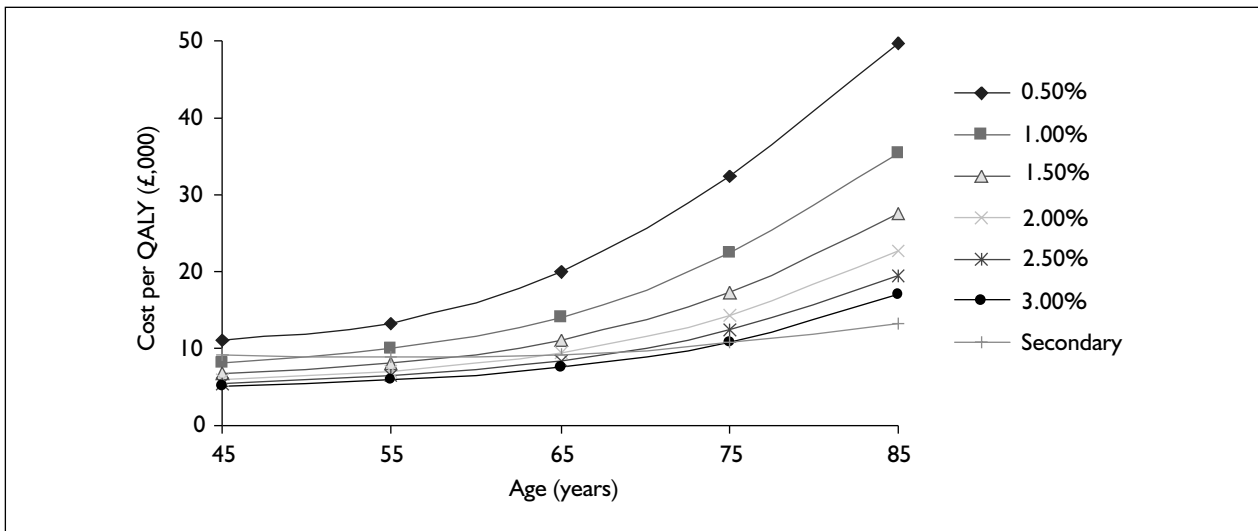
FIGURE 34 *Scenario 2 (CVD analysis): estimated cost per QALY for men at various annual CHD risk levels compared with secondary prevention. The annual CVD risk corresponding to the annual CHD risk in the legend differs by gender and age group and is provided in* Table 82.
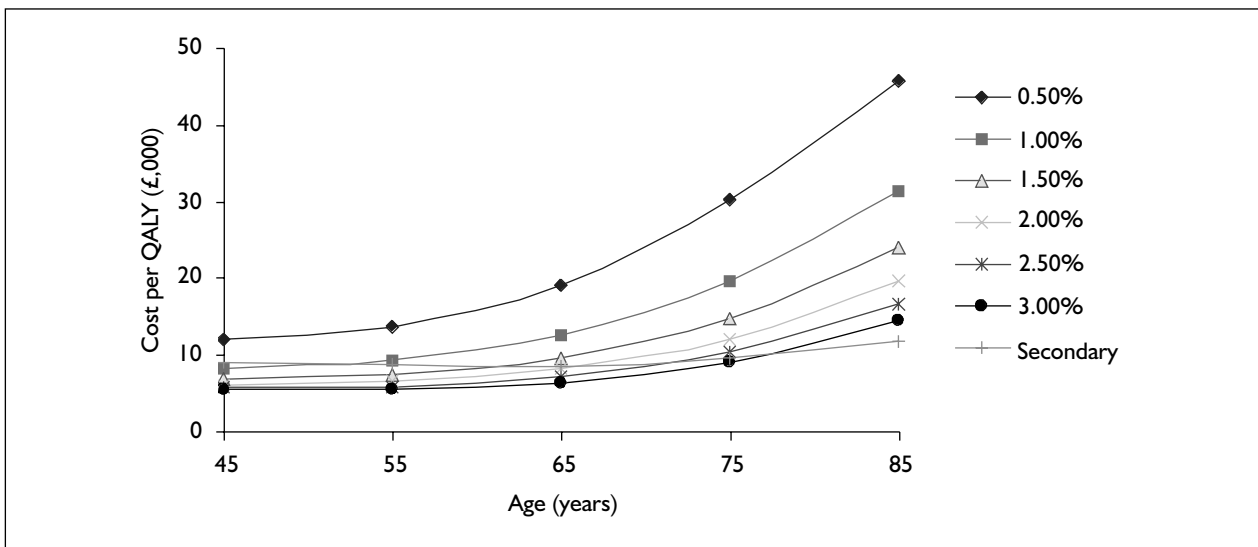
FIGURE 35 *Scenario 2 (CVD analysis): estimated cost per QALY for women at various CHD annual risk levels compared with secondary prevention. The annual CVD risk corresponding to the annual CHD risk in the legend differs by gender and age group and is provided in* Table 82.

and TIA outcomes when exploring the cost-effectiveness of statin treatment has a significant impact on the cost-effectiveness results, particularly at older age levels where the benefits of avoided stroke and TIA events are greater.

Validation

The predictive accuracy of the ScHARR model was validated against three secondary prevention RCTs: 4S, LIPID and CARE, and against the WOSCOPS primary prevention trial. These RCTs were chosen as they represent some of the largest

RCTs conducted. The outcome validated was non-fatal MI or CHD death, a common primary end-point for which information was available in all three trials. *Figure 36* shows the proportion by which the ScHARR model either overestimated or underestimated these trials. The ScHARR model underestimated the outcome measure compared with the 4S and CARE trials and overestimated compared with the LIPID and WOSCOPS trials. The model prediction of non-fatal or CHD death was –20%, +2%, –12% and +15% compared with 4S, LIPID, CARE and WOSCOPS, respectively.

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TABLE 84 *Scenario 2 (CVD prevention): probabilistic discounted cost per QALY results for cohorts of 1000 patients using 5000 simulations for each evaluation (£,000)*

Age (years)		Secondary prevention	Primary prevention
CHD annual risk			1.5%
CVD annual risk <54 years			2.0%
CVD annual risk >54 years			2.4%
Men	45	£9.1	£6.7
	55	£9.0	£8.1
	65	£9.2	£11.2
	75	£10.9	£17.4
	85	£13.0	£27.5
CHD annual risk		1.5%	
CVD annual risk <54 years			1.5%
CVD annual risk >54 years		Secondary	1.8%
Women	45	£9.1	£6.7
	55	£8.7	£7.5
	65	£8.5	£9.7
	75	£9.7	£14.7
	85	£11.6	£23.8

Discussion of results

The cost-effectiveness of statins depends on the CHD risk in the population treated and the age and gender of the population under consideration.

CHD analysis

The base-case analysis considers the cost-effectiveness of statins for a population with CHD or at risk of CHD, taking into account CHD outcomes only.

In secondary prevention the cost per QALY is estimated to vary between approximately £10,000 and £15,700 between the ages of 45 and 85 years. The ICERs are very similar between the ages of 45 and 65 years, but increase with age beyond this point. There is little difference between ICERs for men and women. The estimated ICERs for diabetic patients with a history of CHD range from £5800 to £8800 per QALY, approximately 50% lower than the estimated ICERs in the base case.

Univariate sensitivity analysis shows that results are most sensitive to assumptions on the cost of statins, discount rates and the time-frame of the model. The model is robust to changes in other parameters, including relative risks, cost of health states, health state utilities, and assumptions on incidence, prevalence and compliance. Shortening the time-frame of the model to 10 years increases the costs per QALY from base-case levels, particularly in the lower age groups (from £10,000 to £99,000 for men and from £10,000 to £124,000 for women). However, given that statin therapy has costs and benefits that extend over the lifetime of a patient, a lifetime horizon for analysing cost-effectiveness is appropriate. If there was, however, a reduction in benefit at time intervals over 10 years then this would tend to cancel out the
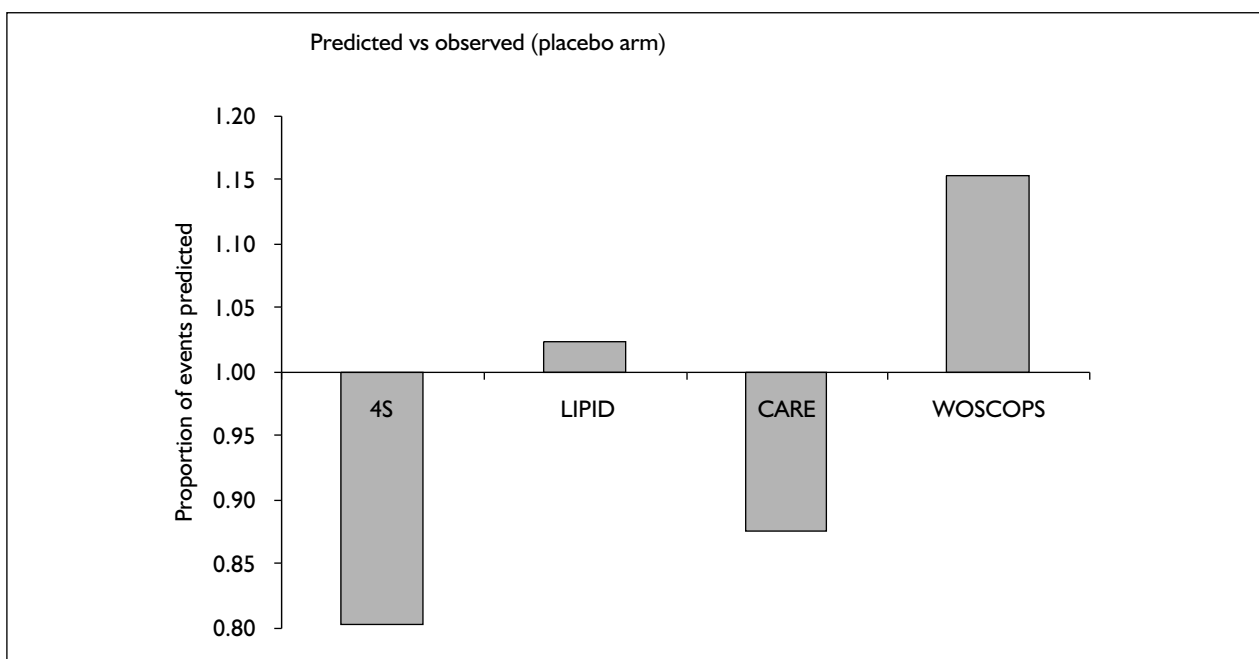
FIGURE 36 *Predictive ability of the ScHARR model validated against major trials*

variation in ICER with age seen in the base-case analysis. The PSA produces results similar to base-case deterministic analysis. Using a threshold of £30,000 per QALY the results of the PSA show that statin therapy is cost-effective for all patients with a history of CHD.

In primary prevention the estimated lifetime ICERs vary according to risk level and age. The estimated average ICER by risk level rises from around £20,000 to £27,000 for men between 3% and 0.5% CHD risk and from £21,300 to £56,800 for women. There is, however, significant variation within risk levels by age. At an annual CHD risk of 3%, the estimated cost per QALY ranges from around £9500 to £36,800 for men and from £13,700 to £47,400 for women between the ages of 45 and 85. At the age of 85 years the estimated cost per QALY rises from £36,800 and £47,400 for men and women, respectively, at 3% CHD risk, to around £105,200 and £110,600 for men and women at 0.5% CHD risk. The rise in ICERs with age is much greater for primary prevention than for secondary prevention. This is the result of the benefits that patients in the event-free health state receive. Preventing an event at an early age offers the benefit of more healthy life-years over the patient's remaining lifetime and also the benefit of fewer subsequent events; this leads to benefits for the younger patient and also avoids the costs associated with these events.

The ICERs for primary prevention are sensitive to the modelling time-frame. Shortening the time-frame of the model to 10 years increases the costs per QALY from base-case levels, particularly at the lower risk levels (from £21,000 to £170,000 for men and £30,000 to £296,000 for women aged 45 years at 0.5% CHD risk, and from £105,000 to £237,000 for men and £110,000 to £367,000 for women aged 85 years at 0.5% CHD risk). In addition, the results are again sensitive to the discount rates used, with ICERs increasing to £19,000 for men and £30,000 for women aged 45 years at 3% CHD risk when using 3.5% discounting for both costs and benefits. At 1.5% CHD risk from the age of 45 to 85 years the ICER risk increases from £26,000 to £74,000 for men and £38,000 to £91,000 for women. A fall in the price of statins of 40% reduces the ICERs for males and females at the age of 65 from around £60,000–£70,000 to around £35,000 at 0.5%. The PSA produces results similar to the base-case results of the deterministic analysis.

Modelling clinical outcome on cholesterol lowering inherently favours drugs that are more potent at lowering cholesterol. In the absence of strong and conclusive evidence on the exact relationship between cholesterol lowering and clinical end-points, cost-effectiveness results for rosuvastatin are subject to significant uncertainty. Evidence on clinical end-points is therefore required.

Scenario 1 (CHD analysis with CVD outcomes)

This analysis explores the impact of statin treatment on reducing secondary CHD events and associated subsequent fatal CVD and stroke events in patients with a history of CHD. The estimated cost per QALY in secondary prevention ranges from £9000 to £14,000 across all ages. These are similar to the base-case results (CHD analysis) which ranged from £9000 to £16,000 for similar cohorts. In primary prevention the cost per QALY values are once again very close to the base-case values.

Scenario 2 (CVD analysis)

When exploring the effect of statin treatment in reducing all cardiovascular outcomes, the additional benefits of statins on reductions in stroke and TIA events reduce the cost per QALY further from base-case levels. The estimated cost per QALY in secondary prevention ranges from £8000 to £13,000 across all ages. In primary prevention the reduction in cost per QALY is more marked. At 3% CHD risk the ICERs remain below £17,000 for all ages (relative to a maximum of £47,000 in the base case). At 1.5% CHD risk the maximum ICER across all ages is around £28,000 and at 0.5% CHD risk the ICERs reach a maximum of £50,000. This provides support for the more aggressive treatment recommendation issued by new guidelines in the UK.[47]

Key issues

Cost-effectiveness by age

The analyses for primary and secondary prevention by age show that the ICER is lower at younger ages. This is not unexpected, since at younger ages there is a greater period over which to accrue the benefits of statins. In older age groups death rates from other causes are higher, reducing the potential of avoiding CHD events when on treatment. Considering the ICER at different risk levels without taking age into account would result in undertreatment of younger patients and overtreatment of the elderly, an issue highlighted by Johannesson.[194]

However, it should be noted that there is larger uncertainty in the ICERs at younger ages. This is partly because the modelling is undertaken over

the lifetime of the patients. Therefore, for younger patients the length of extrapolation required is significant as the modelling time-frame goes well beyond the duration of major outcome trials to date. In addition, there is greater uncertainty in the baseline data at younger ages; for instance, transition probabilities taken from data sets such at the NHAR and SLSR have much smaller numbers of patients at younger ages and therefore there is greater uncertainty in the estimated transition rates.

Quality of evidence used in the economic model
Event rate data
Data to populate the model in terms of incidence and prevalence of CHD and CVD and the transitions between heath states are taken from a variety of sources. This is not ideal, but where possible these parameters have been tested in sensitivity analysis.

In some cases data were not available in the required form for input to the model and assumptions have had to be made. For instance, data on transitions from stable angina and TIA to other heath states were not available by age and assumptions had to be made regarding the impact of age on these parameters.

Effectiveness data
Based on the meta-analysis results from sections 'Placebo-controlled studies: summary of results' and 'Results from Bayesian meta-analysis' (pp. 36 and 38), relative risks for different outcomes were applied in the model. As the confidence intervals overlap for each outcome in primary and secondary prevention studies, it was not possible to differentiate between the effectiveness of statins in primary and secondary prevention and therefore the evidence was combined to produce a relative risk for each outcome.

Cost data
Costs of health states are taken from a range of sources and in some cases are based on clinical opinion. However, sensitivity analysis demonstrated that the results were not unduly influenced by changes to the assumptions made.

The cost of statins (£317 per annum), a key input parameter in the analysis, is expected to be subject to change over the short to medium term. For instance, Pfizer announced a change in the price of atorvastatin in January 2005, which was too late for inclusion in the analysis. The base-case analysis will only be valid for a short period.

Utility data
None of the major RCTs collected utility data and therefore a literature search was undertaken and data were taken from a range of sources. There are therefore major issues regarding the comparability of the populations on which the data were based. However, sensitivity analysis demonstrated that the results were not unduly influenced by changes to the assumptions made.

Compliance and continuance
The base-case results are based on the assumption that the relative risks derived from the ITT analyses can be generalised to patients taking statin treatment in general clinical practice. Evidence to date suggests that after the first few years compliance and continuance stabilise and remain fairly constant in the long term. It is acknowledged that this assumption is based on relatively poor-quality evidence and is subject to significant uncertainty. The impact of this assumption was therefore tested in sensitivity analysis.

For scenarios where it is assumed that lower rates of compliance are accompanied by lower costs of treatments, with patients failing to pick up their prescriptions, the impact on cost-effectiveness is limited. In an extreme scenario where compliance is assumed to fall to 55% in secondary prevention and 50% in primary preventions, but retaining full statin treatment costs, the impact on ICERs ranges between 20 and 40%. In secondary prevention the maximum ICER increases from £16,000 to £22,000, and in primary prevention the maximum ICER increases from £111,000 to £133,000. Although the issues surrounding compliance, particularly in primary prevention, are subject to huge uncertainty, the impact on cost-effectiveness is relatively limited, particularly in cases where patients are not picking up their prescriptions and therefore not accruing treatment costs.

Comparing results of the CHD and CVD analyses
The CVD analyses produce substantially lower ICERs than the CHD analyses, particularly in older age groups. This is unsurprising given that they are taking into account the impact of statins on reducing the risk of stroke and TIA, as well as CHD events. The ScHARR model excludes PAD events owing to the paucity of trial evidence, the lack of PAD data in the HSE used as UK population data in some of the modelling, and the lack of PAD data in current cardiovascular risk assessment tools. This means that the model underestimates potential avoided CVD events and

the cost-effectiveness results will therefore be conservative.

In the CVD analysis the results of the primary prevention analyses are sometimes lower than the ICERs estimated for secondary prevention. This may seem counter-intuitive as secondary care patients are at higher risk of CVD events and therefore statins offer the opportunity to avoid more events. However, other factors are involved. In primary prevention patients start in a 'well' state with highest possible utility. Avoiding primary events prevents a large reduction in utility for the patient and also the costs associated with events. Costs include both the first-year cost of the event itself and the follow-on costs in subsequent years. In the secondary prevention analysis patients start in a CHD health state (stable angina, unstable angina or MI) and therefore they are already a cost to the NHS and have lower utility than the 'well' population in primary prevention. This impact offsets the cost-saving argument above. The difference is more noticeable in the analyses exploring the benefits associated with CVD as the relative risk of statin treatment is applied to primary stroke and TIA events in addition to the CHD events. Thus, these analyses accrue a large amount of benefits from the patients remaining in the event-free health state enhancing the benefits from secondary strokes avoided following a CHD event. In addition, there are more patients dying at younger ages from secondary disease than primary; hence, when treatment is commenced at young ages, the potential to avoid events over a lifetime is increased.

Limitations of the cost–utility estimates

One of the major limitations of the analyses is the requirement to extrapolate well beyond the time-frame of the trial period. The majority of trials are under 5 years in duration, but given that statin therapy has costs and benefits that extend over the lifetime of a patient, a lifetime time-horizon is appropriate for examining cost-effectiveness. This period of extrapolation will be longer for younger patients and therefore the results for the lower age bands are subject to greater uncertainty.

The analyses for primary prevention extrapolate effectiveness results from relatively high risk primary prevention populations to the treatment of populations at much lower risk. The results, therefore, have to be treated with caution. Evidence does not currently exist to demonstrate whether the same level of relative risk reductions will be achieved in very low-risk populations.

A further limitation is the question of generalisability of the results of RCT evidence to routine clinical practice. The selection of patients for trials may result in a sample of patients who are not typical of the population likely to receive statins in general practice. Effectiveness of statins in routine clinical practice could be lower than suggested by the trials owing to a number of issues, particularly compliance and continuance. However, sensitivity analysis on compliance and continuance assumptions shows that the impact on cost-effectiveness results is not likely to be significant. If patients discontinue treatment then the treatment costs will fall along with the effectiveness. Only in the case of patients who are long-term poor compliers, failing to take the medication according to the prescription but continuing to pick up prescriptions, will treatment costs be accrued without the corresponding benefit.

The analyses are sensitive to the cost of statins. The future cost of statins is a key unknown. The recent availability of simvastatin and pravastatin as generics may put further downward pressure on statins. The cost-effectiveness results will need to be reviewed in the light of any significant changes in the price of statins.

This analysis does not take into account the costs of identifying and screening the relevant population. In primary prevention, as the risk threshold decreases the size of the population eligible for treatment increases. These costs will vary according to the strategy used by individual GPs and it will become increasingly important to consider the cost-effectiveness of alternative strategies for implementing CHD prevention strategies. The number of patients who will require regular monitoring will expand as the risk threshold for treatment drops, placing additional demands on staff and resources at GP surgeries.

Comparison of sponsor models and ScHARR model

A comparison of the results from the sponsor models and the ScHARR model is difficult owing to the different aims of the models and the methodologies used. Parameters that are most likely to lead to differences in results are the time-horizons and modelling methodology used, and variations in the assumptions regarding the effectiveness of the drugs. Other parameters that may impact on results include the scope of the model (CHD or CVD event), the transition probabilities between health states, health state costs, drug costs and quality of life measures.

Summary of key observations

A summary of the methods used is given in *Table 85*. Of the two sponsor submissions that used clinical end-point modelling (Novartis and Bristol-Myers Squibb), the Bristol-Myers Squibb model investigates the same disease area as the ScHARR model, whereas the Novartis model evaluates the prevention of cardiac events following PCI. The Bristol-Myers Squibb model is similar to the ScHARR model in the following elements: it has a Markov structure and similar

outcomes, primary treatment cost-effectiveness is investigated at various CHD risk levels and both estimate secondary treatment cost-effectiveness. However, the Bristol-Myers Squibb model uses a shorter time-horizon and reports in terms of life-years gained as opposed to QALYs.

The Pfizer and AstraZeneca submissions use the surrogate end-point of this method. AstraZeneca uses a combined short-term and long-term model. The short-term (1-year) model estimates cost-

TABLE 85 *Comparison of sponsors' models and ScHARR model*

Study	Pfizer	Novartis	Bristol-Myers Squibb	AstraZeneca	ScHARR
Intervention and comparator	Atorvastatin placebo (or generic simvastatin)	Fluvastatin	Pravastatin	Rosuvastatin atorvastatin, fluvastatin, pravastatin, simvastatin vs no treatment	All statins licensed in UK vs placebo
Definition of effectiveness	Percentage reduction in cholesterol	Relative risk reduction on clinical events from trial	Relative risk reduction on clinical events from trial	Percentage reduction in cholesterol	Relative risk reduction on clinical events
Study type (effectiveness)	Meta-analysis of RCTs	RCT	RCT	Randomised trial	Meta-analysis of RCTs
Population	Starting age 35 years, secondary, primary, CHD + stroke	Secondary patients post-revascularisation; subgroup with diabetes	Primary, secondary, CHD + stroke, CVD	Patients with high cholesterol, starting age 55 years	Secondary, primary at various risk levels and ages, CHD, CHD and CVD outcomes, CVD
Perspective	NHS	NHS	NHS	NHS	NHS
Discounting	Costs = 6%, benefits = 1.5%	Costs = 3.5%, benefits = 3.5%	Costs = 3.5%, benefits = 3.5%	Costs = 3.5%, benefits = 3.5%	Costs = 6%, benefits = 1.5%
Model type	Markov	Markov	Markov	(1) Short term: decision tree; (2) Long term: Markov model	Markov
Time-horizon	Lifetime	10 years	Primary 5 years, secondary 5 years	(1) 12 months, (2) 21 years	Lifetime
Cycle length	1 year	1 month	1 month	(1) 3 months, (2) 4 years	1 year
Country	UK	UK	UK	UK	UK
Main outcome measure	Cost per QALY	Cost per QALY	Cost per LYS	(1) % achieving target cholesterol levels, (2) cost per QALY	Cost per QALY
Probabilistic analysis?	Yes	Yes	Yes	Yes	Yes
Type of sensitivity analysis	Diabetic population, discount rates			High risk level (smoker and drinker), discounting rates	Univariate; costs, utilities, discount rates, compliance, relative risks

effectiveness based on the achievement of NSF total cholesterol and LDL lipid targets using efficacy data from the 6-week STELLAR study. The baseline and estimated reduction in cholesterol levels are then used in the Framingham equations to predict a primary and a subsequent secondary CHD/CVD event for the no treatment and the statin arms in the long-term model. The Pfizer model also uses Framingham risk equations to predict the annual likelihood of a CHD event. Results from the Pfizer model are reported for CHD and stroke outcomes collectively and not for CHD only. The ScHARR model uses RCT evidence on reductions in clinical end-points to model the effectiveness of statins. Because rosuvastatin has no clinical end-point, the ScHARR model was adapted to model the cost-effectiveness of statins in the treatment of CHD by the surrogate end-point of cholesterol lowering. The proportion of patients in the ScHARR model who develop angina or MI, or die from CHD, is based on UK epidemiological data, whereas the

events in the AstraZeneca and Pfizer models are predicted by the Framingham equations.

The Merck Sharpe & Dohme submission presented results from a within-trial analysis of 4S (secondary prevention) and HPS (primary prevention). The cost-effectiveness of simvastatin based on HPS is presented as the cost per vascular event avoided and is therefore not comparable with the ScHARR model. A comparison between an economic analysis based on the 4S trial and the ScHARR model is restricted by many factors, including the time-frame, the population investigated and the effectiveness evidence base.

Comparison of results
The ScHARR and sponsors' results are summarised in *Tables 86* and *87*.

In secondary prevention, the results from Pfizer, Novartis and Merck Sharpe & Dohme are all of a similar magnitude, approximately £1000–6000.

TABLE 86 *Summary of base-case results from the sponsors' models (£,000)*

	Pfizer (atorvastatin)	Novartis (fluvastatin)	Bristol-Myers Squibb (pravastatin)	AstraZeneca (rosuvastatin)	Merck Sharp & Dohme (simvastatin)
Disease area	CHD and stroke	Prevention of cardiac events following PCI	CHD/CVD	CHD/CVD	CHD/CVD
Results: secondary[a]	£3.2–5.0 (men), £4.5–5.9 (women)[a]	£3.2 (all patients)	Pravastatin dominated	£13–19 (men), £24–31 (women)	Cost per LYG £1.2–2.7
Results: primary[a]	£1.9–7.3 (men), £1.2–5 (women)[a]	NA	Cost per LYG £0.06–8[a] (30–15% 10-year risk, men/women)	£2–3 (men), £3–5 (women)	Cost per major vascular event avoided £8.5–16

[a] For the purposes of comparison with the ScHARR model, results presented here are for 10-year CHD risk levels between 30 and 15% only.

TABLE 87 *Summary of base-case results from the ScHARR model (£,000)*

Secondary CHD		Primary CHD		
Men	**Women**	**Risk level**	**Men**	**Women**
£10–16	£10–14	0.5% annual CHD risk	£21–105	£31–111
		3% annual CHD risk	£10–37	£14–47
Secondary CVD		**Primary CVD**		
Men	**Women**	**Risk level**	**Men**	**Women**
£9–13	£8–12	0.5% annual CHD risk	£11–50	£12–46
		0.5% annual CHD risk	£5–17	£5–14

These estimates are all lower than the results from the ScHARR evaluation, which range between £10,000 and £16,000 for the CHD analysis and £8400 and £13,100 for the CVD analysis. In secondary prevention for men, the AstraZeneca evaluation produced very similar results (£13,000–19,000) to the ScHARR CHD analysis (£10,000–16,000). The results for women (£24,000–31,000), however, are twice the magnitude of the ScHARR CHD analysis results (£10,000–14,000). This discrepancy is probably due to the different methodologies used in predicting events, as the ScHARR model uses secondary event rates that are equal for both genders, whereas the Framingham equations used by AstraZeneca have different algorithms for each gender.

In primary prevention, the results from Pfizer (£1000–7000), Bristol-Myers Squibb (£0–8000) and AstraZeneca (£2000–5000) are well below the ScHARR estimates of £10,000–111,000 for CHD analysis and £5200–49,800 for CVD analysis. However, the higher estimates presented in the ScHARR evaluation are for the age groups 75–85 years, and when these are weighted by the distributions in the UK the CVD results range from £9000 and £7000 to £13,000 and £19,000 for men and women, respectively.

Conclusions of ScHARR analysis

The base-case analysis considers the cost-effectiveness of statins for a population with CHD or at risk of CHD, taking into account CHD outcomes only. In secondary prevention the cost per QALY is estimated to vary between £10,000 and £15,700 between the ages of 45 and 85 years. The ICERs are very similar between the ages of 45 and 65, but increase with age beyond this point. There is little difference between ICERs for men and women. The estimated ICERs for diabetic patients with a history of CHD are approximately 50% lower than the estimated ICERs in the base case. Sensitivity analysis shows that results are robust to changes in key modelling parameters. Results are most sensitive to the discount rates used and the time-frame of the analysis. Using a threshold of £20,000 per QALY, the results of the PSA show that statin therapy is likely to be considered cost-effective for all patients with a history of CHD.

In the base-case primary prevention analyses, the ICERs vary according to risk level and age. The estimated average ICER by risk level increases from £20,000 to £28,000 for men between 3% and 0.5% CHD risk, and from £21,000 to £57,000 for

women. There is, however, significant variation within risk levels with age. At an annual CHD risk of 3%, the estimated cost per QALY ranges from £9500 to £36,800 for men and from £13,700 to £47,400 for women between the ages of 45 and 85 years. At 85 years of age the estimated cost per QALY rises from £36,800 and £47,400 for men and women, respectively, at 3% CHD risk, to around £105,200 and £110,600 for men and women at 0.5% CHD risk. The ICERs for primary prevention are sensitive to the discount rates and the modelling time-frame. The PSA produces results similar to the base-case results of the deterministic analysis.

The results of the CVD analysis in both primary and secondary prevention indicate that taking stroke and TIA outcomes into account when exploring the cost-effectiveness of statin treatment results in a significant reduction in the cost-effectiveness ratios, particularly at older age levels where the benefits of avoided stroke and TIA events are greater.

Although levels of compliance and continuance are subject to huge uncertainty, particularly in low-risk primary prevention where patients are asymptomatic, the impact on cost-effectiveness is relatively limited.

The price of statins is a key factor in the cost-effectiveness ratio and the future price of statin is uncertain. A fall in the price of statins of 40% reduces the ICERs for primary and secondary prevention by around 35%. The recent availability of simvastatin and pravastatin as generics may put downward pressure on statin prices in general, which will impact on the cost-effectiveness results.

NHS impact

The impact on the NHS budget will depend on several factors:

- the incidence rate of CHD
- the CHD risk level at which statins are recommended
- the number of asymptomatic patients identified as at risk by practitioners
- the uptake rate of statins by asymptomatic patients
- continuance and compliance
- the future price of statins
- cost savings due to a reduction in CHD events.

Incidence rate of CHD

The incidence of CHD is available from community surveys. The BCHDR[7] identifies all

symptomatic medical presentations of CHD in one specific population from 1996 to 1998. The incidence per annum of CHD in this community was 537 per 100,000 population. This translates to approximately 170,000 new cases per annum in England and Wales. The majority of these people will be eligible for statin treatment. However, a proportion of them may already have been on statins for primary prevention. These people should be deducted from this estimate, but the numbers are unknown at this time.

Number of primary prevention patients in England and Wales eligible for treatment
The number of people in England and Wales who are eligible for treatment with statins for primary prevention will have a major impact on the NHS budget. The number of eligible patients at different risk thresholds is estimated. This represents the total number eligible and not the number who will ultimately receive treatment. The number actually receiving treatment will depend on a number of factors, including the policies used at practice level to identify patients at risk and the willingness of asymptomatic patients to take statins.

Method for estimating the number of patients in England and Wales who are eligible for statins therapy in primary prevention
The 1998 HSE[197] contains records of nearly 10,000 people with sufficient information to calculate a CHD/CVD risk level and to categorise by primary or secondary treatment. The CHD risk data from the survey were aggregated according to the same age and risk groups that are used in the economic model, that is, annual risks of between 0.5% and 3% (in 0.5% intervals), and subdivided by age groups. The proportions in each age group and risk level were calculated. Costs per QALY were then estimated from the economic model for each age group and risk level. If the cost per QALY for a particular age and risk group was below the threshold, the proportion at risk from the survey data was multiplied by the actual number of people in each age group in England and Wales[263] to determine an estimate of the number of eligible people in England and Wales. Eligibility for treatment was based on willingness-to-pay thresholds of both £20,000 and £30,000.

Results
Table 88 shows the number of people eligible for treatment at willingness-to-pay thresholds of £20,000 and £30,000. The number of people eligible is cumulative from the bottom up. Reading the numbers from a given risk level

therefore includes people at all higher risks. For example, at a threshold of £20,000 with a guideline of treating patients in primary prevention of down to 1.5% annual risk, the number of people eligible is estimated at around 3.5 million.

Estimated cost impact of treating eligible patients
Current statin prescribing is estimated at around £675 million per annum [see the section 'Current service provision' (p. 8)]. The predicted annual prescribing costs for the number of eligible people from the above estimation (using a £20,000 threshold) is shown in *Table 89*. The cost of a statin prescription is based on the average overall cost of statins used in the economic model, an average cost of £316.80 per annum [see the section 'Costs' (p. 93)]. No published audit data were found on the split in statins prescribing between primary and secondary prevention. A 1998 survey of 21 practices in Sheffield found that 24% of statin prescriptions were for primary prevention.[264] Expert opinion estimates that primary prevention prescribing of statins is in the region of 35–65% of total prescribing (Minhas R, Medway PCT & Swale PCT: personal communication, March 2005). In the absence of a recent data source, primary prevention prescribing is assumed to be 25% of total prescribing (around £169 million). The third column in *Table 89* shows the primary care prescribing cost for the predicted number of eligible people. The fourth column shows the additional cost of treating all eligible people; this takes into account the fact that some of these people are already prescribed statins. The estimated additional prescribing cost to the NHS for primary prevention ranges from £300 million at an annual CHD risk level of 3% to £1.9 billion at a risk of 0.5%. This does not include current secondary prevention prescribing, which would be an additional £506 million, under the above assumption that secondary prevention prescribing is 75% of total current prescribing. *Table 89* is based on the cumulative numbers of people eligible from *Table 88*. The additional cost of prescribing at a guideline of 1.5% annual risk is therefore estimated to be approximately £934 million (£1103 m–£169 m). This additional cost will be lower if the proportion of primary prevention prescribing is higher than the assumed 25% of the total.

Risk assessment tools
A crucial element affecting the impact to the NHS will be the number of patients identified as being at risk and therefore eligible for treatment. One of the factors that could influence patient numbers identified is the type of risk assessment tool used

TABLE 88 *Reverse cumulative number of people (millions) eligible for treatment*

Annual risk level	£20,000 threshold			£30,000 threshold		
	Men	Women	Total	Men	Women	Total
0.5	5.88	0.57	6.44	7.67	2.03	9.70
0.6	5.33	0.54	5.87	6.96	1.88	8.84
0.7	4.93	0.53	5.46	6.38	1.80	8.18
0.8	4.57	0.53	5.10	5.86	1.60	7.46
0.9	4.33	0.53	4.87	5.46	1.44	6.90
1.0	4.16	0.53	4.69	5.15	1.23	6.38
1.1	3.98	0.50	4.48	4.83	1.15	5.98
1.2	3.67	0.48	4.15	4.45	1.05	5.50
1.3	3.42	0.46	3.88	4.13	0.97	5.10
1.4	3.24	0.45	3.69	3.88	0.84	4.73
1.5	3.05	0.43	3.48	3.62	0.72	4.34
1.6	2.87	0.40	3.27	3.37	0.63	3.99
1.7	2.77	0.37	3.14	3.18	0.56	3.74
1.8	2.66	0.34	3.00	3.01	0.50	3.50
1.9	2.57	0.31	2.88	2.84	0.44	3.29
2.0	2.51	0.30	2.81	2.70	0.39	3.09
2.1	2.42	0.29	2.71	2.56	0.36	2.92
2.2	2.26	0.27	2.53	2.39	0.35	2.74
2.3	2.13	0.26	2.39	2.26	0.32	2.58
2.4	1.99	0.25	2.24	2.13	0.29	2.42
2.5	1.89	0.23	2.13	2.00	0.26	2.26
2.6	1.74	0.23	1.97	1.82	0.23	2.06
2.7	1.67	0.23	1.89	1.73	0.23	1.96
2.8	1.57	0.20	1.77	1.62	0.20	1.82
2.9	1.51	0.19	1.70	1.54	0.19	1.73
3.0	1.44	0.17	1.61	1.44	0.17	1.61
>3.0	1.34	0.14	1.49	1.34	0.14	1.49

by the clinician. A study comparing the Joint British Societies Coronary Risk Prediction Chart with the Sheffield Table for Primary Prevention of Cardiovascular Disease found that the number of patients identified at a given level of risk can vary by as much as 30%.

Seven tools are in common use in England and Wales:

- Joint British Societies Coronary Risk Prediction Chart[43]
- Joint British Societies Cardiac Risk Assessor Computer Program
- Sheffield Table for Primary Prevention of Cardiovascular Disease
- University College London Computer Program – CardioRisk Manager
- European Coronary Risk Chart
- New Zealand Cardiovascular Risk Prediction Charts
- Egton Medical Information Systems (EMIS) GP computer system.

Although all of the above tools are based on Framingham Heart Study equations, they differ in

two main ways: they are either computerised tools or chart/table-based tools. The likelihood of variation is greatest between the tools in the format of either a chart or a table. This is because patient characteristics are either dichotomised or approximated, resulting in broad categories of risk.

The computer-based tools have similar patient characteristics as inputs and should therefore give similar answers. However, differences exist in the type of Framingham equation used and assumptions made about missing patient data.

Medical professionals have various reasons for using a particular tool. The charts and tables are favoured by many clinicians because of their ease of use and because an estimate of risk can be obtained without knowledge of all the patients characteristics. The advantage of the computer-based tools is their ability to allow fine graduations instead of broad categories of risk. The disadvantage is that patient characteristics have to either be available or be measured by the clinician.

The impact of the use of various risk tools on the NHS budget will depend on two factors; the

TABLE 89 *Predicted annual primary prevention prescribing costs (millions) of adopting different annual risk level thresholds*

Annual risk level	Predicted no. of asymptomatic people eligible (million)	Predicted primary prevention prescribing cost (£ million)	Additional cost (predicted – current) (£ million)
0.5	6.4	£2042	£1873
0.6	5.9	£1861	£1693
0.7	5.5	£1731	£1562
0.8	5.1	£1616	£1447
0.9	4.9	£1542	£1373
1.0	4.7	£1486	£1317
1.1	4.5	£1421	£1252
1.2	4.2	£1315	£1146
1.3	3.9	£1230	£1062
1.4	3.7	£1169	£1001
1.5	3.5	£1103	£934
1.6	3.3	£1037	£868
1.7	3.1	£996	£827
1.8	3.0	£951	£782
1.9	2.9	£913	£745
2.0	2.8	£889	£720
2.1	2.7	£858	£690
2.2	2.5	£801	£632
2.3	2.4	£756	£587
2.4	2.2	£709	£540
2.5	2.1	£674	£505
2.6	2.0	£624	£456
2.7	1.9	£600	£431
2.8	1.8	£562	£393
2.9	1.7	£539	£370
3.0	1.6	£510	£341
>3.0	1.5	£471	£302

accuracy of the tools compared with Framingham and the distribution of the use of the tools among clinicians.

Accuracy of Framingham-based risk tools
A MEDLINE search was undertaken to identify studies that have compared Framingham-based charts and tables with Framingham equations. Seven studies[234,265–270] were found, which included comparisons of three of the tools identified as commonly used in England and Wales: the Joint British Societies Charts, the Sheffield Tables and the New Zealand Charts. Studies varied in the source of data used to identify risk (patient charts, laboratory assessments, etc.), the assessors of risk (clinicians, medical students, computer operators, etc.) and the risk reference standard (>3% risk, >2% risk, etc.). The Joint British Chart was found to be the most accurate predictor of risk compared with Framingham equations, with sensitivity ranging from 77 to 100% and specificity ranging from 91 to 100%. The Sheffield Tables performed reasonably well in some studies but poorly in others, with sensitivity ranging from 61 to 96% and specificity ranging from 88 to 100%. The New Zealand Charts also had the potential to predict

poorly, with sensitivity ranging from 56 to 94% and specificity ranging from 58 to 100%.

Based on these studies, it would appear that the Joint British Charts when compared with Framingham equations would predict a similar number of patients at risk with reasonable accuracy, at the levels of risk used in the studies. The Sheffield Tables and the New Zealand Charts have the potential to be considerably less accurate and the widescale use of these tools would lead to more uncertainty in the numbers of patients identified at risk.

Survey of risk assessment tools
The reviewers are not aware of any studies that have identified the distribution of the use of these tools among medical professionals. A survey of GP practices was undertaken to quantify the distribution of the use of the tools.

The main purpose of the survey was to find out which CHD risk assessment tools are used by GPs. A secondary purpose was to gain information that may help in determining how many patients will be identified at risk based on the guidelines used

for prescribing policy and the policy used to identify patients at risk. The questionnaire therefore contained three questions:

- Which risk assessment tool do you most commonly use? (The above list was provided.)
- Which guidelines do you use to determine whether patients are prescribed statins?
- What kind of policy does your practice have for identifying patients at risk in primary prevention?

GP surgeries were identified from the NHS website (www.nhs.uk). This source provides the names and addresses of GP surgeries in England and Wales. A random sample of 250 GP surgeries was selected from all regions. Of these, 30 were duplicate surgery addresses. The questionnaire was therefore sent by post to a total of 230 practices.

Results of survey
In total, 88 (38%) responses were received, of which two were illegible. Forty-seven per cent of the responders used a computerised risk equation tool and 34% used the Joint British Charts. The Joint British Societies Cardiovascular Disease Risk Prediction Charts were used by 10% of responders, Sheffield Tables by 6% and the New Zealand Charts by 4% (*Table 90*).

Conclusion of survey results
Studies comparing the accuracy of risk assessment tools with Framingham generally show that the Joint British Societies Charts will identify, with a reasonable degree of accuracy, the same number of patients as the Framingham equations. Over 80% of GP practices use either a computerised program or the Joint British Societies Charts to assess patients' risk. It is therefore likely that, for those patients whose risk is assessed in primary practice, the level of assessed risk will correspond fairly closely with the levels used in the economic model.

Limitations of Framingham-based risk assessment tools
Risk prediction is typically based on Framingham on the basis that it is the only method of estimating the risk of CHD and CVD in both men and women that includes most of the risk factors routinely available to clinicians. A full review of risk assessment tools is beyond the scope of this report. However, there are known limitations with risk assessment tools based on Framingham equations. These include the applicability to ethnic groups or low socio-economic groups, owing to a lack of representation by these groups in the original study population. The use of average risk prediction without adjustment for ethnic or social differences could lead to these groups, who may be at a higher than predicted risk, being undertreated. The Framingham equations are also open to the criticism of being out of date compared with current morbidity rates and of lacking accuracy when variables such as age, blood pressure and cholesterol levels are at their extremes. Recent studies[212,271] suggest that the Framingham equation may overpredict CHD events. If this is the case, patients may receive treatment even though their actual risk level falls below the recommended threshold for treatment. Further research in this area is important.

Given that UK clinicians are currently using Framingham-based tools to estimate the risk of patients, it is considered appropriate to use the Framingham equation, despite its known limitations, to estimate the impact on the NHS within this report.

TABLE 90 *Results of question 'Which risk assessment tool is used?'*

	n	%
Joint British Societies Coronary Risk Prediction Chart[43]	35	33.7
Egton Medical Information Systems (EMIS) GP computer system	30	28.8
Joint British Societies Cardiac Risk Assessor Computer Program	13	12.5
Joint British Societies Cardiovascular Disease Risk Prediction Chart	10	9.6
Sheffield Table for Primary Prevention of Cardiovascular Disease	6	5.8
Other computer programs	5	4.8
New Zealand Cardiovascular Risk Prediction Charts	4	3.8
University College London Computer Program – CardioRisk Manager	1	1.0
European Coronary Risk Chart	0	0.0
Total	104	100

TABLE 91 *Comparison of the price of proprietary simvastatin in 2003 and generic simvastatin in 2004*

	Proprietary simvastatin 2003	Generic simvastatin 2004	% Reduction
10 mg	£18.03	£11.99	33%
20 mg	£29.69	£16.00	45%
40 mg	£29.69	£21.00	29%
80 mg	£29.69	£28.77	3%

Major issues affecting the NHS impact
Price of statins

As the cost of statins falls, treatment becomes more cost-effective and therefore the CHD risk level at which statins are considered to be cost-effective will decrease.

The cost of statins has fallen since simvastatin became available as a generic in 2003. The price of proprietary simvastatin in 2003 and generic simvastatin in 2004[43] and the percentage reduction are shown in *Table 91*.

In August 2004 pravastatin also became available as a generic. This is expected to put further downward pressure on the price of statins. However, the UK generics market has seen some significant changes with the introduction by the government of maximum price proposals and changes in the way that community pharmacies are reimbursed for purchasing generic medicines. These changes may affect the savings to the NHS expected from the introduction of generics. In the past, price reductions due to the introduction of generics have varied. Some generics have fallen quite rapidly in price while for others, such as gliclazide and domperidone, the reduction has been modest or non-existent.[44]

The extent to which generic pravastatin impacts on the NHS budget will depend on a number of factors and is difficult to quantify. Prescribing patterns are likely to be influenced by PCT policy, which will vary by region.

In 2003, generic simvastatin accounted for approximately 70% of the market share of simvastatin products. If generic pravastatin products follow this trend then the savings to the NHS could be significant. Three pravastatin generics are currently available in the UK. The prices of these generics are available from the BNF September 2004 and the UK Medicines Information website and are listed below.[49,56] The percentage price reduction of these generics compared with proprietary pravastatin varies between 0% (Alpharma, 40 mg) and 54% (Almus, 10 mg). Potential savings will therefore also depend on which generic pravastatins are prescribed.

- BNF-listed generic pravastatin: 10 mg = £15.76, 20 mg = £28.80, 40 mg = £29.01[49]
- Almus: 10 mg = £8.5, 20 mg = £13.75, 40 mg = £21.60[56]
- Alpharma: 10 mg = £16.18, 20 mg = £29.69, 40 mg = £29.69[56]
- Ivax: 10 mg = £14.26, 20 mg = £26.72, 40 mg = £28.20.[56]

Table 91 shows that the impact of generics on the price of statins could be somewhere in the order of 30–45%. The potential impact of the introduction of generics on the cost-effectiveness of statins was therefore explored in the economic modelling by applying a 20% and 40% reduction in the overall price of statins. The results of this sensitivity analysis were used to explore the potential impact to the NHS of price reductions due to the introduction of generic statins.

The impact of price reductions will depend on the treatment guidance in place. If treatment thresholds remain unchanged any fall in the price of statins will reduce the NHS impact. However, in the longer term a drop in the price of statins may lead to a review of treatment thresholds. *Table 92* is based on a £20,000 threshold and an annual risk level of 1.5% (approximately 15% 10-year risk). The table is purely for illustrative purposes to enable a discussion of the issues relating to potential decreases in the price of statins and the subsequent impact to the NHS. The table shows

TABLE 92 *The potential future financial impact on the NHS of lower statin prices*

	Predicted no. of asymptomatic people eligible	Predicted primary prescribing cost	Additional cost (predicted – current)
Current price	3.5	£1103	£934
20% reduction in price	4.1	£1284	£1115
40% reduction in price	4.4	£1385	£1216

that as statins are reduced in price then more people become eligible for treatment and therefore the additional cost to the NHS increases. This can be explained by the fact that as price is reduced the cost per QALY subsequently reduces, making statins more cost-effective. As statins become more cost-effective then some age groups who were previously above the willingness-to-pay-threshold and therefore not eligible for treatment are now below the threshold and become eligible for treatment. This proportion of the population who were previously excluded is now included. In this illustration, a 20% reduction in the price of statins results in approximately 600,000 additional people becoming eligible for treatment, at an additional annual cost of £180 million. This additional cost, however, will be offset by savings achieved through events avoided due to these additional 600,000 thousand people being treated.

This discussion of the potential impact to the NHS of a reduction in statin price is based on the premise that prescribing decisions will also be made according to age and gender.

Other issues impacting on the NHS
Benefit of statins to individual patients

At lower risk levels the benefit in terms of absolute risk reduction of taking statins decreases for an individual patient, and this is likely to impact on an individual's decision whether or not to take statins. The adjusted (15% 10-year risk) NNT for three major trials is approximately 50.[272] If an asymptomatic patient was told that only one out of 50 patients would gain a clinical benefit from taking a statin, then uptake may be affected. It is not known how this will impact on uptake and is likely to depend on the way the risk is explained to and perceived by the patient. Further studies on this would be useful.

Rate of case identification

At lower risk thresholds, more patients will become eligible for statin treatment. This has major time and resource implications for GPs. The total cost of contacting and screening the targeted population is expected to be significant. Consideration must be given to the most cost-effective method of implementing a revised risk threshold target. The method of implementation will impact on the rate of case identification.

Continuance and compliance

Clinical trials have shown that the benefit derived from statin use is dependent on the level of compliance. For instance, in the WOSCOPS trial, the greatest reduction in morbidity and mortality was achieved by those patients who took more than 75% of their medication. This is particularly pertinent for asymptomatic patients, as research has shown that these patients are less well motivated to comply in the long term with treatment, owing to no immediate apparent benefit.[273,274] These patients are also less likely to accept side-effects associated with the medication.

It is generally accepted that continuance and compliance are lower in general clinical practice than in RCTs. However, UK-based evidence on continuance and compliance in general practice is sparse, and only three studies were identified from the systematic review. Continuance and compliance will impact on total costs of statin prescriptions to the NHS, but are difficult to quantify owing to the sparsity of evidence.

Prescription costs

The proportion of patients paying for statins prescriptions will have an impact on NHS income, and the impact is likely to change as the risk threshold reduces. As the threshold falls, the proportion of younger patients who will be paying for their prescriptions will increase. The impact of this income on the NHS will to some extent offset the costs of the drugs. Prescription charge levels themselves are relevant as they are likely to increase more rapidly than the cost of statins (which, as discussed earlier, will be likely to fall).

Quantifying the impact to the NHS of the above issues

It would be helpful if the above issues could be quantified to give an estimate of how they may impact on the NHS budget. However, there is much uncertainty around some of the major issues and for others there is a total lack of evidence. For example, there is no evidence available to help to quantify the proportion of asymptomatic patients who will agree to take statins. Uptake is also likely to vary with age, for which there is also no evidence. Of those patients who do agree to take statins there is very little evidence in primary treatment of the expected continuance and compliance rates, which are again likely to vary with age. There is also much uncertainty around identifying asymptomatic patients at risk. Without a clear government-led strategy, the numbers of patients who will be identified and the related cost are unknown. There is clearly a need to monitor the prescribing of statins over the next few years to quantify some of these uncertainties, as well as a need for further research.

Chapter 5
Implications for other parties

Ethical issues

In primary prevention people who are asymptomatic and at relatively low risk may be offered medical intervention with drug treatment and monitoring. Treating these patients results in medicalisation of previously healthy people, who then need to attend for blood tests and monitoring.

At low risk levels the number needed to treat is high. Large numbers of patients will need to take the drug long term to prevent one event and the majority of patients will not receive any benefit. The move to OTC prescribing exaggerates this issue: many patients would be spending £10–15 per month for no health benefit.

There is also a significant issue of how statins are offered to patients by the GP; in particular, how the risks and benefits are explained, relative to other treatment and lifestyle choices. Treatment choices by patients depend on the beliefs, values and circumstances of the patients, and patient preferences need to be taken into account.

The fact that statin prescribing is expected to continue for life presents a further issue. Although statins have been generally shown to be well tolerated and to have a good safety profile, long-term safety over a lifetime remains unproven. For patients at high risk of a future event, exposing the patient to a potential, but as yet undefined, long-term risk is easier to justify. At lower risk levels it becomes harder to justify.

Legal implications

There is a potential legal issue relating to the use of statins within ordinary medical practice but perhaps not strictly within their licensed indications. However, it is likely to remain a potential problem rather than a real one, as guidance from the Department of Health[49] and the Joint British Society guidelines[275] recommend the use of statins for high-risk individuals by extrapolating from the evidence from clinical outcome trials. Statins are recommended as a class of drugs with the best evidence to lower cholesterol to reduce CVD, without close scrutiny of their licensed indications.

Chapter 6
Factors relevant to the NHS

NSF and other health targets

Current Department of Health guidance recommends that patients with established CHD should receive statins and dietary advice to lower serum cholesterol concentrations either to less than 5 mmol l^{-1} (LDL-C to below 3 mmol l^{-1}) or by 25% (30% for LDL-C), whichever is greater. For primary prevention, drug intervention is recommended in patients with an absolute risk of developing CHD of 30% or more over 10 years.[46] The evidence base for current treatment criteria has now been superseded by new trial evidence. The revised British Hypertension Society guidelines,[47] issued in 2004, have followed an international trend[48] towards lower risk thresholds and treatment targets. This guidance and the recent general medical services (GMS) contract are both focused in terms of avoiding CVD events.

In practice, the different guidance will leave medical practice with different priorities or standards of care, from GMS contract (minimum acceptable standard) through NSF to specialist society guidance (optimum management standard).

Whatever the recommendations from NICE, urgent attention will be needed to modify recommendations in the NFS and other key guidance to ensure that they reflect the current evidence base and are consistent.

Public health approach to primary prevention of CHD

Cholesterol lowering is only one of a range of possible interventions to reduce the risk of CHD. Other important interventions include smoking cessation, exercise and the use of diet, as well as a range of drug treatments, such as antihypertensives, β-blockers and aspirin. Several of these interventions have been shown to be more cost-effective than statins.[23] Use of other interventions prior to statin prescribing to reduce CHD risk potentially has the effect of reducing an individual's risk to levels below which they would become eligible for statin treatment. In the authors' opinion, therefore, significant efforts need to be made to ensure that use of other interventions is optimised, to minimise the potential impact on the NHS of statin prescribing.

Other national guidance

New British guidelines for hypertension management were published by the British Hypertensive Society in March 2004.[47] The guidelines replaced CHD risk assessment with CVD risk assessment "to reflect the importance of stroke prevention as well as CHD prevention". The CVD risk threshold of 20% or above is equivalent to a CHD risk of approximately 15% or above over 10 years. The lower cholesterol goals are in line with the 2003 European Society of Hypertension/European Society of Cardiology guidelines.[276]

The new British guidelines recommend statins for treatment of all people with high blood pressure complicated by CVD, irrespective of baseline concentrations of total cholesterol or LDL-C. Statins are also recommended for primary prevention in people with high blood pressure who have a 10-year risk of CVD of at least 20%. Risk prediction is based on Framingham on the basis that it is the only method of estimating the risk of CVD in men and women that includes most of the risk factors routinely available to clinicians. A new CVD chart and risk calculator program has been produced, which predicts 10-year CVD risk (combined fatal and non-fatal stroke and CHD). In addition, the tool has been adapted so that anyone below the age of 50 years will be assessed as if they were 49 years old, and all those aged 60 years and above will be assessed as if they were 69 years old. This is an attempt to correct undertreatment of young people and overtreatment of older people. In addition, there is no separate chart for people with diabetes, in the belief that the need for risk assessment is rarely if ever required. These characteristics are generally supported by results from the ScHARR cost-effectiveness analysis.

Fair access

OTC statins

In July 2004 the UK became the first country to make statins available without a prescription, or OTC. The medication is called Zocor Heart-Pro and contains 10 mg of simvastatin. The decision to make statins available OTC was made by the Department of Health on the advice of the Committee on Safety and Medicines (CSM). According to the CSM consultation document, simvastatin is intended to reduce the risk of a first major coronary event in people at moderate risk of CHD. These groups are all men aged 55 years and over, and men aged between 45 and 55 years and women aged over 55 years with certain risk factors (family history of CHD, smoker, obese or of South Asian ethnicity).

The availability of OTC statins has raised some concerns in the medical community. A recent article published in the *Lancet* discussed some of these concerns.[277] One of the main points raised was the lack of trial evidence for low-dose simvastatin. The CSM consultation document states that treatment with simvastatin 10 mg will produce a 27% reduction in LDL-C. However, it concedes that there are no trial data for this population: "While no specific clinical trials have been conducted with simvastatin 10 mg in this particular patient population, it is reasonable to assume that these benefits would also apply to this group of people given that the effect of lowering LDL-cholesterol by simvastatin is consistent between populations, and the relation of LDL-cholesterol to risk is linear."[278] The CSM bases the 27% reduction on a systematic review of trials which includes some short-term trials and includes patients with CHD. However, the reduction in major coronary events of one-third over 3 years in these trials is contradicted by a meta-analysis of the five major primary prevention trials by the University of British Columbia.[279] They found that the key measure of total mortality was not reduced by statin therapy. Statins have therefore not been shown to provide an overall health benefit in primary prevention trials and it is unlikely that low-dose statins will achieve an effect that high-dose statins failed to achieve in clinical trials.

This study also found that 71 patients with cardiovascular risk factors have to be treated with a statin for 3–5 years to prevent one MI or stroke. This means that, at the drug dose used in the trial, 70 patients will take the drug long term with no benefit. It is therefore likely that with a low dose of statins hundreds of patients would need to be treated to prevent one event. Many patients would therefore be spending £10–15 per month for no health benefit.

There have been no trials of OTC statins and therefore no data on long-term patient compliance, reliance on statins as opposed to lifestyle modifications and the ability of pharmacists to determine an individual's risk accurately.

Other concerns raised by the *Lancet* article include the inequality of healthcare, with many people unable to afford OTC statins long term, the potential for interaction with other drugs, the hazards of adverse events, and the potential for patients at high risk to remain undetected and therefore undertreated.

The article concludes that the motive behind the government's decision is to save money and that a surveillance system must be set up to collect evidence of benefit and risk.

Equity issues

Variation in prescribing relating to socio-economic deprivation

In 1996, before the introduction of national and local guidelines on statin prescribing, Packham and colleagues measured the variation in statin prescribing by Nottingham GPs against a number of practice variables.[280] Practices with higher levels of socio-economic deprivation had significantly lower levels of statin prescribing per 1000 population aged 35–69 years. This relationship persisted when adjustment was made for the level of fibrate prescribing, and was highly significant ($p < 0.0001$).[280] However, this relationship is no longer so evident. Following the introduction of national and local guidelines, Packham found that, in 1997 and 1998, statin prescribing rates increased, with proportionally larger increases among practices in more deprived areas, so that no significant relationship was found between deprivation and prescribing rates.[281]

Limitations of risk tools in identifying particular groups of patients

The current risk assessment tools do not take into account the increased risk associated with certain ethnic groups or low socio-economic class.[23] These patients will be at a higher risk than that predicted by the risk tool and may therefore be denied treatment because they fall below a selected threshold.

No evidence for an alternative risk assessment tool was identified that could be used for ethnic minorities to assess CVD risk. In ordinary practice the Framingham risk function is used by doctors for ethnic minorities. A correction factor of 1.5 is usually used as non-caucasian people, specially South Asians, have a risk of CVD that is approximately 50% higher than would be expected from the risk factor profile. This seems a good compromise until equivalent validated cardiovascular risk assessment tools are available for ethnic minorities.

Chapter 7

Discussion

Main results

Clinical effectiveness

There is evidence from placebo-controlled studies to suggest that statin therapy is associated with a statistically significant reduction in the risk of:

- all-cause mortality, fatal and non-fatal MI, and a composite end-point of CHD death plus non-fatal MI, in both primary and secondary prevention
- stable angina in primary prevention
- cardiovascular mortality, CHD mortality, non-fatal stroke, PAD, unstable angina and coronary revascularisation in secondary prevention.

As the confidence intervals for each outcome in each prevention category overlap, it is not possible to differentiate, in terms of relative risk, between the effectiveness of statins in primary and secondary prevention. However, the absolute risk of CHD death plus non-fatal MI is higher, and the number needed to treat to avoid such an event is consequently lower, in secondary than in primary prevention.

There is no evidence that, at comparable levels of cardiovascular risk, the effectiveness of statins differs in women relative to men, in patients with diabetes compared with those without, or in older patients compared with those under 65 years of age, nor is there evidence that statins differ in effectiveness in patients with lower or higher cholesterol levels at baseline.

Because of poor study design, it is difficult to interpret the results of the studies that compared a statin with 'usual care', while those that compared a statin with no statin therapy very largely failed to achieve statistically significant results in relation to clinical outcomes.

It is not possible to differentiate between the different statins on the basis of the evidence from the placebo-controlled trials; although the point estimates of their effect sizes may vary, in each case the confidence intervals overlap. Only three head-to-head comparisons of one statin with another have reported clinical outcomes, and only one of these, the PROVE IT-TIMI trial, reported

statistically significant results. These results suggest that aggressive reduction in LDL-C with atorvastatin is more effective than moderate LDL-C reduction using pravastatin in reducing the risk of hospitalisation for unstable angina, and of coronary revascularisation; however, there was no statistically significant difference between the two statins in terms of the key composite end-point of CHD death or non-fatal MI.

However, it should be noted that the different statins vary in terms of the volume of evidence available from placebo-controlled studies that report clinical outcomes. As noted earlier, there is no such evidence relating to rosuvastatin. Of the remaining four statins, there is least evidence for fluvastatin (four studies of secondary CHD prevention in a total of 3416 patients). For atorvastatin, there are five studies (14,969 patients), in high-risk primary prevention, secondary and mixed prevention, and for simvastatin there are eight studies (26,851 patients), all in secondary or mixed prevention. There are 11 studies of pravastatin (29,524 patients): one study in primary prevention, six in secondary prevention and four with mixed populations. There is no RCT evidence for the effectiveness of the 10-mg OTC dose of simvastatin. Each statin is represented by both studies that appear to be of good quality, and others whose quality is difficult to assess in that it is not clear from published sources whether the method used to assign participants to the treatment group was really random or the allocation of treatment was concealed.

Statins are generally considered to be well tolerated and to have a good safety profile. Although increases in creatine kinase and myopathy have been reported, rhabdomyolysis and hepatotoxicity are rare. However, some patients may receive lipid-lowering therapy for as long as 50 years, and long-term safety over such a timespan remains unproven.

Cost-effectiveness

The base-case analysis considers the cost-effectiveness of statins for a population with CHD or at risk of CHD, taking into account CHD outcomes only. In secondary prevention the cost

per QALY is estimated to vary between approximately £10,000 and £15,700 between the ages of 45 and 85 years. The ICERs are very similar between the ages of 45 and 65, but increase with age beyond this point. There is little difference between ICERs for men and women. Results are sensitive to the discount rates used and the time-frame of the analysis. Using a threshold of £20,000 per QALY, the results of the PSA show that statin therapy is cost-effective for all patients with a history of CHD.

In the base-case primary prevention analyses the ICERs vary according to risk level and age. The estimated average ICER by risk level increases from £20,000 to £28,000 for men between 3% and 0.5% CHD risk, and from £21,000 to £57,000 for women. There is, however, significant variation within risk levels by age. At an annual CHD risk of 3%, the estimated cost per QALY ranges from £9500 to £36,800 for men and from £13,700 to £47,400 for women between the ages of 45 and 85. At the age of 85 the estimated cost per QALY rises from £36,800 and £47,400 for men and women, respectively, at 3% CHD risk, to around £105,200 and £110,600 for men and women at 0.5% CHD risk. Results are sensitive to the discount rates and the modelling time-frame. The PSA produces results similar to the base-case results of the deterministic analysis.

The results of the CVD analysis for both primary and secondary evaluations indicate that taking stroke and TIA outcomes into account when exploring the cost-effectiveness of statin treatment results in a significant reduction in the cost-effectiveness ratios, particularly at older age levels where the benefits of avoided stroke and TIA events are greater.

Current statin prescribing is estimated at around £675 million per annum. The estimated additional prescribing cost to the NHS for primary prevention ranges from £300 million at an annual CHD risk level of 3% to £1.9 billion at a risk of 0.5%.

Assumptions, limitations and uncertainties

Clinical effectiveness
The review of clinical effectiveness has several limitations. The foremost is the lack of RCT evidence for clinical outcomes; this is most notable in the case of rosuvastatin, for which no relevant studies have yet reported. Consequently, it is not possible to demonstrate whether rosuvastatin's lipid-lowering effects are translated into comparable reductions in clinical events. There is also insufficient RCT evidence to demonstrate whether statins differ in effectiveness in specific subgroups of interest (primary compared with secondary prevention, women compared with men, people with diabetes compared with those without, in people aged 65 and over compared with those younger than 65, and people with familial hypercholesterolaemia). Moreover, although people from the Indian subcontinent living in the UK are known to be at increased risk of CVD, no placebo-controlled studies were identified that studied the clinical effectiveness of statins in this population.

Even when relevant RCTs are available, limitations inevitably arise from the fact that studies do not all report the same outcomes in the same format. Some studies may not have collected data relating to some outcomes. Others may have collected, but not reported, the relevant data. Because of the number of relevant studies, and the tight timescale of the review, it was not considered feasible to contact the study investigators to request missing data.

Further limitations relate to the quality of the included studies, as reported in published articles. A surprising number of studies did not provide enough information to allow the reader to judge whether the allocation of patients to treatment groups was truly random, and even fewer indicated whether allocation to treatment groups was adequately concealed. In addition, although most studies were double-blind, only one (LIPS) assessed the success of the blinding process, and then only informally; anecdotal evidence suggested that many patients became unblinded to their treatment allocation as their primary care physicians had measured their total cholesterol levels.[91] Clearly, this may also have occurred in other studies, and may have caused patients in the control groups to attempt to reduce their cholesterol levels either by modifying their behaviour or by seeking non-study lipid-lowering therapy, thus reducing the apparent effect of the study therapy. Many studies reported the presence of cointerventions (generally statin or other lipid-lowering therapy in the control group), which potentially influenced the study outcome. As a result of such cointerventions, combined with non-compliance with study therapy in the statin group, many studies may underestimate the potential effect of statin therapy in their study populations. However, this may be counterbalanced by the

exclusion from some studies of patients who were hypersensitive to, intolerant of or known to be unresponsive to statins, or who were not adequately compliant with study medication during a placebo run-in phase. As the numbers involved may be large, this limits the generalisability of the results of those studies. In the largest statin study (HPS), around 30% of patients who entered the run-in phase were not included in the study because they either chose not to continue in the study or were deemed unlikely to be compliant in the long term;[121] despite this, only 82% of participants allocated to statin therapy were still compliant with that therapy at 5 years, and most of the non-compliant patients appeared to have discontinued therapy.[74] Thus, although the results of the meta-analyses may underestimate the true effects of statin therapy compared with placebo, by limiting their populations to those patients most likely to be able to comply with long-term therapy they may nonetheless overestimate the effects of statins in unselected populations.

Cost effectiveness

One of the major limitations of the analyses is the requirement to extrapolate well beyond the time-frame of the trial period. This period of extrapolation will be longer for younger patients and therefore the results for the lower age bands are subject to greater uncertainty. In addition, the analyses for primary prevention are extrapolating effectiveness results from higher risk primary prevention populations to the treatment of populations at much lower risk, and have to be treated with caution.

A further limitation is the question of generalisability of the results of RCT evidence to routine clinical practice. Effectiveness of statins in routine clinical practice could be lower than suggested by the trials owing to a number of issues, particularly compliance and continuance. However, sensitivity analysis on compliance and continuance assumptions shows that the impact on cost-effectiveness results is not likely to be significant.

The analyses are sensitive to the cost of statin, and the future cost of statins is a key unknown. Therefore, the cost-effectiveness results will need to be reviewed in the light of any significant changes in the price of statins. The impact of reductions in the price of statins on the NHS impact will depend on the treatment guidance in place. If treatment thresholds remain unchanged any fall in the price of statins will reduce the NHS

impact. However, in the longer term a drop in the price of statins may lead to a review of treatment thresholds. As statins become more cost-effective then some age groups who were previously above the willingness-to-pay threshold and therefore not eligible for treatment will move below the threshold and become eligible for treatment. A 20% reduction in the price of statins is estimated to result in approximately 600,000 additional people becoming eligible for treatment, at an additional annual cost of £180 million. This additional cost, however, will be offset to some degree by savings achieved through events avoided owing to these additional 600,000 people being treated.

This analysis does not take into account the costs of identifying and screening the relevant population. In primary prevention as the risk threshold falls the size of the population eligible for treatment increases. The number of patients who will require regular monitoring will expand, placing additional demands on staff and resources at GP surgeries.

Modelling clinical outcome on cholesterol lowering inherently favours drugs that are more potent at lowering cholesterol. Rosuvastatin was marketed and priced at a time when clinical evidence was available for other statins, and following the withdrawal of cerivastatin because of toxicity. It was priced competitively on the basis of its potency in lowering cholesterol. Not surprisingly, models that take into account cholesterol lowering, rather than actual clinical effectiveness from RCTs, favour rosuvastatin and show that it is cost-effective. Cholesterol reduction used in the analyses for rosuvastatin is based on a cholesterol-lowering trial. RCTs have consistently underperformed in terms of cholesterol lowering, usually achieving a reduction in total cholesterol of only about 25%, compared with trials where cholesterol lowering has been the primary end-point. This also favours rosuvastatin in the analysis.

The proportion of a low-risk population willing to take long-term medication is a major unknown. This, along with uncertainties regarding the rate of case identification in primary care and the potential rates of long-term compliance and continuation among asymptomatic patients, means that the estimated NHS impact is highly uncertain. Given the relatively slow uptake of statins in primary prevention over the past few years, the likely uptake rate at lower thresholds is expected to be slow and therefore the full NHS

impact will not be realised in the short to medium term.

The role of statins must be seen in the context of other interventions to reduce CHD risk, including smoking cessation, exercise and the use of diet, as well a range of drug treatments, such as antihypertensives, β-blockers and aspirin. Several of these interventions have been shown to be more cost-effective than statins.[23] Use of other interventions, before statin prescribing, to reduce CHD risk potentially has the effect of reducing an individual's risk to levels below which they would become eligible for statin treatment. Therefore, significant efforts need to be made to ensure that use of other interventions is optimised, to minimise the potential NHS impact of statin prescribing.

Need for further research

Clinical effectiveness
The most urgent need is for further research into the clinical effectiveness of statin therapy in populations at relatively low risk of a coronary event, and the impact of such therapy in terms of adverse events and quality of life. However, any study that was powered for clinical outcomes in a low-risk population would of necessity be very large and expensive.

Studies of the comparative efficacy of different statins in terms of clinical end-points would be desirable, but unfeasibly large and expensive.

Cost effectiveness
Robust published evidence on quality of life, compliance and continuance is required to ensure that cost-effectiveness results are as robust as possible.

The current analysis is based on extrapolating results from much higher risk patients to the treatment of apparently healthy people. Large outcome studies at lower CHD/CVD risk thresholds would be useful to determine whether the relative risk reduction figures remain valid at lower risk levels and the extent to which potential disutility due to statins may become an issue as treatment is extended to a vast proportion of the 'well' population.

Given the uncertainty of the results of the surrogate end-point analysis, clinical end-point data for rosuvastatin are required. Studies are currently in progress that will provide such data.

Future service implementation research is important, particularly on effective policies for targeting low-risk populations. Research on the attitudes of low-risk patients and relatively healthy younger 45-year-olds to taking lifetime medication is required, along with research into the optimal methods of explaining risks and benefits of treatment to patients so that they can make informed choices. Explanation will need to be valid across the social and ethnic spectrum of society.

Risk assessment tools
The current risk assessment tools, based on Framingham equations, are leading to overtreatment in some people and undertreatment in others. Current research suggests that it may be possible to adjust the Framingham equations so that they apply more accurately to the UK population.[212] However, this research is limited to men aged 40–59 years. Further research is needed to extend this knowledge to the rest of the population and also to find ways of incorporating these adjustments into the current risk assessment tools.

Chapter 8
Conclusions

There is evidence from placebo-controlled studies to suggest that statin therapy is associated with a statistically significant reduction in the risk of:

- all-cause mortality, fatal and non-fatal MI, and a composite end-point of CHD death plus non-fatal MI, in both primary and secondary prevention
- stable angina in primary prevention
- cardiovascular mortality, CHD mortality, non-fatal stroke, PAD, unstable angina and coronary revascularisation in secondary prevention.

As the confidence intervals for each outcome in each prevention category overlap, it is not possible to differentiate, in terms of relative risk, between the effectiveness of statins in primary and secondary prevention. However, the absolute risk of CHD death/non-fatal MI is higher, and the number needed to treat to avoid such an event is consequently lower, in secondary than in primary prevention.

The generalisability of these results is limited by the exclusion, in some studies, of patients who were hypersensitive to, intolerant of or known to be unresponsive to statins, or who were not adequately compliant with study medication during a placebo run-in phase. A considerable proportion of patients with or at risk of CHD may have been excluded in this way. Consequently, the treatment effect may be reduced when statins are used in an unselected population.

It is not possible, on the evidence available from the placebo-controlled trials, to differentiate between the different statins. In relation to each outcome, although the point estimates of their effect sizes may vary, the confidence intervals overlap. Few studies have directly compared one statin with another, and none of these has demonstrated a statistically significant difference between statins in terms of the key composite end-point of CHD death or non-fatal MI.

There is currently no RCT evidence for the effectiveness of either rosuvastatin or the 10-mg OTC dose of simvastatin in preventing clinical events. The results of rosuvastatin outcome trials are anticipated in 2007.

There is limited evidence for the effectiveness of statins in different subgroups. There is no evidence that, at comparable levels of cardiovascular risk, statins differ in their effectiveness in men and women, in people with diabetes compared with those without, or in people aged 65 and over compared with those younger than 65. In renal transplant patients, statin therapy is associated with a reduced risk of CHD death plus non-fatal MI. However, no benefit has been demonstrated in cardiac transplant patients. For ethical reasons, no placebo-controlled trials have been carried out in patients with familial hypercholesterolaemia. The only randomised trial in this group therefore compared two statins, and found no significant difference between them. People from the Indian subcontinent living in the UK are known to be at increased risk of CVD. However, no placebo-controlled studies were found that studied the clinical effectiveness of statins in this population.

Although, logically, one might expect statin therapy to achieve the greatest relative reduction in risk of CHD death/non-fatal MI in those populations with the highest serum cholesterol levels at baseline, there is no RCT evidence to suggest that statins are less effective in preventing clinical events in people with relatively low baseline LDL-C than in those with higher cholesterol levels.

Statins are generally considered to be well tolerated and to have a good safety profile. This view is generally supported both by the evidence of the trials included in this review and by postmarketing surveillance data. Increases in CK and myopathy have been reported, but rhabdomyolysis and hepatotoxicity are rare. However, some patients may receive lipid-lowering therapy for as long as 50 years, and long-term safety over such a timespan remains unproven.

The cost-effective modelling presented here has shown that statin therapy in secondary prevention is likely to be considered cost-effective compared

with other current standard treatments available on the NHS. Sensitivity analysis has shown the results to be robust. In primary prevention the cost-effectiveness ratios are dependent on the level of CHD risk and age. The ICERs for primary prevention are sensitive to the the cost of statins, discount rates and the modelling time-frame. In the CHD analysis the weighted average ICER by risk level ranges from £20,000 to £27,500 for men and from £21,000 to £57,000 for women. There is substantial variation in ICERs with age within risk levels. In the CVD analyses, taking into account the benefits of statins on reductions in stroke and TIA events, the costs per QALY are significantly lower than the base-case levels. The weighted average ICER by risk level remains below £20,000 at CHD risk levels down to 0.5%, although there is variation in cost-effectiveness with age within risk levels. This finding offers support for the more aggressive treatment recommendation issued by new guidelines in the UK.

Modelling clinical outcome on cholesterol lowering inherently favours drugs that are more potent at lowering cholesterol. In the absence of strong and conclusive evidence on the relationship between cholesterol lowering and clinical end-points, cost-effectiveness results for rosuvastatin are subject to significant uncertainty. Evidence on clinical end-points for rosuvastatin is therefore awaited.

The analyses are sensitive to the cost of statins, and the future cost of statins is a key unknown. Therefore, the cost-effectiveness results will need to be reviewed in the light of any significant changes in the price of statins.

The potential targeting of statin at low-risk populations raises major uncertainties, including the likely uptake of lifelong medication of asymptomatic patients and potential trends in long-term compliance and continuance, particularly of younger patients. The targeting, assessment and monitoring of low-risk patients in primary care will have major resource implications. These areas require further research.

The role of statins must be seen in the context of other interventions to reduce CHD risk, including smoking cessation, exercise and the use of diet, as well a range of drug treatments, such as antihypertensives, β-blockers and aspirin. Use of other interventions before statin prescribing to reduce CHD risk potentially has the effect of reducing an individual's risk to levels below which they would become eligible for statin treatment. Therefore, significant efforts need to be made to ensure that the use of other interventions of equivalent proven efficacy is optimised, to minimise the potential NHS impact of statin prescribing.

Acknowledgements

References

1. Petersen S, Peto V, Rayner M. *Coronary heart disease statistics*. 2004 ed. London: British Heart Foundation; 2004.

2. Grundy SM, Balady GJ, Criqui MH, Fletcher G, Greenland P, Hiratzka LF, *et al*. Primary prevention of coronary heart disease: guidance from Framingham: a statement for healthcare professionals from the AHA Task Force on Risk Reduction. American Heart Association. *Circulation* 1998;**97**:1876–87.

3. Cairns JA. Medical management of unstable angina. *Lancet* 1995;**346**:1464–5.

4. National Statistics. *Key health statistics from general practice 1998*. London: Office for National Statistics; 2000.

5. British Heart Foundation. British Heart Foundation Statistics Website, 1999. URL: www.heartstats.org. Accessed January 2004.

6. Sproston K, Primatesta P. *Health Survey for England 2003*. Vol. 1. *Cardiovascular disease*. London: Department of Health; 2004.

7. Sutcliffe SJ, Fox KF, Wood DA, Sutcliffe A, Stock K, Wright M, *et al*. Incidence of coronary heart disease in a health authority in London: review of a community register. *BMJ* 2003; **326**:20.

8. Albers GW, Caplan LR, Easton JD, Fayad PB, Mohr JP, Save, JL, *et al*. Transient ischemic attack – proposal for a new definition. *N Engl J Med* 2002;**347**:1713–16.

9. Fisher CM. Transient ischemic attacks. *N Engl J Med* 2002;**347**:1642–3.

10. Johnston SC. Transient ischaemic attack. *N Engl J Med* 2002;**347**:1687–92.

11. Gibbs RGJ, Newson R, Lawrenson R, Greenhalgh RM, Davies AH. Diagnosis and initial management of stroke and transient ischemic attack across UK health regions from 1992 to 1996: experience of a national primary care database. *Stroke* 2001;**32**:1085–90.

12. Stroke Association. *TIA fact sheet*. London: The Stroke Association; 2004.

13. Corvol JC, Bouzamondo A, Sirol M, Hulot JS, Sanchez P, Lechat P. Differential effects of lipid-lowering therapies on stroke prevention: a meta-analysis of randomized trials. *Arch Intern Med* 2003;**163**:669–76.

14. Gaziano JM, Hebert PR, Hennekens CH Cholesterol reduction: weighing the benefits and risks. *Ann Intern Med* 1996;**124**:914–18.

15. Bamford J, Sandercock P, Dennis M, Warlow C, Jones L, McPherson K, *et al*. A prospective study of acute cerebrovascular disease in the community: the Oxfordshire Community Stroke Project 1981–86. I. Methodology, demography and incident cases of first-ever stroke. *J Neurol Neurosurg Psychiatry* 1988;**51**:1373–80.

16. Du X, Sourbutts J, Cruickshank K, Summers A, Roberts N, Walton E, *et al*. A community based stroke register in a high risk area for stroke in north west England. *J Epidemiol Community Health* 1997;**51**:472–8.

17. British Heart Foundation. British Heart Foundation Statistics Website. URL: www.heartstats.org. Accessed 7 January 2004.

18. Wolfe CDA, Rudd AG, Howard R, Coshall C, Stewart J, Lawrence E, *et al*. Incidence and case fatality rates of stroke subtypes in a multiethnic population: the South London Stroke Register. *J Neurol Neurosurg Psychiatry* 2002;**72**:211–16.

19. Burns P, Gough S, Bradbury AW. Management of peripheral arterial disease in primary care. *BMJ* 2003;**326**:584–8.

20. Golledge J. Lower-limb arterial disease. *Lancet* 1997;**350**:1459–65.

21. Mohler ER III, Hiatt WR, Creager MA. Cholesterol reduction with atorvastatin improves walking distance in patients with peripheral arterial disease. *Circulation* 2003;**108**:1481–6.

22. NHS Centre for Reviews and Dissemination. Cholesterol and coronary heart disease: screening and treatment. *Effective Health Care* 1998;**4**:1–16.

23. Ebrahim S, Davey Smith G, McCabe C, Payne N, Pickin M, Sheldon TA, *et al*. What role for statins? A review and economic model. *Health Technol Assess* 1999;**3**(19).

24. Meads C, Cummins C, Jolly K, Stevens A, Burls A, Hyde C. Coronary artery stents in the treatment of ischaemic heart disease: a rapid and systematic review. *Health Technol Assess* 2000;**4**(23).

25. National Statistics. *Mortality statistics: cause. Review of the Registrar General on deaths by cause, sex and age*, in England and Wales, 2001. DH2 No. 28. London: Office for National Statistics; 2003.

26. Lawlor DA, Ebrahim S, Davey Smith G. Sex matters: secular and geographical trends in sex differences in coronary heart disease mortality. *BMJ* 2001;**323**:541–5.

27. Beery TA. Gender bias in the diagnosis and treatment of coronary artery disease. *Heart Lung* 1995;**24**:427–35.

28. de Belder M. *BCIS audit returns of interventional procedures 2001*. London: British Cardiac Interventional Society; 2002.

29. Hackett ML, Duncan JR, Anderson CS, Broad JB, Bonita R. Health-related quality of life among long-term survivors of stroke: results from the Auckland Stroke Study, 1991–1992. *Stroke* 2000; **31**:440–7.

30. Dennis M, Bamford J, Sandercock P, Warlow C. Prognosis of transient ischemic attacks in the Oxfordshire Community Stroke Project. *Stroke* 1990;**21**:848–53.

31. Lovett JK, Dennis MS, Sandercock PAG, Bamford J, Warlow CP, Rothwell PM. Very early risk of stroke after a first transient ischemic attack. *Stroke* 2003; **34**:e138–40.

32. Johnston SC, Gress DR, Browner WS, Sidney S. Short-term prognosis after emergency department diagnosis of TIA. *JAMA* 2000;**284**:2901–6.

33. Lichtman JH, Krumholz HM, Wang Y, Radford MJ, Brass LM. Risk and predictors of stroke after myocardial infarction among the elderly. *Circulation* 2002;**105**:1082–7.

34. Criqui MH, Langer RD, Fronek A, Feigelson HS, Klauber MR, McCann TJ, *et al*. Mortality over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med* 1992; **326**:381–6.

35. Hiatt WR. Quality of life assessment in peripheral arterial disease. *Atherosclerosis* 1997;**131**:S35–6.

36. Mark DB, Naylor CD, Hlatky MA, Califf RM, Topol EJ, Granger CB, *et al*. Use of medical resources and quality of life after acute myocardial infarction in Canada and the United States. *N Engl J Med* 1994;**331**:1130–5.

37. Lukkarinen H, Hentinen M. Assessment of quality of life with the Nottingham Health Profile among patients with coronary heart disease. *J Adv Nurs* 1997;**26**:73–84.

38. Roebuck A, Furze G, Thompson DR. Health-related quality of life after myocardial infarction: an interview study. *J Adv Nurs* 2001;**34**:787–94.

39. Department of Health. Heart drug available without a prescription. 12 May 2004. URL: http://www.dh.gov.uk/PublicationsAndStatistics/PressReleases/PressReleasesNotices/fs/en?CONTENT_ID=4082004&chk=z/YiI3. Accessed 20 September 2006.

40. Goyder E, McBeath S, Sims A, Ashwell S, Sherry R. *Quantifying the gap between policy and practice in cardiovascular risk reduction. A review of the evidence from recent cardiovascular and diabetes audits in the UK*. Oxford: South East Public Health Observatory and Trent Public Health Observatory; 2003.

41. Department of Health. Prescription cost analysis: England 2003. http://www.dh.gov.uk/assetRoot/04/08/66/05/04086605.xls. Accessed June 2004.

42. Dr Foster's case notes: Prescribing of lipid regulating drugs and admissions for myocardial infarction in England. *BMJ* 2004;**329**:645.

43. Prescription Pricing Authority. Electronic drug tariff. http://www.ppa.org.uk/edt/December_2004/mindex.htm. Accessed December 2004.

44. Thompson A. Patent expiries – how should they affect prescribing advice? *Pharmaceutical Journal* 2003;**271**:587–9.

45. Department of Health. Reimbursement prices for four generic medicines. http://www.dh.gov.uk/assetRoot/04/08/98/51/04089851.pdf. Accessed October 2004.

46. Department of Health. National service framework for coronary heart disease. http://www.dh.gov.uk/assetRoot/04/05/75/26/04057526.pdf. Accessed July 2004.

47. Williams B, Poulter NR, Brown MJ, Davis M, McInnes GT, Potter JF, *et al*. British Hypertension Society Guidelines. Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society, 2004 – BHS IV. *J Hum Hypertens* 2004;**18**:139–85.

48. Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;**106**:3143–421.

49. Joint Formulary Committee. British National Formulary. http://www.bnf.org/bnf. Accessed November 2004.

50. National Heart, Lung and Blood Institute. *Cholesterol lowering medicines: statins*. National Heart, Lung and Blood Institute; 2003. http://www.nhlbi.nih.gov/chd/meds1.htm. Accessed November 2004.

51. Newman TB, Hulley SB. Carcinogenicity of lipid-lowering drugs. *JAMA* 1996;**275**:55–60.

52. Committee on Safety of Medicines. Statins and cytochrome P450 interactions. *Current Problems in Pharmacovigilance* 2004;**30**:1–2.

53. Pfizer Limited. Lipitor 10 mg, 20 mg, 40 mg, 80 mg tablets. Electronic Medicines Compendium. http://emc.medicines.org.uk. Accessed August 2004.

54. Novartis Pharmaceuticals UK Ltd. Lescol. Electronic Medicines Compendium. 2005. http://emc.medicines.org.uk. Accessed August 2004.

55. Bristol-Myers Squibb Pharmaceuticals Ltd. Lipostat 10 mg, 20 mg, and 40 mg tablets. Electronic Medicines Compendium. 2005. http://emc.medicines.org.uk. Accessed August 2004.

56. Wan Y. Generic pravastatin available in UK. *Drug Infozone*; 2005. http://www.druginfozone.nhs.uk/ record%20viewing/viewrecord.aspx?id=537133.

57. AstraZeneca UK Limited. Crestor 10 mg, 20 mg and 40 mg film-coated tablets. Electronic Medicines Compendium. 2005. http://emc.medicines.org.uk. Accessed August 2004.

58. EMEA. Press release: European Medicines Agency Committee for Medicinal Products for Human Use 15–18 November 2004. http://www.emea.eu.int/ pdfs/human/press/pr/15298904en.pdf. Accessed December 2004.

59. Merck Sharp & Dohme Limited. Zocor. Electronic Medicines Compendium. 2005. http://emc.medicines.org.uk. Accessed August 2004.

60. Merck Sharp & Dohme. Simvastatin (Zocor®). The use of statins in the management of patients at increased risk of death or other cardiovascular events from coronary heart disease (CHD). Submission to the National Institute for Clinical Excellence; 2004.

61. Royal Pharmaceutical Society of Great Britain. Practice guidance on: sale of over-the-counter simvastatin. URL: http://www.rpsgb.org.uk/pdfs/ otcsimvastatinguid.pdf. Accessed August 2004.

62. Kedward J, Dakin L. A qualitative study of barriers to the use of statins and the implementation of coronary heart disease prevention in primary care. *Br J Gen Pract* 2003;**53**:684–9.

63. Bandolier. Statins and the law of unintended consequences. *Bandolier* 2003;**113**. URL: http://www.jr2.ox.ac.uk/bandolier/band113/ b113-2.html. Accessed September 2006.

64. Prospective Studies Collaboration. Cholesterol, diastolic blood pressure, and stroke: 13,000 strokes in 450,000 people in 45 prospective cohorts. *Lancet* 1995;**346**:1647–53.

65. Davey Smith G. Low blood cholesterol and non-atherosclerotic disease mortality: where do we stand? *Eur Heart J* 1997;**18**:6–9.

66. Crouse JR III, Byington RP, Hoen HM, Furberg CD. Reductase inhibitor monotherapy and stroke prevention. *Arch Intern Med* 1997;**157**:1305–10.

67. Cranney A, Tugwell P, Wells G, Guyatt G. Systematic reviews of randomized trials in osteoporosis: introduction and methodology. *Endocr Rev* 2002;**23**:497–507.

68. Cramer JA. Effect of partial compliance on cardiovascular medication effectiveness. *Heart* 2002;**88**:203–6.

69. Insull W, Troendle A, Silvers A, Dunne CW. Substantial non-compliance to dose and time prescriptions for medications treating hypercholesterolemia. *Atherosclerosis* 1995;**115**:S93.

70. Stephenson BJ, Rowe BH, Haynes RB, Macharia WM, Leon G. Is this patient taking the treatment as prescribed? *JAMA* 1993;**269**:2779–81.

71. Voss S, Quail D, Dawson A, Backstrom T, Aguas F, Erenus M, *et al*. A randomised, double-blind trial comparing raloxifene HCI and continuous combined hormone replacement therapy in postmenopausal women: effects on compliance and quality of life. *BJOG* 2002;**109**:874–85.

72. McDonald HP, Garg AX, Haynes RB. Interventions to enhance patient adherence to medication prescriptions: scientific review. *JAMA* 2002;**288**:2868–79.

73. Howell N, Trotter R, Mottram DR, Rowe PH. Compliance with statins in primary care. *Pharmaceutical Journal* 2004;**272**:23–6.

74. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;**360**:7–22.

75. Centre for Reviews and Dissemination. *Undertaking systematic reviews of research on effectiveness*. CRD's guidance for those carrying out or commissioning reviews. 2001; CRD Report No. 3. 2nd ed. York: Centre for Reviews and Dissemination.

76. Windeler J, Lange S. Events per person year – a dubious concept. *BMJ* 1995;**310**:454–6.

77. Ross SD, Allen IE, Connelly JE, Korenblat BM, Smith ME, Bishop D, Luo D. Clinical outcomes in statin treatment trials: a meta-analysis. *Arch Intern Med* 1999;**159**:1793–802.

78. Review Manager (RevMan). URL: http://www.cc-ims.net/RevMan. Accessed September 2000.

79. GraphPad Software. GraphPad QuickCalcs. URL: http://www.graphpad.com/quickcalcs/index.cfm. Accessed September 2006.

80. Smith GD, Song F, Sheldon TA. Cholesterol lowering and mortality: the importance of considering initial level of risk. *BMJ* 1993; **306**:1367–73.

81. Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, *et al*. PROSPER Study

Group. PROspective Study of Pravastatin in the Elderly at Risk. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002; **360**:1623–30.

82. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, Macfarlane PW, *et al*. West of Scotland Coronary Prevention Study Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med* 1995;**333**:1301–7.

83. Olsson AG, Eriksson M, Johnson O, Kjellstrom T, Lanke J, Larsen ML, *et al*. 3-Study Investigators. A 52-week, multicenter, randomized, parallel-group, double-blind, double-dummy study to assess the efficacy of atorvastatin and simvastatin in reaching low-density lipoprotein cholesterol and triglyceride targets: the Treat-to-Target (3T) study. *Clin Ther* 2003;**25**:119–38.

84. Wanner C, Krane V, Ruf G, Marz W, Ritz E. Rationale and design of a trial improving outcome of type 2 diabetics on hemodialysis. *Kidney Int* 1999;**56**:S222–6.

85. Smilde TJ, van Wissen S, Wollersheim H, Trip MD, Kastelein JJ, Stalenhoef AF. Effect of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolaemia (ASAP): a prospective, randomised, double-blind trial. *Lancet* 2001; **357**:577–81.

86. Diabetes Atorvastatin Lipid Intervention (DALI) Study Group. The effect of aggressive versus standard lipid lowering by atorvastatin on diabetic dyslipidemia: the DALI study: a double-blind, randomized, placebo-controlled trial in patients with type 2 diabetes and diabetic dyslipidemia. *Diabetes Care* 2001;**24**:1335–41.

87. Sato S, Kobayashi T, Awata N, Reiber JHC, Nakagawa Y, Hiraoka H, *et al*. Randomized, controlled trial of secondary prevention of coronary sclerosis in normocholesterolemic patients using pravastatin: two-year follow-up of the prevention of coronary sclerosis study. *Current Therapeutic Research, Clinical and Experimental* 2001; **62**:473–85.

88. Koren MJ, Hunninghake DB, ALLIANCE Investigators. Clinical outcomes in managed-care patients with coronary heart disease treated aggressively in lipid-lowering disease management clinics: the ALLIANCE study. *J Am Coll Cardiol* 2004;**44**:1772–9.

89. Okazaki S, Yokoyama T, Miyauchi K, Shimada K, Kurata T, Sato H, *et al*. Early statin treatment in patients with acute coronary syndrome. Demonstration of the beneficial effect on atherosclerotic lesions by serial volumetric intravascular ultrasound analysis during half a year after coronary event: the ESTABLISH study. *Circulation* 2004;**110**:1061–8.

90. Nissen SE, Tuzcu EM, Schoenhagen P, Brown BG, Ganz P, Vogel RA, *et al*. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis. A randomized controlled trial. *JAMA* 2004; **291**:1071–80.

91. Lesaffre E, Kocmanova D, Lemos PA, Disco CM, Serruys PW. A retrospective analysis of the effect of noncompliance on time to first major adverse cardiac event in LIPS. *Clin Ther* 2003;**25**:2431–47.

92. Foley DP, Bonnier H, Jackson G, Macaya C, Shepherd J, Vrolix M, *et al*. FLARE Study Group. Prevention of restenosis after coronary balloon angioplasty: rationale and design of the Fluvastatin Angioplasty Restenosis (FLARE) trial. *Am J Cardiol* 1994;**73**:50–61D.

93. Riegger G, Abletshauser C, Ludwig M, Schwandt P, Widimsky J, Weidinger G, *et al*. The effect of fluvastatin on cardiac events in patients with symptomatic coronary artery disease during one year of treatment. *Atherosclerosis* 1999;**144**:263–70.

94. Mehra MR, Uber PA, Vivekananthan K, Solis S, Scott RL, Park MH, *et al*. Comparative beneficial effects of simvastatin and pravastatin on cardiac allograft rejection and survival. *J Am Coll Cardiol* 2002;**40**:1609–14.

95. Crouse JR III, Byington RP, Bond MG, Espeland MA, Craven TE, Sprinkle JW, *et al*. Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries (PLAC-II). *Am J Cardiol* 1995; **75**:455–9.

96. Pravastatin Multinational Study Group for Cardiac Risk Patients. Effects of pravastatin in patients with serum total cholesterol levels from 5.2 to 7.8 mmol/liter (200 to 300 mg/dl) plus two additional atherosclerotic risk factors. *Am J Cardiol* 1993; **72**:1031–7.

97. Pedersen TR. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;**344**:1383–9.

98. Bestehorn HP, Rensing UF, Roskamm H, Betz P, Benesch L, Schemeitat K, *et al*. The effect of simvastatin on progression of coronary artery disease. The multicenter Coronary Intervention Study (CIS). *Eur Heart J* 1997;**18**:226–34.

99. Teo KK, Burton JR, Buller C, Plante S, Yokoyama S, Montague TJ. SCAT Investigators. Rationale and design features of a clinical trial examining the effects of cholesterol lowering and angiotensin-converting enzyme inhibition on coronary atherosclerosis: Simvastatin/Enalapril Coronary Atherosclerosis Trial (SCAT). *Can J Cardiol* 1997; **13**:591–9.

100. MAAS Investigators. Effect of simvastatin on coronary atheroma: the Multicentre Anti-Atheroma Study (MAAS). *Lancet* 1994;**344**:633–8.

101. Keech A, Collins R, MacMahon S, Armitage J, Lawson A, Wallendszus K, *et al.* Three-year follow-up of the Oxford Cholesterol Study: assessment of the efficacy and safety of simvastatin in preparation for a large mortality study. *Eur Heart J* 1994;**15**:255–69.

102. Sever PS, Dahlof B, Poulter NR, Wedel H, Beevers G, Caulfield M, *et al.* ASCOT Investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003;**361**:1149–58.

103. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HAW, Livingstone SJ, *et al.* Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004; **364** 685–98.

104. Rauscher M. Atorvastatin lowers LDL but not risk of CV events in diabetics with ESRD. Link via http://www.druginfozone.nhs.uk/Record%20Viewing/viewRecord.aspx?id=540410. Accessed September 2006.

105. Mondillo S, Ballo P, Barbati R, Guerrini F, Ammaturo T, Agricola E, *et al.* Effects of simvastatin on walking performance and symptoms of intermittent claudication in hypercholesterolemic patients with peripheral vascular disease. *Am J Med* 2003;**114**:359–64.

106. White HD, Simes RJ, Anderson NE, Hankey GJ, Watson JDG, Hunt D, *et al.* Pravastatin therapy and the risk of stroke. *N Engl J Med* 2000;**343**:317–26.

107. Mercuri M, Bond MG, Sirtori CR, Veglia F, Crepaldi G, Feruglio FS, *et al.* Pravastatin reduces carotid intima-media thickness progression in an asymptomatic hypercholesterolemic mediterranean population: the Carotid Atherosclerosis Italian Ultrasound Study. *Am J Med* 1996;**101**:627–34.

108. Serruys PW, Foley DP, Jackson G, Bonnier H, Macaya C, Vrolix M, *et al.* A randomized placebo-controlled trial of fluvastatin for prevention of restenosis after successful coronary balloon angioplasty; final results of the Fluvastatin Angiographic Restenosis (FLARE) trial. *European Heart Journal* 1999;**20**:58–69.

109. Liem AH, Van Boven AJ, Veeger NJGM, Withagen AJ, Robles de Medina RM, Tijssen JGP, *et al.* Effect of fluvastatin on ischaemia following acute myocardial infarction: a randomized trial. *Eur Heart J* 2002;**23**:1931–7.

110. Serruys PWJC, de Feyter P, Macaya C, Kokott N, Puel J, Vrolix M, *et al.* Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002;**287**:3215–22.

111. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, *et al.* Cholesterol and Recurrent Events Trial Investigators. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996;**335**:1001–9.

112. Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998;**339**:1349–57.

113. Pitt B, Mancini GB, Ellis SG, Rosman HS, Park JS, McGovern ME. Pravastatin limitation of atherosclerosis in the coronary arteries (PLAC I): reduction in atherosclerosis progression and clinical events. PLAC I investigation. *J Am Coll Cardiol* 1995;**26**:1133–9.

114. Bertrand ME, McFadden EP, Fruchart JC, Van Belle E, Commeau P, Grollier G, *et al.* PREDICT Trial Investigators. Effect of pravastatin on angiographic restenosis after coronary balloon angioplasty. Prevention of Restenosis by Elisor after Transluminal Coronary Angioplasty. *J Am Coll Cardiol* 1997;**30**:863–9.

115. Jukema JW, Bruschke AVG, Van Boven JA, Reiber JHC, Bal ET, Zwinderman AH, *et al.* Effects of lipid lowering by pravastatin on progression and regression of coronary artery disease in symptomatic men with normal to moderately elevated serum cholesterol levels. The Regression Growth Evaluation Statin Study (REGRESS). *Circulation* 1995;**91**:2528–40.

116. Teo KK, Burton JR, Buller CE, Plante S, Catellier D, Tymchak W, *et al.* Long-term effects of cholesterol lowering and angiotensin-converting enzyme inhibition on coronary atherosclerosis: the Simvastatin/Enalapril Coronary Atherosclerosis Trial (SCAT). *Circulation* 2000;**102**:1748–54.

117. Strandberg TE, Pyorala K, Cook TJ, Wilhelmsen L, Faergeman O, Thorgeirsson G, *et al.* Mortality and incidence of cancer during 10-year follow-up of the Scandinavian Simvastatin Survival Study (4S). *Lancet* 2004;**364**:771–7.

118. Aronow WS, Nayak D, Woodworth S, Ahn C. Effect of simvastatin versus placebo on treadmill exercise time until the onset of intermittent claudication in older patients with peripheral arterial disease at six months and at one year after treatment. *Am J Cardiol* 2003;**92**:711–12.

119. Tonkin AM, Colquhoun D, Emberson J, Hague W, Keech A, Lane G, *et al.* Effects of pravastatin in

147

3260 patients with unstable angina: results from the LIPID study. *Lancet* 2000;**356**:1871–5.

120. Tonkin A, Aylward P, Colquhoun D, Glasziou P, Harris P, Hunt D, *et al*. Design features and baseline characteristics of the LIPID (Long-Term Intervention with Pravastatin in Ischemic Disease) study: a randomized trial in patients with previous acute myocardial infarction and/or unstable angina pectoris. *Am J Cardiol* 1995;**76**:474–9.

121. MRC/BHF. Heart Protection Study of cholesterol-lowering therapy and of antioxidant vitamin supplementation in a wide range of patients at increased risk of coronary heart disease death: early safety and efficacy experience. *Eur Heart J* 1999;**20**:725–41.

122. Sacks FM, Pfeffer MA, Moye L, Brown LE, Hamm P, Cole TG, *et al*. Rationale and design of a secondary prevention trial of lowering normal plasma cholesterol levels after acute myocardial infarction: the Cholesterol and Recurrent Events trial (CARE). *Am J Cardiol* 1991;**68**:1436–46.

123. Anon. The Lescol in Severe Atherosclerosis (LiSA) trial. *Br J Cardiol* 1998;**5**:1–2.

124. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, *et al*. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;**350**:1495–504.

125. Olsson AG, Istad H, Luurila O, Ose L, Stender S, Tuomilehto J, *et al*. Rosuvastatin Investigators Group. Effects of rosuvastatin and atorvastatin compared over 52 weeks of treatment in patients with hypercholesterolemia. *Am Heart J* 2002;**144**:1044–51.

126. Brown WV, Bays HE, Hassman DR, McKenney J, Chitra R, Hutchinson H, *et al*. Efficacy and safety of rosuvastatin compared with pravastatin and simvastatin in patients with hypercholesterolemia: a randomized, double-blind, 52-week trial. *Am Heart J* 2002;**144**:1036–43.

127. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). *JAMA* 2002;**288**:2998–3007.

128. Athyros VG, Papageorgiou AA, Mercouris BR, Athyrou VV, Symeonidis AN, Basayannis EO, *et al*. Treatment with atorvastatin to the National Cholesterol Educational Program goal versus 'usual' care in secondary coronary heart disease prevention. The GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study. *Curr Med Res Opin* 2002;**18**:220–8.

129. Colivicchi F, Guido V, Tubaro M, Ammirati F, Montefoschi N, Varveri A, *et al*. Effects of

atorvastatin 80 mg daily early after onset of unstable angina pectoris or non-Q-wave myocardial infarction. *Am J Cardiol* 2002;**90**:872–4.

130. GISSI Prevenzione Investigators (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico). Results of the low-dose (20 mg) pravastatin GISSI Prevenzione trial in 4271 patients with recent myocardial infarction: do stopped trials contribute to overall knowledge? *Ital Heart J* 2000;**1**:810–20.

131. Blazing MA, De Lemos JA, Dyke CK, Califf RM, Bilheimer D, Braunwald E. The A-to-Z trial: methods and rationale for a single trial investigating combined use of low-molecular-weight heparin with the glycoprotein IIb/IIIa inhibitor tirofiban and defining the efficacy of early aggressive simvastatin therapy. *Am Heart J* 2001;**142**:211–17.

132. Ito H. A comparison of low versus standard dose pravastatin therapy for the prevention of cardiovascular events in the elderly: the Pravastatin Anti-atherosclerosis Trial in the Elderly (PATE). *J Atheroscler Thromb* 2001;**8**:33–44.

133. Salonen R, Nyyssonen K, Porkkala-Sarataho E, Salonen JT. The Kuopio Atherosclerosis Prevention Study (KAPS): effect of pravastatin treatment on lipids, oxidation resistance of lipoproteins, and atherosclerotic progression. *Am J Cardiol* 1995;**76**:34–9C.

134. Dennis M, Bamford J, Sandercock P, Warlow C. Prognosis of transient ischemic attacks in the Oxfordshire Community Stroke Project. *Stroke* 1990;**21**:848–53.

135. Keech A, Colquhoun D, Baker J, Simes RJ, Bradfield R, Best J, *et al*. Benefits of long term cholesterol lowering therapy using pravastatin among patients with diabetes in the Lipid Study. *Aust N Z J Med* 2000;**30**:172.

136. Haffner SM, Alexander CM, Cook TJ, Boccuzzi, SJ, Musliner TA, Pedersen TR, *et al*. Reduced coronary events in simvastatin-treated patients with coronary heart disease and diabetes or impaired fasting glucose levels: subgroup analyses in the Scandinavian Simvastatin Survival Study. *Arch Intern Med* 1999;**159**:2661–7.

137. Keech A, Colquhoun D, Best J, Kirby A, Simes RJ, Hunt D, *et al*. LIPID Study Group. Secondary prevention of cardiovascular events with long-term pravastatin in patients with diabetes or impaired fasting glucose. *Diabetes Care* 2003;**26**:2713–21.

138. Colhoun HM, Thomason MJ, Mackness MI, Maton SM, Betteridge DJ, Durrington PN, *et al*. Design of the Collaborative AtoRvastatin Diabetes Study (CARDS) in patients with type 2 diabetes. *Diabet Med* 2002;**19**:201–11.

139. O'Rourke B, Barbir M, Mitchell AG, Yacoub MH, Banner NR. Efficacy and safety of fluvastatin

therapy for hypercholesterolaemia after heart transplantation. Results of a randomised double blind placebo controlled study. *Int J Cardiol* 2004; **94**:235–40.

140. Kobashigawa JA, Katznelson S, Laks H, Johnson JA, Yeatman L, Wang XM, *et al*. Effect of pravastatin on outcomes after cardiac transplantation. *N Engl J Med* 1995;**333**:621–7.

141. Wenke K, Meiser B, Thiery J, Nagel D, von Scheidt W, Steinbeck G, *et al*. Simvastatin reduces graft vessel disease and mortality after heart transplantation: a four-year randomized trial. *Circulation* 1997;**96**:1398–402.

142. Holdaas H, Fellstrom B, Jardine AG, Holme I, Nyberg G, Fauchald P, *et al*. Assessment of LEscol in Renal Transplantation (ALERT) Study Investigators. Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo-controlled trial. *Lancet* 2003;**361**:2024–31.

143. Keech AC, Armitage JM, Wallendszus KR, Lawson A, Hauer AJ, Parish SE, *et al*. Absence of effects of prolonged simvastatin therapy on nocturnal sleep in a large randomized placebo-controlled study. Oxford Cholesterol Study Group. *Br J Clin Pharmacol* 1996;**42**:483–90.

144. Wardle J, Armitage J, Collins R, Wallendszus K, Keech A, Lawson A. Oxford Cholesterol Study Group. Randomised placebo controlled trial of effect on mood of lowering cholesterol concentration. *BMJ* 1996;**313**:75–8.

145. Ho C. Rosuvastatin: do we need another statin? *Issues in Emerging Health Technologies* 2001;**20**:1–4.

146. Benghozi R, Bortolini M, Jia Y, Isaacsohn JL, Troendle AJ, Gonasun L. Frequency of creatine kinase elevation during treatment with fluvastatin. *Am J Cardiol* 2002; **89**:231–3.

147. Furberg CD, Pitt B. Withdrawal of cerivastatin from the world market. *Current Controlled Trials in Cardiovascular Medicine* 2001;**2**:205–7.

148. Anon. The statin wars: why AstraZeneca must retreat. *Lancet* 2003;**362**:1341.

149. Therapeutics Initiative. Serious adverse event analysis: lipid lowering therapy revisited. *Therapeutics Letters* 2001;**42**:1–2.

150. Brewer T, Colditz GA. Postmarketing surveillance and adverse drug reactions: current perspectives and future needs. *JAMA* 1999;**281**:824–9.

151. Fontanarosa PB, Rennie D, DeAngelis CD. Postmarketing surveillance – lack of vigilance, lack of trust. *JAMA* 2004;**292**:2647–50.

152. Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. *JAMA* 2003;**289**:1681–90.

153. Hunninghake DB, Koren M, on behalf of the ALLIANCE Investigators. Comparison of clinical outcomes in managed care patients with CHD treated in aggressive lipid lowering programs using atorvastatin versus usual care. The ALLIANCE study. Program and abstracts from the American College of Cardiology 53rd Annual Scientific Session, 7–10 March 2004, New Orleans, LA. Late-Breaking Clinical Trials I; 2004.

154. Gaist D, Rodriguez LAG, Huerta C, Hallas J, Sindrup SH. Lipid-lowering drugs and risk of myopathy: a population-based follow-up study. *Epidemiology* 2001;**12**:565–9.

155. Staffa JA, Chang J, Green L. Cerivastatin and reports of fatal rhabdomyolysis. *N Engl J Med* 2002;**346**:539–40.

156. Chang JT, Staffa JA, Parks M, Green L. Rhabdomyolysis with HMG-CoA reductase inhibitors and gemfibrozil combination therapy. *Pharmacoepidemiol Drug Saf* 2004;**13**:417–26.

157. Graham DJ, Staffa JA, Shatin D, Andrade SE, Schech SD, La Grenade L, *et al*. Incidence of hospitalised rhabdomyolysis in patients treated with lipid lowering drugs. *JAMA* 2004;**292**:2585–90.

158. Food and Drug Administration. FDA approves new drug for lowering cholesterol. URL: http://www.fda.gov/bbs/topics/ANSWERS/2003/ANS01247.html. Accessed September 2006.

159. Food and Drug Administration. Crestor (ZD4522, rosuvastatin calcium) tablets. FDA Advisory Committee Meeting Briefing Document NDA 21-366 for use of Crestor. URL: http://www.fda.gov/OHRMS/DOCKETS/ac/03/briefing/3968B1_02_A-FDA-Clinical%20Review.pdf#search=%22FDA%20Advisory%20Committee%20Meeting%20Briefing%20Document%20NDA%2021-366%20%22. Accessed September 2006.

160. Wolfe SM. Dangers of rosuvastatin identified before and after FDA approval. *Lancet* 2004; **363**:2189–90.

161. AstraZeneca. Statins for the prevention of coronary events: the clinical and cost effectiveness of rosuvastatin. Submission to the National Institute for Clinical Excellence; 2004.

162. Wolfe SM. Author's reply. *Lancet* 2004;**364**:1578–9.

163. Olsson GO, Fox JC. Correspondence: should rosuvastatin be withdrawn from the market? Company's reply. *Lancet* 2004;**364**:1579–80.

164. Waknine Y. Rosuvastatin label change in EU indicates risk of myopathy. *Medscape* 2004. http://www.medscape.com/reviewarticle/480577. Accessed June 2004.

165. Rao S, Porter DC, Chen X, Herliczek T, Lowe M, Keyomarsi K. Lovastatin-mediated G1 arrest is through inhibition of the proteasome, independent of hydroxymethyl glutaryl-Co-A reductase. *Proc Nat Acad Sci USA* 1999;**96**:7797–802.

149

166. Weverling-Rijnsburger, AWE, Blauw GJ, Lagaay AM, Knook DL, Meinders AE, Westendorp RGJ. Total cholesterol and risk of mortality in the oldest old. *Lancet* 1997;**350**:1119–23.

167. Bandolier. Statins and cancer. URL: http://www.jr2.ox.ac.uk/bandolier/booth/cardiac/statcanc.html. Accessed 1 December 2004.

168. Gaist D, Jeppesen U, Andersen M, Garcia-Rodriguez LA, Hallas J, Sindrup SH. Statins and risk of polyneuropathy: a case–control study. *Neurology* 2002;**58**:1333–7.

169. Gaist D, Rodriguez LA, Huerta C, Hallas J, Sindrup SH. Are users of lipid-lowering drugs at increased risk of peripheral neuropathy? *Eur J Clin Pharmacol* 2001;**56**:931–3.

170. Shepherd J, Cobbe SM, Lorimer AR, McKillop JH, Ford I, Packard CJ, *et al*. Compliance and adverse event withdrawal: their impact on the West of Scotland Coronary Prevention Study. *Eur Heart J* 1997;**18**:1718–24.

171. Shepherd J, Blauw GJ, Murphy MB, Cobbe SM, Bollen ELEM, Buckle BM, *et al*. The design of a Prospective Study of Pravastatin in the Elderly at Risk (PROSPER). *Am J Cardiol* 1999;**84**:1192–7.

172. Wei L, Wang J, Thompson P, Wong S, Struthers AD, MacDonald TM. Adherence to statin treatment and readmission of patients after myocardial infarction: a six year follow up study. *Heart* 2002;**88**:229–33.

173. Tolmie EP, Lindsay GM, Kerr SM, Brown MR, Ford I, Gaw A. Patients' perspectives on statin therapy for treatment of hypercholesterolaemia: a qualitative study. *European Journal of Cardiovascular Nursing* 2003;**2**:141–9.

174. Drummond M, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. *BMJ* 1996;**313**:275–83.

175. Eddy DM. Technology assessment: the role of mathematical modeling. In *Assessing medical technology*. Washington DC: National Academy Press; 1985. pp. 144–54.

176. Marshall T. Coronary heart disease prevention: insights from modelling incremental cost effectiveness. *BMJ* 2003;**327**:1264.

177. Marshall T, Rouse A. Resource implications and health benefits of primary prevention strategies for cardiovascular disease in people aged 30 to 74: mathematical modelling study. *BMJ* 2002;**325**:197–9.

178. Grover SA, Coupal L, Zowall H, Dorais M. Cost-effectiveness of treating hyperlipidemia in the presence of diabetes: who should be treated? *Circulation* 2000;**102**:722–7.

179. Caro J, Klittich W, McGuire A, Ford I, Norrie J, Pettitt D, *et al*. The West of Scotland Coronary Prevention Study: economic benefit analysis of primary prevention with pravastatin. *BMJ* 1997; **315**:1577–82.

180. Glick H, Heyse JF, Thompson D, Epstein RS, Smith ME, Oster G. A model for evaluating the cost-effectiveness of cholesterol-lowering treatment. *Int J Technol Assess Health Care* 1992; **8**:719–34.

181. Pharoah PD, Hollingworth W. Cost effectiveness of lowering cholesterol concentration with statins in patients with and without pre-existing coronary heart disease: life table method applied to health authority population. *BMJ* 1996;**312**:1443–8.

182. Pickin DM, McCabe CJ, Ramsay LE, Payne N, Haq IU, Yeo WW, Jackson PR. Cost effectiveness of HMG-CoA reductase inhibitor (statin) treatment related to the risk of coronary heart disease and cost of drug treatment. *Heart* 1999;**82**:325–32.

183. Pickin DM, Payne JN, Haq IU, McCabe C, Ward S, Jackson PR, *et al*. Statin therapy/HMG Co-A reductase treatment in the prevention of coronary heart disease. Trent Institute for Health Services Research Guidance Note for Purchasers; 1996.

184. Elliott WJ, Weir DR. Comparative cost-effectiveness of HMG-CoA reductase inhibitors in secondary prevention of acute myocardial infarction. *Am J Health Syst Pharm* 1999;**56**:1726–32.

185. Barry M, Heerey A. Cost effectiveness of statins for the secondary prevention of coronary heart disease in Ireland. *Ir Med J* 2002;**95**:133–5.

186. Muls E, Van Ganse E, Closon MC. Cost-effectiveness of pravastatin in secondary prevention of coronary heart disease: comparison between Belgium and the United States of a projected risk model. *Atherosclerosis* 1998;**137**:S111–16.

187. Ashraf T, Hay JW, Pitt B, Wittels E, Crouse J, Davidson M, *et al*. Cost-effectiveness of pravastatin in secondary prevention of coronary artery disease. *Am J Cardiol* 1996;**78**:409–14.

188. van Hout BA, Simoons ML. Cost-effectiveness of HMG coenzyme reductase inhibitors; whom to treat? *Eur Heart J* 2001;**22**:751–61.

189. McAlister FA, Teo KK. Antiarrhythmic therapies for the prevention of sudden cardiac death. *Drugs* 1997;**54**:235–52.

190. Grover SA, Coupal L, Paquet S, Zowall H. Cost-effectiveness of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors in the secondary prevention of cardiovascular disease: forecasting the incremental benefits of preventing coronary and cerebrovascular events. *Arch Intern Med* 1999; **159**:593–600.

191. Glasziou PP, Eckermann SD, Mulray SE, Simes RJ, Martin AJ, Kirby AC, *et al*. Cholesterol-lowering therapy with pravastatin in patients with average

cholesterol levels and established ischaemic heart disease: is it cost-effective? *Med J Aust* 2002; **177**:428–34.

192. Riviere M, Wang S, Leclerc C, Fitzsimon C, Tretiak R. Cost-effectiveness of simvastatin in the secondary prevention of coronary artery disease in Canada. *CMAJ* 1997;**156**:991–7.

193. Lim SS, Vos T, Peeters A, Liew D, McNeil JJ. Cost-effectiveness of prescribing statins according to pharmaceutical benefits scheme criteria. *Med J Aust* 2001;**175**:459–64.

194. Johannesson M. At what coronary risk level is it cost-effective to initiate cholesterol lowering drug treatment in primary prevention? *Eur Heart J* 2001;**22**:919–25.

195. D'Agostino RB, Russell MW, Huse DM, Ellison RC, Silbershatz H, Wilson PWF, *et al*. Primary and subsequent coronary risk appraisal: new results from the Framingham study. *Am Heart J* 2000; **139**:272–81.

196. Stevens RJ, Kotari V, Adler AI, Stratton IM. The UKPDS risk engine: a model for the risk of coronary heart disease in type II diabetes (UKPDS 56). *Clin Sci (London)* 2001;**101**:671–9.

197. Department of Health. Health Survey for England 1998: cardiovascular disease. http://www.dh.gov.uk/ PublicationsAndStatistics/Publications/ PublicationsStatistics/PublicationsStatisticsArticle/ fs/en?CONTENT_ID=4009101&chk=cb7Po1. Accessed March 2004.

198. Office for National Statistics. Mortality Statistics: cause. England and Wales. London: Office for National Statistics, Stationery Office; http://www. statistics.gov.uk/StatBase/xsdataset.asp?vlnk= 5670&more=y. Accessed September 2004. 2001.

199. Department of Health. Reimbursement prices for four generic medicines. http://www.dh.gov.uk/ assetRoot/04/08/98/51/04089851.pdf. Accessed October 2004.

200. Clarke P, Gray A, Legood R, Briggs A, Holman R. The impact of diabetes-related complications on healthcare costs: results from the United Kingdom Prospective Diabetes Study (UKPDS Study No. 65). *Diabet Med* 2003;**20**:442–50.

201. Chambers M, Hutton J, Gladman J. Cost-effectiveness analysis of antiplatelet therapy in the prevention of recurrent stroke in the UK. Aspirin, dipyridamole and aspirin dipyridamole. *Pharmacoeconomics* 1999;**16**:577–93.

202. Youman P, Wilson K, Harraf F, Kalra L. The economic burden of stroke in the United Kingdom. *Pharmacoeconomics* 2003;**21**(Suppl 1):43–50.

203. Erens B, Primatesta P. *Health Survey for England 1998: cardiovascular disease*. London: The Stationery Office; 1999.

204. Clarke P, Gray A, Holman R. Estimating utility values for health states of type 2 diabetic patients using the EQ-5D (UKPDS 62). *Med Decis Making* 2002;**22**:340–9.

205. Serruys P, Unger F, Sousa JE, Jatene A, Bonnier HJRM, Schonberger JPAM. Comparison of coronary artery bypass surgery and stenting for the treatment of multivessel disease. *Eur Heart J* 2001;**344**:1117–24.

206. National Institute for Clinical Excellence. Health technology appraisal: review of coronary stents and appraisal of drug-eluting stents. London: NICE; 2003. http://www.nice.org.uk/page.aspx?o= appraisals.inprogress.drugelutingstents. Accessed October 2004. 2003.

207. Meslop K, Boothroyd DB, Hlatky MA. Quality of life and time trade-off utility measures in patients with coronary artery disease. *Am Heart J* 2003; **145**:36–41.

208. Jones PH, Davidson MH, Stein EA, Bays HE, McKenney JM, *et al*. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR* Trial). *Am J Cardiol* 2003;**92**:152–60.

209. Ballantyne CM. Reducing atherothrombotic events in high-risk patients: recent data on therapy with statins and fatty acids. *Curr Atheroscler Rep* 1999; **1**:6–8.

210. Wilson K, Marriott J, Fuller S, Lacey L, Gillen D. A model to assess the cost effectiveness of statins in achieving the UK National Service Framework target cholesterol levels. *Pharmacoeconomics* 2003; **21**:1–11.

211. Lachin JM. *Biostatistical methods: the assessment of relative risks*. Chichester: John Wiley; 2000.

212. Brindle P, Emberson LF, Walker M, Whincup P. Predictive accuracy of the Framingham coronary risk score in British men: prospective cohort study. *BMJ* 2003;**327**:1267.

213. Frolkis JP, Pearce GL, Nambi V, Minor S, Sprecher DL. Statins do not meet expectations for lowering low-density lipoprotein cholesterol levels when used in clinical practice. *Am J Med* 2002; **113**:625–9.

214. Palmer S, Sculpher M, Philips Z, Robinson M, Ginnelly L, Bakhai A, *et al*. A cost-effectiveness model comparing alternative management strategies for the use of glycoprotein IIb/IIIa antagonists in non-ST-elevation acute coronary syndrome. Report to the National Institute for Clinical Excellence. http://www.nice.org.uk/Docref.asp?d=32030. London: NICE; 2002. Accessed September 2006.

215. Mant J, Wade D, Winner S. Health care needs assessment: stroke. In: Stevens A, Raftery J, Mant J, Simpson S, editors. *Health care needs assessment:*

the epidemiologically based needs assessment reviews, 2nd ed. Oxford: Radcliffe Medical Press; 2004.

216. Lacey EA, Walters SJ. Continuing inequality: gender and social class influences on self perceived health after a heart attack. *J Epidemiol Community Health* 2003;**57**:622–7.

217. Sandercock P, Berge E, Dennis M, Forbes J, Hand P, Kwan J, *et al*. Cost-effectiveness of thrombolysis with recombinant tissue plasminogen activator for acute ischemic stroke assessed by a model based on UK NHS costs. *Stroke* 2004; **35**:1490–7.

218. Bosch JL, Hunink MG. Comparison of the Health Utilities Index Mark 3 (HUI3) and the EuroQol EQ-5D in patients treated for intermittent claudication. *Qual Life Res* 2000;**9**:591–601.

219. Jonsson B, Johannesson M, Kjekshus J, Olsson AG, Pedersen TR, Wedel H. Cost-effectiveness of cholesterol lowering. Results from the Scandinavian Simvastatin Survival Study (4S). *Eur Heart J* 1996;**17**:1001–7.

220. Morris S. A comparison of economic modelling and clinical trials in the economic evaluation of cholesterol-modifying pharmacotherapy. *Health Econ* 1997;**6**:589–601.

221. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. *Med Decis Making* 1993;**13**:322–39.

222. Mueck AO, Seeger H. Statins and menopausal health. *Journal of the British Menopause Society* 2002; **8**:141–6.

223. National Institute for Clinical Excellence. *Guidance for manufacturers and sponsors*. London: NICE; 2001.

224. National Institute for Clinical Excellence. *Guide to the methods of technology appraisal*. London: NICE; 2004. http://www.nice.org.uk/page.aspx?o=201973. Accessed October 2004.

225. Dennis MS, Bamford JM, Sandercock PA, Warlow CP. Incidence of transient ischemic attacks in Oxfordshire, England. *Stroke* 1989;**20**: 333–9.

226. Yeo WW, Yeo KR. Coronary risk versus cardiovascular risk for treatment decisions in mild hypertension. *J Cardiovasc Risk* 2002;**9**:275–80.

227. British Heart Foundation. http://www.heartstats.org/ topic.asp?id=18. Accessed October 2004. Statistics database.

228. Bots ML, van der Wilk EC, Koudstaal PJ, Hofman A, Grobbee DE. Transient neurological attacks in the general population: prevalence, risk factors and clinical relevance. *Stroke* 1997;**28**:768–73.

229. Gray D, Hapton JR. Twenty years' experience of myocardial infarction: the value of a heart attack register. Nottingham Heart Attack Register. *Br J Clin Pharmacol* 1993;**47**:292–5.

230. Juul-Moller S, Edvardsson N, Jahnmatz B, Rosen A, Sorenson S, Omblus R. Double blind trial of aspirin in primary prevention of MI in patients with stable chronic angine pectoris. *Lancet* 1992; **340**:1421–5.

231. Rehnqvist N, Hjemdahl P, Billing E, Bjorkander I, Eriksson SV, Forslund L, *et al*. Effects of metoprolol vs verapamil in patients with stable angina pectoris. The Angina Prognosis Study in Stockholm (APSIS) [published erratum appears in *Eur Heart J* 1996;**17**:483]. *Eur Heart J* 1996; **17**:76–81.

232. Dargie HJ, Ford I, Fox KM. Effects of ischaemia and treatment with atenolol, nifedipine SR and their combination on outcome in patients with chronic stable angina. Total Ischaemic Burden European Trial (TIBET). *Eur Heart J* 1996; **17**:104–12.

233. Pepine CJ, Cohn PF, Deedwania PC, Gibson RS, Handberg E, Hill JA, Miller E, *et al*. Effects of treatment on outcome in mildly symptomatic patients with ischaemia during daily life. The Atenolol Silent Ischaemia Study (ASIST). *Circulation* 1994;**90**:762–8.

234. Haq IU, Ramsey LE, Yeo WW, Jackson PR, Wallis EJ. Is the Framingham risk function valid for northern European populations? A comparison of methods for estimating absolute coronary risk in high risk men. *Heart* 1999;**81**:40–6.

235. Maron DJ. Percutaneous coronary intervention versus medical therapy for coronary heart disease [review]. *Curr Atheroscler Rep* 2000;**2**:290–6.

236. Ridker PM, Cannon CP, Morrow D, Rifai N, Rose LM., McCabe CH, *et al*. C-Reactive protein levels and outcomes after statin therapy. *N Engl J Med* 2005;**352**:20–8.

237. Nissen SE, Tuzcu EM, Schoenhagen P, Crowe T, Sasiela WJ, Tsai J, *et al*. Statin therapy, LDL cholesterol, C-reactive protein and coronary artery disease. *N Engl J Med* 2005;**352**:29–38.

238. Di Napoli P, Taccardi AA, Oliver M, De Caterina R. Statins and stroke: evidence for cholesterol-independent effects. *Eur Heart J* 2002;**23**:1908–21.

239. Anderson KM, Odell PM, Wilson PWF, Kannel WB. Cardiovascular disease risk profiles. *Am Heart J* 1990;**121**:293–8.

240. Curtis L, Netten A. *Unit costs of health and social care 2004*. Canterbury: PSSRU;2004.

241. Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey. *BMJ* 1998;**316**:736–41.

242. Brazier JE, Deverill M, Harper R, Booth A. A review of the use of health status measures

in economic evaluation. *Health Technol Assess* 1999;**3**(9).

243. Brazier JE, Green C, Kanis JA. A systematic review of health state utility values for osteoporosis related conditions. *Osteoporosis Int* 2002;**13**:768–76.

244. Van Exel NJA. Assessment of post-stroke quality of life in cost-effectiveness studies: the usefulness of the Barthel Index and the EuroQol-5D, quality of life research. *Qual Life Res* 2004;**13**:427–33.

245. Tengs TO, Lin TH. A meta-analysis of quality of life estimates for stroke. *Pharmacoeconomics* 2003; **21**:191–200.

246. BARI Investigators. Protocol for the Bypass Angioplasty Revascularization Investigation. *Circulation* 1991;**84**:1–27.

247. Goodacre S, Nicholl J, Dixon S, Cross E, Angelina K, Arnold J, *et al*. Randomised controlled trial and economic evaluation of a chest pain observation unit compared with routine care. *BMJ* 2004;**328**:254.

248. Bradley CJ, Kroll J, Holmes-Rover M. The health and activities limitation index in patients with acute myocardial infarction. *J Clin Epidemiol* 2000; **53**:55–562.

249. Jacobs D, Blackburn H, Higgins M, Reed D, Iso H, McMillan G, *et al*. Report of the conference on low blood cholesterol: mortality associations. *Circulation* 1992;**86**:1046–60.

250. Neaton JD, Blackburn H, Jacobs D, Kuller L, Lee DJ, Sherwin R, *et al*. Serum cholesterol and mortality findings for men screened in the multiple risk factor intervention trial. *Arch Intern Med* 1992;**152**:1490–500.

251. Zureik M, Courbon D, Ducimetiere P. Serum cholesterol concentration and death from suicide in men: Paris prospective study. *BMJ* 1996; **313**:649–51.

252. Muldoon MF, Manuck SB, Matthews KA. Lowering cholesterol concentrations and mortality: a quantitative review of primary prevention trials. *BMJ* 1990;**301**:309–14.

253. Davey Smith G, Pekkanen J. Should there be a moratorium on the use of cholesterol lowering drugs? *BMJ* 1992;**304**:431–4.

254. Davy Smith G, Song F, Sheldon TA. Cholesterol lowering and mortality: the importance of considering initial level of risk. *BMJ* 1993; **306**:1367–73.

255. Carlsson CM, Papcke-Benson K. Health-related quality of life and long-term therapy with pravastatin and tocopherol (vitamin E) in older adults. *Drugs Aging* 2002;**19**:793–805.

256. Tsevat J, Kuntz KM, Orav EJ, Weinstein MC, Sacks FM, Goldman L. Cost-effectiveness of pravastatin therapy for survivors of myocardial infarction with average cholesterol levels. *Am Heart J* 2001;**141**:727–34.

257. Prosser LA, Stinnett AA, Goldman PA, Williams LW, Hunink MG, Goldman L, *et al*. Cost-effectiveness of cholesterol-lowering therapies according to selected patient characteristics. *Ann Intern Med* 2000;**132**:769–79.

258. Berto P, Munro V, Gaddi A, Negrini C, Hutton J, Mast O. Cost-effectiveness analysis for statin therapies in the primary prevention of coronary heart disease in Italy. *Clinical Drug Investigation* 2000;**20**:109–21.

259. Huse DM, Russell MW, Miller JD, Kraemer DF, D'Agostino RB, Ellison RC, *et al*. Cost-effectiveness of statins. *Am J Cardiol* 1998;**82**:1357–63.

260. Russell MW, Huse DM, Miller JD, Kraemer DF, Hartz SC. Cost effectiveness of HMG-CoA reductase inhibition in Canada. *Can J Clin Pharmacol* 2001;**8**:9–16.

261. Yeo KR, Yeo WW. Lipid lowering in patients with diabetes mellitus: what coronary heart disease risk threshold should be used? *Heart* 2002;**87**:423–7.

262. Yeo WW, Yeo KR. Predicting CHD risk in patients with diabetes mellitus. *Diabet Med* 2001;**18**:341–4.

263. National Statistics Online. Population Estimates for UK, England and Wales, Scotland and Northern Ireland. http://www.statistics.gov.uk/ statbase/Product.asp?vlnk=601&More=N.

264. Statins – who gets them? http://www.innovate.org.uk/ frameset.asp?Link=WhatsNew

265. Jones AF, Walker J, Jewkes C. Comparative accuracy of cardiovascular risk prediction methods in primary care patients. *Heart* 2001;**85**:37–43.

266. Durrington PN, Prais H, Bhatnagar D, France M, Crowley V, Khan J, *et al*. Indications for cholesterol-lowering medication: comparison of risk-assessment methods. [published erratum appears in *Lancet* 1999;**354**:166]. *Lancet* 1999; **353**:278–81.

267. McManus RJ, Mant J, Meulendijks CF. Comparison of estimates and calculations of risk of coronary heart disease by doctors and nurses using different calculation tools in general practice. *BMJ* 2002;**324**:459–64.

268. Wierzbicki AS, Reynolds TM, Gill K, Alg S, Crook MA. A comparison of algorithms for initiation of lipid lowering therapy in primary prevention of coronary heart disease. *J Cardiovasc Risk* 2000;**7**:63–71.

269. Sheridan S, Pignone M, Mulrow C. Framingham-based tools to calculate the global risk of coronary heart disease. *J Gen Intern Med* 2003;**18**:1039–52.

270. Haq IU, Ramsay LE, Jackson PR, Wallis EJ. Prediction of coronary risk for primary prevention

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of coronary heart disease: a comparison of methods. *QJM* 1999;**92**:379–85.

271. Empana JP, Ducimetiere P, Arveiler D, Ferrieres J, Evans A, Ruidavets JB. Are the Framingham and PROCAM coronary heart disease risk functions applicable to different European populations? The PRIME Study. *Eur Heart J* 2003;**24**:1903–11.

272. Belsey J. Lipid-lowering in coronary heart disease. 1998;**1**:1–8. http://www.evidence-based-medicine.co.uk/ebmfiles/Gavel_vol1no1.pdf.

273. Furnham A. Overcoming the obstacles – the outsider's view. *Arteriosclerosis* 1999;**147**(Suppl 1): S53–6.

274. Dunbar JJ, Stunkard AJ. Adherence to diet and drug regimens. In: Levy RI, Rifkind BM, Dennis BH, Ernst N, editors. *Nutrition, lipids and coronary heart disease: a global view*. New York: Raven Press; 1979; pp. 391–417.

275. British Cardiac Society, British Hyperlipidaemia Association, British Hypertension Society, British Diabetic Association. Joint British recommendations on prevention of coronary heart disease in clinical practice: summary. *BMJ* 2000; **320**:705–8.

276. Guidelines Committee. European Society of Hypertension, European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 2003;**21**:1053.

277. Editorial. OTC statins: a bad decision for public health. *Lancet* 2004;**363**:1659.

278. Medicines and Healthcare Products Regulatory Agency (MHRA).The reclassification of simvastatin 10mg (Zocor Heart-Pro) over the counter (OTC). London: MHRA; 2004.

279. Do statins have a role in primary prevention? *Therapeutics Letter* 2003;**48**(April–June). http://www.ti.ubc.ca/pages/letter48.htm. Accessed December 2004.

280. Packham C, Robinson J, Morris J, Richards C, Marks P, Gray D. Statin prescribing in Nottingham general practices: a cross-sectional study. *J Public Health Med* 1999;**21**:60–4.

281. Packham C, Pearson J, Robinson J, Gray D. Use of statins in general practices, 1996–8: cross sectional study. *BMJ* 2000;**320**:1583–4.

282. Diaz C, Aristegui R, Hernandez G. Primary prevention in patients with non-insulin dependent diabetes mellitus (NIDDM) and albuminuria: AIDA study ('Atorvastatin In Diabetes with Albuminuria'). *Atherosclerosis* 1997;**134**:46.

283. ASPEN Atorvastatin as Prevention of CHD Endpoints in patients with Non-insulin dependent diabetes mellitus. 2005. http://www.incirculation.net/whatswhat. Accessed 2005.

284. Fellstrom B, Zannad F, Schmieder R, Holdaas H, Jardine A, Armstrong J, *et al*. A study to evaluate the use of rosuvastatin in subjects on regular haemodialysis: an assessment of survival and cardiovascular events – the aurora study. *Nephrol Dial Transplant* 2003;**18**:713.

285. Von Haehling S, Anker SD. Statins for heart failure: at the crossroads between cholesterol reduction and pleiotropism? *Heart* 2005;**91**:1–2.

286. Novartis. Lescol® following angioplasty sharply reduces risk of cardiac events in patients with advanced coronary artery disease down to that of patients with early stage disease. Manufacturer's website. 31 March 2003.

287. Nakamura H. The design and background characteristics of the study on the primary prevention of coronary events with pravastatin among Japanese with mildly elevated cholesterol levels (Japanese Mega Study). *Atherosclerosis* 2000; **151**:136.

288. Ridker PM, on behalf of the JUPITER Study Group. Rosuvastatin in the primary prevention of cardiovascular disease among patients with low levels of low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein. *Circulation* 2003;**108**:2292–7.

289. Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH). http://www.ctsu.ox.ac.uk/projects/search. Accessed July 2005.

290. Amarenco P, Bogousslavsky J, Callahan AS, Goldstein L, Hennerici M, Sillsen H, *et al*. SPARCL, Investigators. Design and baseline characteristics of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study. *Cerebrovasc Dis* 2003;**16**:389–95.

291. Stegmayr BG, Nasstrom BG, Brannstrom M, Bucht S, Dimeny E, Gosch J, *et al*. Safety and efficacy of atorvastatin in patients with severe renal dysfunction. *J Am Soc Nephrol* 2001;**9**:161A.

292. Waters DD, Guyton JR, Herrington DM, McGowan MP, Wenger NK, Shear C. Treating to New Targets (TNT) study: does lowering low-density lipoprotein cholesterol levels below currently recommended guidelines yield incremental clinical benefit? *Am J Cardiol* 2004; **93**:154–8.

293. Herd JA, Ballantyne CM, Farmer JA, Ferguson JJ III, Jones PH, West MS, *et al*. Effects of fluvastatin on coronary atherosclerosis in patients with mild to moderate cholesterol elevations (Lipoprotein and Coronary Atherosclerosis Study [LCAS]). *Am J Cardiol* 1997; **80**:278–86.

294. Sawayama Y, Shimizu C, Maeda N, Tatsukawa M, Kinukawa N, Koyanag S, *et al*. Effects of probucol

and pravastatin on common carotid atherosclerosis in patients with asymptomatic hypercholesterolemia. Fukuoka Atherosclerosis Trial (FAST). *J Am Coll Cardiol* 2002;**39**:610–16.

295. Betteridge D, Gibson M. Effect of rosuvastatin and atorvastatin on LDL-C and CRP levels in patients with type 2 diabetes: results of the ANDROMEDA study. *Atheroscler Suppl* 2004;**5**:107, Abstract M.464.

296. Franken A, Wolffenbuttel B, Vincent H. Cholesterol-lowering effects of rosuvastatin compared with atorvastatin in patients with type 2 diabetes. *Atheroscler Suppl* 2004;**5**:118, Abstract M.513.

297. Schuster H, Barter PJ, Stender S, Cheung RC, Bonnet J, Morrell JM, *et al*. Effect of switching statins on achievement of lipid goals: Measuring Effective Reductions in Cholesterol Using Rosuvastatin Therapy (MERCURY I) study. *Am Heart J* 2004;**147** 705–12.

298. Jukema J, Liem A, Dunselman P, van der Sloot J, Lok D, Zwinderman A. LDL-C/HDL-C ratio in patients with coronary artery disease and low HDL-C: the RADAR study [abstract]. *Atheroscler Suppl* 2004;**5**:125, Abstract M.542.

299. Davidson M, Ma P, Stein EA, Gotto AM Jr, Raza A, Chitra R, *et al*. Comparison of effects on low-density lipoprotein cholesterol and high-density lipoprotein cholesterol with rosuvastatin versus atorvastatin in patients with type IIa or IIb hypercholesterolemia. *Am J Cardiol* 2002;**89**:268–75.

300. Schwartz GG, Bolognese MA, Tremblay BP, Caplan R, Hutchinson H, Raza A, *et al*. Efficacy and safety of rosuvastatin and atorvastatin in patients with hypercholesterolemia and a high risk of coronary heart disease: a randomized, controlled trial. *Am Heart J* 2004;**148**:H1–9.

301. Paoletti R. Rosuvastatin demonstrates greater reduction of low-density lipoprotein cholesterol compared with pravastatin and simvastatin in hypercholesterolaemic patients: a randomized, double-blind study. *J Cardiovasc Risk* 2001; **8**:383–90.

302. Stein EA, Strutt K, Southworth H, Diggle PJ, Miller E, HeFH Study Group. Comparison of rosuvastatin versus atorvastatin in patients with heterozygous familial hypercholesterolemia. *Am J Cardiol* 2003;**92**:1287–93.

303. Schneck DW, Knopp RH, Ballantyne CM, McPherson R, Chitra RR, Simonson SG. Comparative effects of rosuvastatin and atorvastatin across their dose ranges in patients with hypercholesterolemia and without active arterial disease. *Am J Cardiol* 2003;**91**:33–41.

304. Berne C, Siewert-Delle A. Use of rosuvastatin versus atorvastatin in type 2 diabetes mellitus

subjects: results of the URANUS study [abstract]. *Atheroscler Suppl* 2004;**5**:107, Abstract M.463.

305. Wiegman A, Hutten BA, de Groot E, Rodenburg J, Bakke HD, Buller H, *et al*. Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized controlled trial. *JAMA* 2004;**292**:331–7.

306. Baggio G, De Candia O, Forte PL, Mello F, Andriolli A, Donazzan S, *et al*. Efficacy and safety of fluvastatin, a new HMG CoA reductase inhibitor, in elderly hypercholesterolaemic women. *Drugs* 1994;**47**(Suppl 2):59–63.

307. Ballantyne CM, McKenney J, Trippe BS. Efficacy and safety of an extended-release formulation of fluvastatin for once-daily treatment of primary hypercholesterolemia. *Am J Cardiol* 2000;**86**:759–63.

308. Bruckert E, Lievre M, Giral P, Crepaldi G, Masana L, Vrolix M, *et al*. Short-term efficacy and safety of extended-release fluvastatin in a large cohort of elderly patients. *Am J Geriatr Cardiol* 2004;**12**:225–31.

309. Buzzi AP, Pastore M. Argentine multicenter evaluation of fluvastatin in the treatment of patients with hypercholesterolemia. *Current Therapeutic Research* 1997;**58**:1013–28.

310. Farnier M. Effect of combined fluvastatin-fenofibrate therapy compared with fenofibrate monotherapy in severe primary hypercholesterolemia. *Am J Cardiol* 2000;**85**:53–7.

311. Farnier M, Salko T, Isaacsohn JL, Troendle AJ, Dejager S, Gonasun L. Effects of baseline level of triglycerides on changes in lipid levels from combined fluvastatin + fibrate (bezafibrate, fenofibrate, or gemfibrozil). *Am J Cardiol* 2003;**92**:794–7.

312. Davidson MH. Fluvastatin Long-Term Extension Trial (FLUENT): summary of efficacy and safety. *Am J Med* 1994;**96**:41–4S.

313. Marcus A. Fluvastatin titrate-to-goal clinical practice study: interim results. *Clin Cardiol* 1994; **17**:IV16–20.

314. Hunninghake DB, Davidson MH, Knapp HR, Schrott HG, Manfreda S and the Fluvastatin Study Group. Extended-release fluvastatin 80 mg shows greater efficacy, with comparable tolerability, versus immediate-release fluvastatin 40 mg for once daily treatment of primary hypercholesterolaemia. *Br J Cardiol* 2002;**9**:469–75.

315. Insull W Jr, Black D, Dujovne C, Hosking JD, Hunninghake D, Keilson L, *et al*. Efficacy and safety of once-daily vs twice-daily dosing with fluvastatin, a synthetic reductase inhibitor, in primary hypercholesterolemia. *Arch Intern Med* 1994;**154**:2449–55.

316. Insull W, Marais AD, Aronson R, Manfreda S. Efficacy and safety of fluvastatin ER 80 mg

compared with fluvastatin IR 40 mg in the treatment of primary hypercholesterolaemia. *Br J Cardiol* 2004;**11**:148–55.

317. Isaacsohn JL, LaSalle J, Chao G, Gonasun L. Comparison of treatment with fluvastatin extended-release 80-mg tablets and immediate-release 40-mg capsules in patients with primary hypercholesterolemia. *Clin Ther* 2003;**25**:904–18.

318. Jacotot B, Banga JD, Pfister P, Mehra M. Efficacy of a low dose-range of fluvastatin (XU 62-320) in the treatment of primary hypercholesterolaemia. A dose–response study in 431 patients. The French–Dutch Fluvastatin Study Group. *Br J Clin Pharmacol* 1994;**38**:257–63.

319. Leitersdorf E, Muratti EN, Eliav O, Peters TK. Efficacy and safety of triple therapy (fluvastatin–bezafibrate–cholestyramine) for severe familial hypercholesterolemia. *Am J Cardiol* 1995;**76**:84–8A.

320. Lye M. Elderly patients with hypercholesterolaemia: results with fluvastatin. *Atherosclerosis* 1997;**130**:S29.

321. Olsson AG, Pauciullo P, Soska V, Luley C, Pieters RE, Broda G, *et al*. Comparison of the efficacy and tolerability of fluvastatin extended-release and immediate-release formulations in the treatment of primary hypercholesterolemia: a randomized trial. *Clin Ther* 2001;**23**:45–61.

322. Pauciullo P, Borgnino C, Paoletti R, Mariani M, Mancini M. Efficacy and safety of a combination of fluvastatin and bezafibrate in patients with mixed hyperlipidaemia (FACT study). *Atherosclerosis* 2000;**150**:429–36.

323. Peters TK, Muratti EN, Mehra M. Efficacy and safety of fluvastatin in women with primary hypercholesterolaemia. *Drugs* 1994;**47**(Suppl 2): 64–72.

324. Teramoto T, Goto Y, Kurokawa K, Nakamura H, Yoshida S, Saito Y, *et al*. Clinical efficacy of fluvastatin for hyperlipidemia in Japanese patients. *American Journal of Cardiology* 1995;**76**:33–6A.

325. Tomlinson B, Mak TW, Tsui JY, Woo J, Shek CC, Critchley JA, *et al*. Effects of fluvastatin on lipid profile and apolipoproteins in Chinese patients with hypercholesterolemia. *Am J Cardiol* 1995;**76**:136–9A.

326. Winkler K. Effect of fluvastatin slow-release on low density lipoprotein (LDL) subfractions in patients with type 2 diabetes mellitus: baseline LDL profile determines specific mode of action. *J Clin Endocrinol Metab* 2002;**87**:5485–90.

327. Andrews TC, Ballantyne CM, Hsia JA, Kramer JH. Achieving and maintaining National Cholesterol Education Program low-density lipoprotein cholesterol goals with five statins. *Am J Med* 2001; **111**:185–91.

328. Bays HE, Dujovne CA, McGovern ME, White TE, Kashyap ML, Hutcheson AG. ADvicor Versus Other Cholesterol-Modulating Agents Trial Evaluation. Comparison of once-daily, niacin extended-release/lovastatin with standard doses of atorvastatin and simvastatin (the ADvicor Versus Other Cholesterol-Modulating Agents Trial Evaluation [ADVOCATE]). *Am J Cardiol* 2003;**91**:667–72.

329. Taylor AJ, Kent SM, Flaherty PJ, Coyle LC, Markwood TT, Vernalis MN. ARBITER: Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol: a randomized trial comparing the effects of atorvastatin and pravastatin on carotid intima medial thickness. *Circulation* 2002;**106**:2055–60.

330. Insull W, Kafonek S, Goldner D, Zieve F. Comparison of efficacy and safety of atorvastatin (10 mg) with simvastatin (10 mg) at six weeks. *Am J Cardiol* 2001;**87**:554–9.

331. Assmann G, Huwel D, Schussman K-M, Smilde JG, Kosling M, Withagen AJAM, *et al*. Efficacy and safety of atorvastatin and pravastatin in patients with hypercholesterolemia. *Eur J Intern Med* 1999; **10**:33–9.

332. Athyros VG, Papageorgiou AA, Hatzikonstandinou HA, Athyrou VV, Kontopoulos AG. Effect of atorvastatin versus simvastatin on lipid profile and plasma fibrinogen in patients with hypercholesterolaemia. *Clinical Drug Investigation* 1998;**16**:219–27.

333. Cortellaro M. Atorvastatin and thrombogenicity of the carotid atherosclerotic plaque: the ATROCAP study. *Thromb Haemost* 2002;**88**:41–7.

334. Bakker-Arkema RG, Davidson MH, Goldstein RJ, Davignon J, Isaacsohn JL, Weiss SR, *et al*. Efficacy and safety of a new HMG-CoA reductase inhibitor, atorvastatin, in patients with hypertriglyceridemia. *JAMA* 1996;**275**:128–33.

335. Ballantyne CM, Houri J, Notarbartolo A, Melani L, Lipka LJ, Suresh R, *et al*. Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. *Circulation* 2003; **107**:2409–15.

336. Raggi P, Callister TQ, Davidson M, Welty FK, Bachmann GA, Laskey R, *et al*. Aggressive versus moderate lipid-lowering therapy in postmenopausal women with hypercholesterolemia: rationale and design of the Beyond Endorsed Lipid Lowering with EBT Scanning (BELLES) trial. *Am Heart J* 2001;**141**:722–6.

337. Bertolami MC, Ramires JAF, Nicolau JC, Novazzi JP, Bodanese LC. Open, randomized, comparative study of atorvastatin and simvastatin, after 12 weeks treatment, in patients with hypercholesterolemia alone or with combined hypertriglyceridemia. *Revista Brasileira de Medicina* 2002;**59**:577–84.

338. Bertolini S, Bittolo Bon G, Campbell LM, Farnier M, Langan J, Mahla G, *et al*. Efficacy and safety of atorvastatin compared to pravastatin in patients with hypercholesterolemia. *Atherosclerosis* 1997; **130**:191–7.

339. Best JD, Nicholson GC, O'Neal DN, Kotowicz MA, Tebbutt NC, Chan KW, *et al*. Atorvastatin and simvastatin reduce elevated cholesterol in non-insulin dependent diabetes. *Diabetes Nutr Metab* 1996;**9**:74–80.

340. Bo M, Nicolello MT, Fiandra U, Mercadante G, Piliego T, Fabris F. Treatment of heterozygous familial hypercholesterolemia: atorvastatin vs simvastatin. *Nutr Metab Cardiovasc Dis* 2001; **11**:17–24.

341. Boquist S, Karpe F, Danell-Toverud K, Hamsten A. Effects of atorvastatin on postprandial plasma lipoproteins in postinfarction patients with combined hyperlipidaemia. *Atherosclerosis* 2002; **162**:163–70.

342. Branchi A, Fiorenza AM, Torri A, Muzio F, Rovellini A, Berra C, *et al*. Effects of atorvastatin 10 mg and simvastatin 20 mg on serum triglyceride levels in patients with hypercholesterolemia. *Current Therapeutic Research, Clinical and Experimental* 2001;**62**:408–15.

343. Soedamah-Muthu SS, Colhoun HM, Thomason MJ, Betteridge DJ, Durrington PN, Hitman GA, *et al*., CARDS Investigators. The effect of atorvastatin on serum lipids, lipoproteins and NMR spectroscopy defined lipoprotein subclasses in type 2 diabetic patients with ischaemic heart disease. *Atherosclerosis* 2003;**167**:243–55.

344. Ma P. CAVEAT: a randomised, double-blind, parallel group evaluation of cerivastatin 0.4 mg and 0.8 mg compared to atorvastatin 10 mg and 20 mg once daily in patients with combined (type IIb) dyslipidaemia. *Br J Cardiol* 2000;**7**:780–6.

345. Chan DC, Watts GF, Mori TA, Barrett PHR, Beilin LJ, Redgrave TG. Factorial study of the effects of atorvastatin and fish oil on dyslipidaemia in visceral obesity. *Eur J Clin Invest* 2002;**32**:429–36.

346. Jones P, Kafonek S, Laurora I, Hunninghake D. Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin, and fluvastatin in patients with hypercholesterolemia (the CURVES study). *Am J Cardiol* 1998;**81**:582–7.

347. Dalla Nora E, Passaro A, Zamboni PF, Calzoni F, Fellin R, Solini A. Atorvastatin improves metabolic control and endothelial function in type 2 diabetic patients: a placebo-controlled study. *J Endocrinol Invest* 2003;**26**:73–8.

348. Dallongeville J, Fruchart JC, Maigret P, Bertolini S, Bon GB, Campbell MM, *et al*. Double-blind comparison of apolipoprotein and lipoprotein particle lowering effects of atorvastatin and pravastatin monotherapy in patients with primary hypercholesterolemia. *J Cardiovasc Pharmacol Ther* 1998;**3**:103–10.

349. Dart A. A multicenter, double-blind, one-year study comparing safety and efficacy of atorvastatin versus simvastatin in patients with hypercholesterolemia. *Am J Cardiol* 1997;**80**:39–44.

350. Davidson M, McKenney J, Stein E, Schrott H, Bakker-Arkema R, Fayyad R, *et al*. Comparison of one-year efficacy and safety of atorvastatin versus lovastatin in primary hypercholesterolemia. *Am J Cardiol* 1997;**79**:1475–81.

351. Farnier M, Portal JJ, Maigret P. Efficacy of atorvastatin compared with simvastatin in patients with hypercholesterolemia. *J Cardiovasc Pharmacol Ther* 2000;**5**:27–32.

352. Ferrier KE, Muhlmann MH, Baguet JP, Cameron JD, Jennings GL, Dart AM *et al*. Intensive cholesterol reduction lowers blood pressure and large artery stiffness in isolated systolic hypertension. *J Am Coll Cardiol* 2002;**39**:1020–5.

353. Gentile S, Turco S, Guarino G, Sasso CF, Amodio M, Magliano P, *et al*. Comparative efficacy study of atorvastatin vs simvastatin, pravastatin, lovastatin and placebo in type 2 diabetic patients with hypercholesterolaemia. *Diabetes Obes Metab* 2000;**2**:355–62.

354. Harris KPG, Wheeler DC, Chong CC. A placebo-controlled trial examining atorvastatin in dyslipidemic patients undergoing CAPD. *Kidney Int* 2002;**61**:1469–74.

355. Heinonen TM, Stein E, Weiss SR, McKenney JM, Davidson M, Shurzinske L, *et al*. The lipid-lowering effects of atorvastatin, a new HMG-CoA reductase inhibitor: results of a randomized, double-masked study. *Clin Ther* 1996;**18**:853–63.

356. Hunninghake D, Insull W Jr, Toth P, Davidson D, Donovan JM, Burke SK. Coadministration of colesevelam hydrochloride with atorvastatin lowers LDL cholesterol additively. *Atherosclerosis* 2001; **158**:407–16.

357. Hunninghake D, Insull W, Knopp R, Davidson M, Lohrbauer L, Jones P, *et al*. Comparison of the efficacy of atorvastatin versus cerivastatin in primary hypercholesterolemia. *Am J Cardiol* 2001;**88**:635–9.

358. Illingworth DR, Crouse JR, Hunninghake DB, Davidson MH, Escobar ID, Stalenhoef AF, *et al*. A comparison of simvastatin and atorvastatin up to maximal recommended doses in a large multicenter randomized clinical trial. *Curr Med Res Opin* 2001;**17**:43–50.

359. Nakamura H, Ohashi Y, Maruhama Y, Ninomiya K, Toyota T, Oikawa S, *et al*. Efficacy of atorvastatin in primary hypercholesterolemia. *Am J Cardiol* 1997; **79**:1248–52.

157

360. Jialal I, Stein D, Balis D, Grundy SM, Adams-Huet B, Devaraj S. Effect of hydroxymethyl glutaryl coenzyme a reductase inhibitor therapy on high sensitive C-reactive protein levels. *Circulation* 2001;**103**:1933–5.

361. Jilma B, Joukhadar C, Derhaschnig U, Rassoul F, Richter V, Wolzt M, *et al*. Levels of adhesion molecules do not decrease after 3 months of statin therapy in moderate hypercholesterolaemia. *Clin Sci* 2003;**104**:189–93.

362. Joukhadar C, Klein N, Prinz M, Schrolnberger C, Vukovich T, Wolzt M, *et al*. Similar effects of atorvastatin, simvastatin and pravastatin on thrombogenic and inflammatory parameters in patients with hypercholesterolemia. *Thromb Haemost* 2001;**85**:47–51.

363. Kadikoylu G, Yukselen V, Yavasoglu I, Bolaman Z. Hemostatic effects of atorvastatin versus simvastatin. *Ann Pharmacother* 2003;**37**:478–84.

364. Karalis DG, Ross AM, Vacari RM, Zarren H, Scott R. Comparison of efficacy and safety of atorvastatin and simvastatin in patients with dyslipidemia with and without coronary heart disease. *Am J Cardiol* 2002;**89**:667–71.

365. Kinlay S, Timms T, Clark M, Karam C, Bilodeau T, Ridker PM, *et al*. Comparison of effect of intensive lipid lowering with atorvastatin to less intensive lowering with lovastatin on C-reactive protein in patients with stable angina pectoris and inducible myocardial ischemia. *Am J Cardiol* 2002;**89**:1205–7.

366. McCrindle BW, Ose L, Marais AD. Efficacy and safety of atorvastatin in children and adolescents with familial hypercholesterolemia or severe hyperlipidemia: a multicenter, randomized, placebo-controlled trial. *J Pediatr* 2003;**143**:74–80.

367. Magnani G, Carinci V, Magelli C, Potena L, Reggiani LB, Branzi A. Role of statins in the management of dyslipidemia after cardiac transplant: randomized controlled trial comparing the efficacy and the safety of atorvastatin with pravastatin. *J Heart Lung Transplant* 2000;**19**:710–15.

368. Schwartz GG, Olsson AG, Ezekowitz MD, Ganz P, Oliver MF, Waters D, *et al*. Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study Investigators. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA* 2001;**285**:1711–18.

369. Mullen MJ, Wright D, Donald AE, Thorne S, Thomson H, Deanfield JE. Atorvastatin but not L-arginine improves endothelial function in type I diabetes mellitus: a double-blind study. *J Am Coll Cardiol* 2000;**36**:410–16.

370. Muscari A, Bastagli L, Poggiopollini G, Tomassetti V, Massarelli G, Boni P, *et al*. Short term

effect of atorvastatin and vitamin E on serum levels of C3, a sensitive marker of the risk of myocardial infarction in men. *Cardiovasc Drugs Ther* 2001;**15**:453–8.

371. Nawawi H, Osman NS, Yusoff K, Khalid BAK. Reduction in serum levels of adhesion molecules, interleukin-6 and C-reactive protein following short-term low-dose atorvastatin treatment in patients with non-familial hypercholesterolemia. *Horm Metab Res* 2003;**35**:479–85.

372. Nawrocki JW, Weiss SR, Davidson MH, Sprecher DL, Schwartz SL, Lupien PJ, *et al*. Reduction of LDL cholesterol by 25% to 60% in patients with primary hypercholesterolemia by atorvastatin, a new HMG-CoA reductase inhibitor. *Arterioscler Thromb Vasc Biol* 1995;**15**:678–82.

373. Olsson AG, Pears J, McKellar J, Mizan J, Raza A. Effect of rosuvastatin on low-density lipoprotein cholesterol in patients with hypercholesterolemia. *Am J Cardiol* 2001;**88**:504–8.

374. Oranje WA, Sels JP, Rondas-Colbers GJ, Lemmens PJ, Wolffenbuttel BH. Effect of atorvastatin on LDL oxidation and antioxidants in normocholesterolemic type 2 diabetic patients. *Clin Chim Acta* 2001;**311**:91–4.

375. Paiva H, Laakso J, Lehtimaki T, Isomustajarvi M, Ruokonen I, Laaksonen R. Effect of high-dose statin treatment on plasma concentrations of endogenous nitric oxide synthase inhibitors. *J Cardiovasc Pharmacol* 2003;**41**:219–22.

376. Pontrelli L, Parris W, Adeli K, Cheung RC. Atorvastatin treatment beneficially alters the lipoprotein profile and increases low-density lipoprotein particle diameter in patients with combined dyslipidemia and impaired fasting glucose/type 2 diabetes. *Metabolism* 2002;**51**:334–42.

377. Raison J, Rudnichi A, Safar ME. Effects of atorvastatin on aortic pulse wave velocity in patients with hypertension and hypercholesterolaemia: a preliminary study. *J Hum Hypertens* 2002;**16**:705–10.

378. Recto CS, Acosta S, Dobs A. Comparison of the efficacy and tolerability of simvastatin and atorvastatin in the treatment of hypercholesterolemia. *Clin Cardiol* 2000;**23**:682–8.

379. Renders L, Mayer-Kadner I, Koch C, Scharffe S, Burkhardt K, Veelken R, *et al*. Efficacy and drug interactions of the new HMG-CoA reductase inhibitors cerivastatin and atorvastatin in CsA-treated transplant recipients. *Nephrol Dial Transplant* 2001;**16**:141–6.

380. Sardo MA, Castaldo M, Cinquegrani M, Bonaiuto M, Maesano A, Versace A, *et al*. Effects of atorvastatin treatment on sICAM-1 and plasma nitric oxide levels in hypercholesterolemic subjects. *Clin Appl Thromb Hemos* 2002;**8**:257–63.

381. Schrott H, Fereshetian AG, Knopp RH, Bays H, Jones PH, Littlejohn TW 3rd, *et al*. A multicenter, placebo-controlled, dose-ranging study of atorvastatin. *J Cardiovasc Pharmacol Ther* 1998;**3**119–24.

382. Schuster H, Berger J, Luft FC. Randomised, double-blind, parallel-group trial of atorvastatin and fluvastatin on plasma lipid levels in patients with untreated hyperlipidaemia. *Br J Cardiol* 1998; **5**:597–602.

383. Sposito AC, Santos RD, Amancio RF, Ramires JA, Chapman MJ, Maranhao RC. Atorvastatin enhances the plasma clearance of chylomicron-like emulsions in subjects with atherogenic dyslipidemia: relevance to the *in vivo* metabolism of triglyceride-rich lipoproteins. *Atherosclerosis* 2003;**166**:311–21.

384. Stein DT, Devaraj S, Balis D, Adams-Huet B, Jialal I. Effect of statin therapy on remnant lipoprotein cholesterol levels in patients with combined hyperlipidemia. *Arterioscler Thromb Vasc Biol* 2001;**21**:2026–31.

385. Stein E, Strutt KL, Miller E. ZD4522 is superior to atorvastatin in the treatment of patients with heterozygous familial hypercholesterolemia. *Atherosclerosis* 2001;**159**:248.

386. Tan KCB, Chow WS, Tam SCF, Ai VHG, Lam CHL, Lam KSL. Atorvastatin lowers C-reactive protein and improves endothelium-dependent vasodilation in type 2 diabetes mellitus. *J Clin Endocrinol Metab* 2002;**87**:563–8.

387. Tanaka A, Yamada N, Saito Y, Kawakami M, Ohashi Y, Akanuma Y. A double-blind trial on the effects of atorvastatin on glycemic control in Japanese diabetic patients with hypercholesterolemia. *Clin Chim Acta* 2001; **312**:41–7.

388. Tannous M, Cheung R, Vignini A, Mutus B. Atorvastatin increases ecNOS levels in human platelets of hyperlipidemic subjects. *Thromb Haemost* 1999;**82**:1390–4.

389. Marz W, Wollschlaeger H, Klein G, Neiss A, Wehling M. Safety of low-density lipoprotein cholesterol reduction with atorvastatin versus simvastatin in a coronary heart disease population (the target tangible trial). *Am J Cardiol* 1999; **84**:7–13.

390. van den Akker JM, Bredie SJ, Diepenveen SH, van Tits LJ, Stalenhoef AF, van Leusen R, *et al*. Atorvastatin and simvastatin in patients on hemodialysis: effects on lipoproteins, C-reactive protein and *in vivo* oxidized LDL. *J Nephrol* 2003;**16**:238–44.

391. Vansant G, Mertens A, Muls E. The effect of atorvastatin on postprandial lipaemia in overweight or obese women homozygous for apo E3. *Acta Cardiol* 2001;**56**:149–54.

392. Wang K-Y, Ting C-T. A randomized, double-blind, placebo-controlled, 8-week study to evaluate the efficacy and safety of once daily atorvastatin (10 mg) in patients with elevated LDL-cholesterol. *Jpn Heart J* 2001;**42**:725–38.

393. Watts GF, Chan DC, Barrett PHR, O'Neill FH, Thompson GR. Effect of a statin on hepatic apolipoprotein B-100 secretion and plasma campesterol levels in the metabolic syndrome. *Int J Obes Relat Metab Disord* 2003;**27**:862–5.

394. Wierzbicki AS, Lumb PJ, Chik G, Crook MA. Comparison of therapy with simvastatin 80 mg and atorvastatin 80 mg in patients with familial hypercholesterolaemia. *Int J Clin Pract* 1999; **53**:609–11.

395. Wolffenbuttel BHR, Mahla G, Muller D, Pentrup A, Black DM. Efficacy and safety of a new cholesterol synthesis inhibitor, atorvastatin, in comparison with simvastatin and pravastatin, in subjects with hypercholesterolemia. *Neth J Med* 1998;**52:** 131–7.

396. Wu C-C, Sy R, Tanphaichitr V, Hin ATT, Suyono S, Lee YT. Comparing the efficacy and safety of atorvastatin and simvastatin in Asians with elevated low-density lipoprotein-cholesterol – a multinational, multicenter, double-blind study. *J Formos Med Assoc* 2002;**101**:478–87.

397. Colhoun H, Betteridge J, Durrington P, Hitman G, Neil A, Livingstone S, *et al*. Collaborative Atorvastatin Diabetes Study. CARDS. 2004. URL: www.cardstrial.org. Accessed July 2004.

398. Pedersen TR, Kjekshus J, Pyorala K, Olsson AG, Cook TJ, Musliner TA, *et al*. Effect of simvastatin on ischemic signs and symptoms in the Scandinavian Simvastatin Survival Study (4S). *Am J Cardiol* 1998;**81**:333–5.

399. De Lemos JA, Blazing MA, Wiviott SD, Lewis EF, Fox KAA, White HD, *et al*., for the A to Z Investigators. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes. Phase Z of the A to Z trial. *JAMA* 2004;**292**:1307–16.

400. Freeman DJ, Norrie J, Sattar N, Neely RD, Cobbe SM, Ford I, *et al*. Pravastatin and the development of diabetes mellitus: evidence for a protective treatment effect in the West of Scotland Coronary Prevention Study. *Circulation* 2001; **103**:357–62.

401. Pedersen TR, Berg K, Cook TJ, Faergerman O, Haghfelt T, Kjekshus J, *et al*. Safety and tolerability of cholesterol lowering with simvastatin during 5 years in the Scandinavian Simvastatin Survival Study. *Arch Intern Med* 1996;**156**: 2085–92.

402. Collins R, Armitage J, Parish S, Sleigh P, Peto R, Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 2003;**361**:2005–16.

403. Department of Health. NHS reference costs 2003. London: Department of Health.

404. Stewart S, Blue L, Walker A, Morrison C, McMurray JJ. An economic analysis of specialist heart failure nurse management in the UK; can we afford not to implement it? *Eur Heart J* 2002;**23**:1369–78.

405. Nanas JN, Alexopoulos G, Anastasiou-Nana MI, Karidis K, Tirologos A, Zobolos S, *et al*. Outcome of patients with congestive heart failure treated with standard versus high doses of enalapril: a multicenter study. *J Am Coll Cardiol* 2000;**36**:2090–5.

406. Jones L, Griffin S, Palmer S, Main C, Orton V, Sculpher M, *et al*. A rapid and systematic review of the clinical effectiveness and cost-effectiveness of clopidogrel and modified-release dipyridamole in the secondary prevention of occlusive vascular events. http://www.nice.org.uk/pdf/ HTAreportvasculardisease.pdf

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