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Early high-dose lipid-lowering therapy to avoid cardiac events: a systematic review and economic evaluation

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Abstract

Early high-dose lipid-lowering therapy to avoid cardiac events: a systematic review and economic evaluation

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Objective: To evaluate the cost-effectiveness of high-dose statins (atorvastatin 80 mg/day, rosuvastatin 40 mg/day and simvastatin 80 mg/day) versus simvastatin 40 mg/day in individuals with acute coronary syndrome (ACS).
Data sources: Eleven bibliographic databases, including MEDLINE, CINAHL, EMBASE, Cochrane Database of Systematic Reviews, CENTRAL, DARE and NHS EED, were searched from inception to 2008.
Review methods: Data relating to study design, baseline patient characteristics, clinical or surrogate outcome, and adverse events were abstracted, and methodological quality was assessed according to standard methods. A synthesis of the available evidence was performed using a Bayesian mixed treatment meta-analysis using both direct and indirect evidence. An existing Markov model was modified to explore the costs and benefits associated with a lifetime of the differing treatment regimens.
Results: A total of 3345 titles and abstracts were screened for inclusion in the review of clinical effectiveness and 125 full papers retrieved and assessed in detail. Of these, 30 papers met the inclusion criteria for the review, describing 28 trials. The Bayesian mixed treatment meta-analysis demonstrated a clear dose–response relationship in terms of reductions in low-density lipoprotein cholesterol (LDL-c), with rosuvastatin 40 mg/day achieving the greatest percentage reduction (56%) from baseline, followed by atorvastatin 80 mg/day (52%), simvastatin 80 mg/day (45%) and simvastatin 40 mg/day (37%). Although serious adverse events with statins are rare, their incidence is likely to be greater with higher doses. Several clinical scenarios were used to explore the effect of adherence on the cost-effectiveness of the treatment regimens. Using a threshold of £20,000 per quality-adjusted life-year (QALY) and assuming that the benefits and adherence rates observed in the clinical trials are generalisable to a clinical setting and that individuals who do not tolerate the higher-dose statins are prescribed simvastatin 40 mg/day, then simvastatin 80 mg/day, atorvastatin 80 mg/day and rosuvastatin 40 mg/day would be considered cost-effective compared with simvastatin 40 mg/day in individuals with ACS. Simvastatin 80 mg/day is not well tolerated because of the high incidence rates of less severe adverse events such as myopathy (26-fold higher than rates in those receiving simvastatin 20 mg/day), which are likely to affect adherence levels in clinical practice. The reference case shows that rosuvastatin is the optimal treatment for individuals with a recent history of ACS using a threshold of £20,000 per QALY. However, this is based on the assumption that the additional incremental reductions in LDL-c observed in patients treated with rosuvastatin 40 mg/day compared with atorvastatin will transfer into corresponding changes in relative risks of cardiovascular events.
Conclusions: Simvastatin 80 mg/day cannot be recommended because of the high incidence rates of adverse events. If the cost of atorvastatin decreases in line with that observed for simvastatin when the patent ends in 2011, atorvastatin 80 mg/day will be the most cost-effective treatment for all thresholds; if the cost reduces to 25% of the current value, atorvastatin 80 mg/day will be the most cost-effective treatment for thresholds between £5000 and £30,000 per QALY. Large long-term RCTs reporting effects in terms of clinical events are required to determine the optimum statin use for subgroups.

Contents

Glossary and list of abbreviations

Glossary

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

Angina, unstable Unstable angina is a syndrome that is intermediate between stable angina and myocardial infarction (heart attack). It is characterised by an accelerating or 'crescendo' pattern of chest pain that lasts longer than in stable angina.

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).

Cardiovascular Pertaining to the heart and blood vessels.

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

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

Coronary artery disease The condition that arises from accumulation of plaque that narrows the inside diameter of arteries that supply the heart muscle with blood.

Coronary heart disease Narrowing or blockage of the coronary arteries, which 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).

Heterozygous Possessing two different forms of a particular gene.

High-density lipoprotein Class of lipoproteins, varying in their size (8–11 nm in diameter) and contents, which carry cholesterol from the body's tissues to the liver.

Homozygous Possessing two identical forms of a particular gene.

Hypercholesterolaemia High blood cholesterol.

Hyperlipidaemia High blood lipids.

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

Infarction Death of tissue following interruption of the blood supply.

Ischaemic heart disease Coronary heart disease.

Low-density lipoprotein Class and range of lipoprotein particles, varying in their size (18–25 nm in diameter) and contents, which carry fatty acid molecules in the blood and around the body for use by cells.

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 creatine kinase levels (greater than 10 times the upper limit of normal).

continued

Nephrotic syndrome A condition characterised by high levels of protein in the urine, low levels of protein in the blood, tissue swelling and high cholesterol.

Premature death Death before the age of 75 years.

Primary (familial) hypercholesterolaemia High cholesterol level caused by an underlying genetic defect.

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

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.

Secondary (non-familial) hypercholesterolaemia Hypercholesterolaemia caused by another disease state or by drug therapy. Also known as 'acquired' hypercholesterolaemia.

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

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.

Total cholesterol Total cholesterol is the sum of all of the cholesterol in the blood.

Triglycerides Glycerides in which the glycerol is esterified with 3- fatty acids. They constitute the majority of the fat that is stored in the fat tissue to be used as energy.

List of abbreviations

ACS	acute coronary syndrome
ALT	alanine aminotransferase
AMI	acute myocardial infarction
AST	aspartate aminotransferase
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CHD	coronary heart disease
CI	confidence interval
CK	creatine kinase
CVD	cardiovascular disease
EQ-5D	EuroQol 5 dimensions
HDL-c	high-density lipoprotein cholesterol
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
HRQoL	health-related quality of life
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
ITT	intention to treat
LDL-c	low-density lipoprotein cholesterol
MI	myocardial infarction
NICE	National Institute for Health and Clinical Excellence
OR	odds ratio
PCT	primary care trust
PTCA	percutaneous transluminal coronary angioplasty
PVD	peripheral vascular disease
QALY	quality-adjusted life-year
QUOROM	Quality of Reporting of Meta-analyses
RCT	randomised controlled trial
RR	relative risk
TIA	transient ischaemic attack

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

The aim of this research was to evaluate the cost-effectiveness of high-dose statins (atorvastatin 80 mg/day, rosuvastatin 40 mg/day and simvastatin 80 mg/day) versus simvastatin 40 mg/day in individuals with acute coronary syndrome (ACS) who have experienced a recent ACS event.

Methods

Eleven bibliographic databases covering the biomedical, scientific and grey literature were searched from inception to 2008 (supplemented by contact with experts in the field). Data relating to study design, baseline patient characteristics, clinical or surrogate outcome, and adverse events were abstracted and methodological quality was assessed. In addition, results of eligible randomised controlled trials (RCTs) were statistically synthesised (meta-analysed) where appropriate.

Meta-analyses of RCTs have shown that early, intensive statin therapy is of benefit in reducing death and cardiovascular events when prescribed immediately after an ACS compared with standard statin therapy. In the UK, most, if not all, initial prescribing is undertaken at the hospital and the decision to continue specialist prescribing outside the hospital is governed by the NHS primary care trusts (PCTs). However, there is great variation between PCTs in the management (including prescribing practices) of patients with ACS.

An existing Markov model was modified to explore the costs and benefits associated with a lifetime of the differing treatment regimens. Baseline transitions for the no treatment arm were derived from UK registries or UK-based RCTs. Costs and benefits were discounted at 3.5% in accordance with National Institute for Health and Clinical Excellence (NICE) guidelines for economic evaluations. A systematic review was used to identify RCTs of the different statin treatments. As there were no existing clinical data reporting outcomes in terms of hard clinical end points (e.g. numbers of myocardial infarctions or fatal events avoided) for rosuvastatin, benefits of statins were quantified in terms of a proxy measure, changes in low-density lipoprotein cholesterol (LDL-c). A Bayesian mixed treatment meta-analysis was used to combine the data from 28 clinical trials and a published relationship linking changes in LDL-c and relative risk of vascular events was utilised to estimate the benefit of treatment.

Results

A total of 3345 titles and abstracts were screened for inclusion in the review of clinical effectiveness. Of the titles and abstracts screened, 125 full papers were retrieved and assessed in detail. Of these, 30 papers met the inclusion criteria for the review, describing 28 trials. The Bayesian mixed treatment meta-analysis demonstrated a clear dose–response relationship in terms of reductions in LDL-c, with rosuvastatin 40 mg/day achieving the greatest percentage reduction (56%) from baseline, followed by atorvastatin 80 mg/day (52%), simvastatin 80 mg/day (45%) and simvastatin 40 mg/day (37%). Although the literature suggests that serious adverse events with statins are rare, their incidence is likely to be greater with higher doses. Adherence rates in general clinical practice are reported to be lower than those observed in clinical trials. However, there is some evidence that adherence could be higher in individuals with a history of cardiovascular disease, and in those who receive regular monitoring. Several clinical scenarios were used to explore the effect of adherence on the cost-effectiveness of the treatment regimens.

Using a threshold of £20,000 per quality-adjusted life-year (QALY), if it is assumed that the benefits and adherence rates observed in the clinical trials are generalisable to a clinical setting, or if it is assumed that individuals who do not tolerate the higher-dose statins are prescribed simvastatin 40 mg/day, then simvastatin 80 mg/day, atorvastatin 80 mg/day and rosuvastatin 40 mg/day would be considered cost-effective compared with simvastatin 40 mg/day in individuals with ACS. However, simvastatin 80 mg/day is not well tolerated because of the high incidence rates of less severe adverse events such as myopathy, which are likely to affect adherence levels in clinical practice. Recently

published results show that the incidence of myopathy in individuals receiving simvastatin 80 mg/day was 26 times higher than the incidence rate in those receiving simvastatin 20 mg/day. With rates of defined premyositis also increased, simvastatin 80 mg/day cannot be recommended.

The reference case shows that rosuvastatin is the optimal treatment for individuals with a recent history of ACS when using a threshold of £20,000 per QALY. However, this is based on the assumption that the additional incremental reductions in LDL-c observed in patients treated with rosuvastatin 40 mg/day compared with atorvastatin will transfer into corresponding changes in relative risks of cardiovascular events. If the cost of atorvastatin decreases in line with that observed for simvastatin when the patent ends in 2011, atorvastatin 80 mg/day will be the most cost-effective treatment for all thresholds; if the cost reduces to 25% of the current value, atorvastatin 80 mg/day will be the most cost-effective treatment for thresholds between £5000 and £30,000 per QALY.

Conclusion

The Bayesian mixed treatment meta-analysis demonstrated a clear dose–response relationship in terms of reductions in LDL-c, with rosuvastatin 40 mg/day achieving the greatest percentage reduction (56%), followed by atorvastatin 80 mg/day (52%), simvastatin 80 mg/day (45%) and simvastatin 40mg/day (37%). Although the literature suggests that serious adverse events are rare for all statins, incidence rates are likely to be higher for individuals receiving the more potent doses. Adherence rates in general clinical practice are lower than those reported in clinical trials, may be correlated with less severe adverse event rates such as for myalgia, and are likely to vary by statin type and dose.

Using a threshold of £20,000 per QALY, if it is assumed that the benefits and adherence rates observed in the clinical trials are generalisable to a clinical setting, or if it is assumed that individuals who do not tolerate the higher-dose statins are prescribed simvastatin 40 mg/day, then simvastatin 80 mg/day, atorvastatin 80 mg/day and rosuvastatin 40 mg/day would all be considered cost-effective compared with simvastatin 40 mg/day in individuals with ACS. However, because of high incidence rates of myopathy/myalgia in individuals receiving simvastatin 80 mg/day, adherence is likely to be poor.

With current treatment costs and existing evidence our results show that rosuvastatin 40 mg/day is potentially the most cost-effective treatment. However, these results are based on the assumption that the larger benefits in LDL-c measurements will produce an equivalent reduction in cardiovascular event rates. Although data on event rates supporting this assumption are beginning to emerge, the evidence base for atorvastatin 80 mg/day is more robust. If the cost of atorvastatin decreases when the patent ends in 2011, atorvastatin 80 mg/day will be the most cost-effective treatment.

Recommendations for further research

Large long-term RCTs reporting effects in terms of clinical events are required to determine the optimum statin use for subgroups. These include head-to-head studies comparing higher-dose statins with lower-dose statins, studies of rosuvastatin and studies comparing high-dose statin monotherapy with combination therapies such as low-dose statins combined with alternative lipid modifications. Studies recruiting high-risk groups typically excluded from RCTs, such as individuals with recent ACS events or heart failure, diabetics and Asian people, should be considered. Long-term registry data are required to determine adherence rates and adverse event profiles for individual statins and doses when used in general clinical practice. Studies exploring the effects of interventions designed to increase adherence to statin therapy in general clinical practice and in subgroups are also required.

Chapter 1
Introduction

Atherosclerotic cardiovascular disease (CVD) is a disorder of the heart and blood vessels, which can lead to cardiovascular events such as heart attack [myocardial infarction (MI)] and stroke. The most common form of CVD is coronary heart disease (CHD), also known as coronary artery disease (CAD) and ischaemic heart disease. CHD is caused by the narrowing of the arteries that supply the heart as a result of the build-up of fatty material called atheroma. The narrowing can cause MI, angina (pain or discomfort in the chest or neighbouring parts of the body because of insufficient oxygen reaching the heart) and other forms of chronic heart disease. Angina is usually classified as stable or unstable disease. Other forms of CVD are stroke, transient ischaemic attack (TIA), vascular dementia and peripheral vascular disease (PVD). CVD is the most common cause of death in the UK, accounting for over 208,000 deaths in 2005.[1] Approximately 49% of these deaths were from CHD and 28% from stroke. CVD is also a significant cause of morbidity and can have a major effect on quality of life.[2]

Cholesterol is a key component in the development of atherosclerosis (the accumulation of atheroma on the inner lining of the arteries). Mainly as a result of this, serum cholesterol increases the risk of CVD.[3,4] The lowering of cholesterol, whether by diet, drugs or other means, decreases CVD risk.[5] Statin therapy, associated principally with lowering concentrations of total cholesterol and low-density lipoprotein cholesterol (LDL-c), with smaller effects on raising high-density lipoprotein cholesterol (HDL-c) and decreasing triglyceride levels, can reduce the risk of cardiovascular events, morbidity and mortality.[6]

Although blood cholesterol is an important risk factor for CVD, cholesterol lowering with drug therapy is only one of a number of methods of reducing the risk.[7] Dietary and lifestyle modifications (e.g. weight loss, smoking cessation, aerobic exercise) are an integral part of risk management. If these are unsuccessful and the patient is at high risk, more effective therapy, including lipid-regulating drug therapy, is initiated.[8] The decision to initiate therapy with a lipid-regulating drug is generally based on an assessment of overall CVD risk.

Long-term statin therapy reduces CVD events, and the early period following an acute coronary syndrome (ACS; i.e. MI or unstable angina) or coronary revascularisation [coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA)] represents a stage when the individual is at highest risk of recurrent cardiovascular events and mortality.[9] Meta-analyses of randomised controlled trials (RCTs) have shown that early, intensive (high) dose statin therapy is of benefit in reducing death and cardiovascular events when prescribed immediately after an ACS compared with standard (moderate) statin therapy.[10,11] Most, if not all, initial prescribing for ACS in the UK is undertaken at the hospital and the decision to continue specialist prescribing outside the hospital is governed by the NHS primary care trusts (PCTs). Of the 152 NHS PCTs in England, recommendations for the management (including prescribing practices) of patients with ACS vary widely. Initiation of the standard dose would be on the first day of the event and duration is, in theory, for life.

Although there are numerous publications describing economic evaluations comparing the cost-effectiveness of individual statins versus placebo, the literature describing the cost-effectiveness of more potent dose statins compared with moderate doses is more limited. Lindgren *et al.*[12] performed an evaluation based on the IDEAL study, comparing atorvastatin (40/80 mg/day) with simvastatin (20/40 mg/day) in individuals with stable CAD. The authors reported that atorvastatin is moderately cost-effective and when using a threshold of €50,000 (£40,000) per quality-adjusted life-year (QALY) would be considered cost-effective in Denmark, Norway and Sweden (but not in Finland). Chan[13] compared the effectiveness of a higher-dose statin (assumed to be equivalent to atorvastatin 80 mg/day) with that of a conventional dose (assumed to be equivalent to simvastatin 20 mg/day) using a meta-analysis of effectiveness data from the Pravastatin or Atorvastatin Evaluation and Infection Therapy [PROVE-IT][14]

and the Aggrestat to Zocor [A to Z][15] RCTs. Chan reported a cost per QALY of US$12,900 (£6500) for a cohort with ACS in the USA. More recently, analysts in the UK[16] reported results in the region of £4400 per QALY for a cohort with ACS using the same effectiveness data as Chan *et al*.[13]

To our knowledge there are currently no published economic evaluations exploring the cost-effectiveness of atorvastatin 80 mg/day, rosuvastatin 40 mg/day or simvastatin 80 mg/day with that of simvastatin 40 mg/day in individuals with ACS.

Chapter 2

Aims and objectives

The aim of this research was to evaluate the cost-effectiveness of high-dose statins (atorvastatin 80 mg/day, rosuvastatin 40 mg/day and simvastatin 80 mg/day) versus simvastatin 40 mg/day in individuals with ACS. More specifically, the research aimed to:

1. evaluate the clinical effectiveness of higher-dose statins compared with simvastatin 40 mg/day in terms of mortality and cardiovascular morbidity
2. evaluate the adverse effect profile and toxicity associated with higher-dose statins compared with simvastatin 40 mg/day (the dose frequently prescribed for patients with ACS)
3. estimate the incremental cost-effectiveness of higher-dose statins in comparison with simvastatin 40 mg/day.

Chapter 3
Clinical evaluation

Systematic review of clinical efficacy data

Aims and objectives of the assessment

The aim of this review was to systematically evaluate and appraise the clinical effectiveness of switching from the current standard-dose statin (i.e. simvastatin 40 mg/day) to a high-dose statin (i.e. simvastatin 80 mg/day, atorvastatin 80 mg/day or rosuvastatin 40 mg/day) in patients who had recently had an MI or unstable angina, or who had recently undergone revascularisation and who were currently prescribed simvastatin 40 mg/day.

Methods for reviewing effectiveness

Identification of studies

Searches were carried out:

- to identify studies for inclusion in the review of clinical effectiveness
- to inform the development of the independent economic assessment.

Identification of studies for the review of clinical effectiveness

The search strategy used to identify studies for the review of clinical effectiveness is reported in this section.

The aim of the search was to provide as comprehensive a retrieval as possible of RCTs of early high-dose statin therapy for the prevention of cardiac events.

Sources searched

The following 11 electronic databases were searched from inception to 2008: MEDLINE (Ovid); CINAHL; EMBASE; the Cochrane Library including the Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register (CENTRAL), DARE, NHS EED and HTA database; Science Citation Index (SCI); National Research Register (NRR); and Current Controlled Trials. Searches were supplemented by hand searching relevant articles and contacting experts in the field.

Keyword strategies

Sensitive keyword strategies using freetext and, where available, thesaurus terms using Boolean operators and database-specific syntax were developed to search the electronic databases. Synonyms relating to the intervention (e.g. simvastatin, atorvastatin, rosuvastatin) were combined with synonyms relating to the condition (e.g. MI, unstable angina, CABG or PTCA). An example keyword strategy for the MEDLINE electronic database is provided in Appendix 1.

Search restrictions

A methodological filter aimed at restricting search results to RCTs was used in the searches of MEDLINE (Ovid), CINAHL, EMBASE and the Cochrane Library. Date limits or language restrictions were not used on any database. All searches were undertaken between February and March 2008.

Inclusion and exclusion criteria

Two reviewers independently screened all titles and abstracts. Full paper manuscripts of any titles/abstracts that were considered relevant by either reviewer were obtained where possible. The relevance of each study was assessed according to the criteria set out below. Studies that did not meet all of the criteria were excluded and their bibliographic details listed with reasons for exclusion in Appendix 3. Any disagreements were resolved by discussion.

Population

The relevant population was adults (defined as ≥ 18 years of age) who had ACS, i.e. those who had experienced an MI, been hospitalised for unstable angina or undergone a revascularisation procedure (CABG or PTCA) within the previous 28 days. In the absence of RCT evidence in the aforementioned population, the time since event was relaxed to 'less than 6 months'.

Interventions

Statins are a group of drugs that are widely used to reduce the level of cholesterol in the blood. Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, an enzyme involved in cholesterol synthesis. Inhibition of HMG-CoA

reductase lowers LDL-c levels by slowing down the production of cholesterol in the liver and increasing the liver's ability to remove the LDL-c already in the blood.[17]

At present, five statins have a marketing authorisation in the UK: atorvastatin, fluvastatin, pravastatin, rosuvastatin and simvastatin. These statins are generally indicated for the treatment of lipid disorders (e.g. primary hypercholesterolaemia or mixed dyslipidaemia) and the prevention of CVD.[18] Of these, fluvastatin and pravastatin are the least effective in reducing serum LDL-c[19] and thus are not commonly prescribed at standard or high dose in the UK.[4,5]

The intervention of interest for this research was simvastatin 80 mg/day, atorvastatin 80 mg/day or rosuvastatin 40 mg/day. In the absence of data on atorvastatin 80 mg/day or rosuvastatin 40 mg/day evidence will be included from studies using treatment doses of atorvastatin 40 mg/day or rosuvastatin 20 mg/day.

Comparators
The comparator treatment included simvastatin 40 mg/day.

Outcomes
As there are no published RCTs of rosuvastatin (at the time of writing) that assess the outcomes in terms of reductions in either cardiovascular events or mortality, the primary outcome measure included the following:

- effectiveness in reducing LDL-c.

Secondary outcome measures included the following:

- any adverse events
- health-related quality of life (HRQoL).

Study design
For the review of clinical effectiveness, only RCTs of at least 12 weeks' duration were included. Studies of less than 12 weeks' duration were excluded to allow for tachyphalaxis effects. In addition, current licensing authorities (i.e. European Medicines Agency) require a minimum follow-up of 3 months for surrogate end points in lipid-lowering drug therapies.[20] In the absence of sufficient evidence from trials of at least 12 weeks' duration the use of data from trials of less than 12 weeks' (but greater than 6 weeks') duration was considered. This decision was supported by clinical expert opinion. In addition, any dose titration or crossover studies were excluded.

Reviews of primary studies were not included in the analysis but were retained for discussion and identification of additional trials. The following publication types were excluded from the review: non-randomised studies (except for adverse events); animal models; preclinical and biological studies; narrative reviews, editorials, opinions; non-English language papers; and reports in which insufficient methodological details are reported to allow critical appraisal of the study quality.

Other
As it was anticipated that there may be no head-to-head trials comparing all of the treatments, an analysis using the methods of mixed treatment comparisons was planned. For this purpose the following studies were included:

- head-to-head RCTs comparing simvastatin 80 mg/day, atorvastatin 80 mg/day, rosuvastatin 40 mg/day with simvastatin 40 mg/day
- RCTs comparing simvastatin 40 mg/day, simvastatin 80 mg/day, atorvastatin 80 mg/day, rosuvastatin 40 mg/day with placebo
- RCTs comparing any of the following treatments: simvastatin 40 mg/day, simvastatin 80 mg/day, atorvastatin 80 mg/day, rosuvastatin 40 mg/day.

Data abstraction strategy
Data relating to both study design and quality were extracted by one reviewer into a standardised data extraction form. When multiple publications of the same study were identified, data were extracted and reported as a single study.

Critical appraisal strategy
The methodological quality of selected studies was assessed (by a single reviewer) based on Section 6 of the *Cochrane Handbook*[21] and consisted of the following factors: generation of allocation sequence, allocation concealment, blinding and loss to follow-up. Based on these criteria, studies were categorised as having a low, moderate or high risk of bias. Further details are provided in Appendix 4. The purpose of this assessment was to give a narrative account of trial quality for the reader and, where meta-analysis was appropriate, to inform potential exclusions from any sensitivity analysis.

Methods of data synthesis

Data were tabulated and discussed in a narrative review. A synthesis of the available evidence was performed using a mixed treatment meta-analysis using both direct and indirect evidence. The purpose of a mixed treatment meta-analysis is to combine the clinical evidence regarding the efficacy of all treatments for a specified indication. In general terms this consists of identifying a 'network of evidence' between the treatments. In the context of the present review this would mean that, for example, although high-dose statins (simvastatin 80 mg/day, atorvastatin 80 mg/day, rosuvastatin 40 mg/day) and standard-dose statins (simvastatin 40 mg/day) have not been directly compared in a trial, they can be indirectly compared as both may have been assessed against a common comparator (placebo). Similarly, other treatments that have been compared with placebo can also be included in the analysis and compared with high-dose statins and standard-dose statins. The common comparator need not be placebo and, within a mixed treatment meta-analysis, there can be more than one common comparator. For example, if simvastatin 80 mg/day and atorvastatin 80 mg/day have all been compared with placebo but rosuvastatin 40 mg/day has only been compared with atorvastatin 80 mg/day then rosuvastatin 40 mg/day can be indirectly compared with simvastatin 80 mg/day because rosuvastatin 40 mg/day can be linked into the network of evidence. The analysis was primarily for the purposes of decision-making and so its focus was to generate parameter estimates for the cost-effectiveness modelling.

The direct and indirect evidence of the effects of treatments on changes in LDL-c and relative risks (RRs) of differing event types[22] was synthesised using mixed treatment meta-analysis methods. The analysis was carried out from a Bayesian perspective and was implemented in the software package WinBUGS. The mixed treatment meta-analysis automatically induces correlation between parameters, including between the parameters representing population treatment means. In addition, the joint posterior distributions do not necessarily follow a standard parametric form. To preserve the properties of the joint posterior distribution when characterising uncertainty associated with the inputs in the economic model we sampled 5000 realisations from the joint posterior distribution.

To translate changes in LDL-c values observed in the RCTs into benefits in terms of clinical events, the results from a meta-analysis of 90,056 patients in 14 RCTs of statins was utilised.[6] The analysts reported that a 1 mmol/l reduction in LDL-c was associated with a 23% reduction in the 5-year incidence of a major coronary event (non-fatal MI or CHD death), and a 21% reduction in major coronary events, coronary revascularisation and stroke over 5 years. The proportional reduction varied according to event type and the RRs corresponding to a 1 mmol/l reduction in LDL-c are provided in *Table 1*.

A number of assumptions were used to model these relationships:

- the relative risk for unstable angina is equal to the RR for non-fatal MI
- the RR for any stroke is representative of the RR for non-fatal stroke
- the relationship between reductions in LDL-c and first event observed in the studies is also representative of corresponding reductions in subsequent events
- the proportional reduction in event rate per mmol/l reduction in LDL-c is independent of presenting level of lipids ($p = 0.5$)[6]
- the proportional reduction in event rate per mmol/l reduction in LDL-c is independent of

TABLE 1 *Relative risk in event per 1 mmol/l reduction in LDL-c*

Event type	RR (95% CI)	Source
Stroke death	0.91 (0.74 to 1.11)	Baigent *et al.*, 2005[6]
Non-fatal MI	0.74 (0.70 to 0.79)	Baigent *et al.*, 2005[6]
CHD death	0.81 (0.75 to 0.87)	Baigent *et al.*, 2005[6]
Any stroke	0.83 (0.78 to 0.88)	Baigent *et al.*, 2005[6]
Rehospitalisation for unstable angina	0.74 (0.70 to 0.79)	Assumed same as non-fatal MI

CHD, coronary heart disease; CI, confidence interval; LDL-c, low-density lipoprotein cholesterol; MI, myocardial infarction; RR, relative risk.

baseline prognostic factors such as sex ($p = 0.1$), diabetes status ($p = 0.8$) or CVD history ($p = 0.2$).[6]

Bayesian model description

The statistical model was defined as follows. We let the mean percentage change from baseline, y_{ij}, be such that:

$$y_{jk} \sim N(\mu_{jk}, \sigma^2/n_{jk})$$

where y_{jk} is the observed mean for the k^{th} treatment within the j^{th} study with mean μ_{jk} and variance σ^2/n_{jk}. The μ_{jk} are modelled such that:

$$\mu_{jk} = \varphi_{jb} + \theta_{jkb}$$

where φ_{jb} represents the mean on baseline treatment b in the j^{th} study, and θj_{kb} is the trial-specific effect of treatment k relative to treatment b. We defined the control treatment group to be placebo and the treatment effects relative to placebo as the basic parameters.

We give the unknown parameters weak prior distributions such that the basic parameters are $N(0, 1000)$, $\log(\sigma^2) \sim$ Uniform(–50,50), and the placebo between-study standard deviation is distributed Uniform(0,50).

Clinical effectiveness results

Number of studies identified

A total of 3345 titles and abstracts were screened for inclusion in the review of clinical effectiveness. Of the titles and abstracts screened, 125 full papers were retrieved and assessed in detail. A flow chart describing the process of identifying relevant literature can be found in Appendix 2.

Number and type of studies included

To date, no studies (of greater than 12 weeks' duration) were identified that assessed the efficacy of high-dose statins (simvastatin 80 mg/day, atorvastatin 80 mg/day, rosuvastatin 40 mg/day) compared with standard-dose statins (with simvastatin 40 mg/day) in patients with recent (defined as less than 28 days) MI, with unstable angina or who had undergone revascularisation (CABG or PTCA). In the absence of such data we identified and included 28 RCTs of at least 6 weeks' duration (with surrogate end-point data in any adults over 18 years of age) that would enable a mixed treatment comparison. Further details are provided in Summary of included studies.

Number and type of studies excluded

A total of 95 papers were excluded. Although several trials investigated the use of high-dose statins (simvastatin 80 mg/day or atorvastatin 80 mg/day) in patients with post-ACS (PROVE-IT TIMI 22[14] and A to Z[15]) or chronic CAD (TNT,[23] IDEAL,[24] REVERSAL[25] and SAGE[26]), these were excluded as they used an incorrect comparator. Further details and a full list of the excluded publications with rationale are presented in Appendix 3.

Summary of included studies (design and patient characteristics)

The design characteristics of each of the included studies is summarised in *Table 2*. The treatment duration in the trials ranged from 6 weeks[27–33] to 5 years[34,35] with sample sizes ranging from 20[36] to 20,536.[34,35] The primary outcome measure in the majority of studies included surrogate end points such as percentage change in LDL-c from baseline.[28–30,32,33,37–43]

Participants varied widely between trials but generally were at high risk of CVD with mean baseline LDL-c levels ranging from 2.84 mmol/l[36] to 6.38 mmol/l.[42] All of the participants in the trials were aged 18 years or over with a mean age range from 40.2[44] to 75 years.[45] Most studies generally excluded patients with MI, angina, coronary angioplasty or CABG within 3 or 6 months of study entry (prior randomisation). Further details of the patient characteristics at baseline are provided in *Table 3*.

Quality and characteristics of identified studies

The quality assessment of each included study is summarised in *Table 4*. Nine of the 28 studies gave clear descriptions of how random numbers were generated: eight trials utilised computer-generated random numbers and one trial randomised by telephone through a call centre. The remaining 19 studies did not fully specify how random numbers were generated for randomisation.

Two studies clearly described the method of allocation concealment: Charles-Schoeman *et al.*[36] used pharmacy-controlled randomisation and

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TABLE 2 *Summary of design and patient characteristics*

Study	Study name	Design	Intervention groups, dose, timings	Numbers randomised	Mean duration of follow-up	Outcomes (primary)
Aronow, 2003[45]	–	R, PC	T1: Simvastatin 40 mg/day T2: Placebo	T1: 34 T2: 35	6 months	Onset of intermittent claudication
Ballantyne *et al.*, 2003[46]	CHESS	R, DB	T1: Atorvastatin 80 mg/day T2: Simvastatin 80 mg/day	T1: 46 T2: 453	24 weeks	% change from baseline in HDL-c (average across weeks 6 and 12)
Ballantyne *et al.*, 2003[37]	–	Multiarm, R, DB, PC, 2×5 factorial design	T1: Atorvastatin 80 mg/day T2: Placebo	T1: 62 (assumed)[a] T2: 60	12 weeks	% change from baseline in LDL-c
Bauersachs *et al.*, 2007[47]	–	R, DB, PC	T1: Atorvastatin 80 mg/day T2: Placebo	T1: 14 T2: 14	9 months	% change from baseline in left ventricular mass
Bays *et al.*, 2004[38]	–	Multiarm, R ,DB, PC, 2×2 factorial design	T1: Simvastatin 40 mg/day T2: Simvastatin 80 mg/day T3: Placebo	T1: 154 T2: 156 T3: 148	12 weeks	% change from baseline in LDL-c
Charles-Schoeman *et al.*, 2007[36]	–	R, DB, PC	T1: Atorvastatin 80 mg/day T2: Placebo	T1: 11 T2: 9	12 weeks	Change in HDL anti-inflammatory properties and high-sensitivity C-reactive protein
Cowell *et al.*, 2005[48]	SALTIRE	R, DB, PC	T1: Atorvastatin 80 mg/day T2: Placebo	T1: 77 T2: 78	25 months (median) (range 7–36 months)	Progression of stenosis
Davidson *et al.*, 2002[39]	–	Multiarm, R, DB, PC, 2×5 factorial design	T1: Simvastatin 40 mg/day T2: Simvastatin 80 mg/day T3: Placebo	T1: 65 T2: 67 T3: 70	12 weeks	% change from baseline in LDL-c
Dobs *et al.*, 2000[44]	–	Multiarm, R, DB, PC	T1: Simvastatin 40 mg/day T2: Placebo	T1: 41 T2: 40	24 weeks	Gonadal testosterone production and spermatogenesis
Dobs *et al.*, 2000[49]	–	R, DB, PC	T1: Simvastatin 80 mg/day T2: Placebo	T1: 42 T2: 39	12 weeks	Peak cortisol response to Cortrosyn™ (Amphastar Pharmaceuticals)

continued

TABLE 2 *Summary of design and patient characteristics (continued)*

Study	Study name	Design	Intervention groups, dose, timings	Numbers randomised	Mean duration of follow-up	Outcomes (primary)
Goldberg *et al.*, 2004[50]	–	Multiarm, R, DB, PC, 2×2 factorial design	T1: Simvastatin 40 mg/day T2: Simvastatin 80 mg/day T3: Placebo	T1: 90 T2: 87 T3: 93	12 weeks	% change from baseline in LDL-c
Heart Protection Study Collaborative Group, 2002[34] and 2005[35]	HPS	R, PC, 2×2 factorial design	T1: Simvastatin 40 mg/day T2: Placebo	T1: 10,269 T2: 10,267	5 years	All-cause mortality
Isaacsohn *et al.*, 2003[27]	–	Multiarm, R, DB, PC	T1: Simvastatin 40 mg/day T2: Simvastatin 80 mg/day T3: Placebo	T1: 90 T2: 87 T3: 93	6 weeks	% change from baseline in triglycerides
Jones *et al.*, 1998[40]	CURVES	Multiarm, R, OL	T1: Atorvastatin 80 mg/day T2: Simvastatin 40 mg/day	T1: 10 T2: 61	8 weeks	% change from baseline in LDL-c
Jones *et al.*, 2003[28]	STELLAR	Multiarm, R, OL	T1: Rosuvastatin 40 mg/day T2: Atorvastatin 80 mg/day T3: Simvastatin 80 mg/day T4: Simvastatin 40 mg/day	T1: 158 T2: 167 T3: 165 T4: 159	6 weeks	% change from baseline in LDL-c
Karalis *et al.*, 2002[29]	CHALLENGE	Multiarm, R, OL	T1: Atorvastatin 80 mg/day T2: Simvastatin 80 mg/day	T1: 207 T2: 207	6 weeks	% change from baseline in LDL-c
Keech *et al.*, 1994[43]	Oxford Cholesterol Study	Multiarm, R, DB, PC	T1: Simvastatin 40 mg/day T2: Placebo	T1: 206 T2: 207	50 months	Lipids (including LDL-c)
Meredith, 2007[51]	ESP	Multiarm, R, DB, PC	T1: Simvastatin 80 mg/day T2: Placebo	T1: 35 T2: 24	12 weeks	Dose–response relationship for C-reactive protein
Mohler, 2003[52]	–	Multiarm, R, DB, PC	T1: Atorvastatin 80 mg/day T2: Placebo	T1: 120 T2: 114	12 months	Change in maximal walking time
Ose *et al.*, 1998[42]	WSEDP	R, DB	T1: Simvastatin 80 mg/day T2: Simvastatin 40 mg/day	T1: 355 T2: 229	24 weeks	% change from baseline in LDL-c
Schneck, 2003[30]	4522IL/0033	Multiarm, R, DB	T1: Rosuvastatin 40 mg/day T2: Atorvastatin 80 mg/day	T1: 45 T2: 41	6 weeks	% change from baseline in LDL-c

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Study	Study name	Design	Intervention groups, dose, timings	Numbers randomised	Mean duration of follow-up	Outcomes (primary)
Schwartz *et al.*, 2001[53] and Olsson *et al.*, 2005[54]	MIRACL	R, DB, PC	T1: Atorvastatin 80 mg/day T2: Placebo (initiated between 24 and 96 hours after hospital admission)	T1: 1538 T2: 1548	16 weeks	Composite of death, non-fatal MI, cardiac arrest with resuscitation or recurrent symptomatic myocardial ischaemia with objective evidence and requiring emergency rehospitalisation
Sdringola, 2008[55]		R, DB, PC	T1: Atorvastatin 80 mg/day T2: Placebo	T1: 72 T2: 73	6 months	Stress-induced perfusion defects
Stein *et al.*, 2007[31]		R, OL	T1: Rosuvastatin 40 mg/day T2: Simvastatin 80 mg/day	T1: 308 T2: 318	6 weeks	Shift in urine dipstick protein
Stein *et al.*, 1998[41]		R, DB	T1: Simvastatin 80 mg/day T2: Simvastatin 40 mg/day	T1: 314 T2: 207 (randomisation 3:2 ratio)	24 weeks	% change from baseline in LDL-c
Vita *et al.*, 2000[56]	CARATS	R, DB, PC	T1: Simvastatin 40 mg/day T2: Placebo	T1: 34 T2: 26	6 months	Coronary endothelial vasomotor function
Zeneca Pharmaceuticals, 2000[32] (unpublished study)	4522IL/0008	Multiarm, R, PC (DB rosuvastatin, placebo and OL atorvastatin)	T1: Rosuvastatin 40 mg/day T2: Atorvastatin 80 mg/day T3: Placebo	T1: 18 T2: 13 T3: 13	6 weeks	% change from baseline in LDL-c
Zeneca Pharmaceuticals, 2000[33] (unpublished study)	4522IL/0023	Multiarm, R, DB, PC	T1: Rosuvastatin 40 mg/day T2: Placebo	T1: 16 T2: 17	6 weeks	% change from baseline in LDL-c

DB, double blind; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; MI, myocardial infarction; OL, open label; PC, placebo controlled; R, randomised.

a Data from these papers were derived from a pooled statin group. As patients were equally randomised, it is assumed that the baseline data from the pooled statin groups would be similar to the statin intervention dose under consideration.

TABLE 3 *Summary of patient characteristics at baseline*

Study	Description	Exclusion criteria (brief)	Mean age (years)	Male
Aronow, 2003[45]	Patients with intermittent claudication due to PAD	No MI, angina pectoris, coronary angioplasty or CABG within 6 months prior to randomisation	T1: 75 (SD 8) T2: 74 (SD 8)	T1: 55% T2: 52%
Ballantyne *et al.*, 2003[46]	Hypercholesterolaemic adults	Renal insufficiency or significant proteinuria, secondary cause of hypercholesterolaemia, active liver disease	T1: 56.5 (SD 9.8) T2: 56.5 (SD 10.5)	T1: 55.0% T2: 56.1%
Ballantyne *et al.*, 2003[37]	Adult men and women (aged ≥ 18 years) with primary hypercholesterolaemia (LDL-c concentration between 3.75 and 6.48 mmol/l and TG level of ≤ 3.95 mmol/l after 6–12 weeks of lipid-lowering drug washout)	CHF, uncontrolled cardiac arrhythmias, MI, CABG or angioplasty within 6 months of study entry; unstable/severe PAD within 3 months of entry; UA, impaired renal function	T1: 57.8 (SD 11.7) (assumed)[a] T2: 56.9 (SD 12.1)	T1: 38% (assumed)[a] T2: 48%
Bauersachs *et al.*, 2007[47]	Patients with hypertrophic cardiomyopathy	LDL-c > 5.70 mmol/l, history of statin therapy within last 6 months, arterial hypertension, signs of pulmonary congestion, contraindications for CMR scanning	T1: 44.2 (SD 18.3) T2: 52.0 (SD 12.8)	T1: NR T2: NR
Bays *et al.*, 2004[38]	Adult men and women with primary hypercholesterolaemia (LDL-c concentration between 3.77 and 6.50 mmol/l and TG level of ≤ 3.85 mmol/l after 6–8 weeks of lipid-lowering drug washout)	< 50% of ideal body weight or < 100 lb, hypersensitivity to statins	T1: 54.9 (SD 11.2) (assumed)[a] T2: 54.9 (SD 11.2) T3: 56.0 (SD 10.8)	T1: 49.4% (assumed)[a] T2: 49.4% (assumed)[a] T3: 43.9%
Charles-Schoeman *et al.*, 2007[36]	Adult men and women (aged > 18 years) with chronic rheumatoid arthritis (mean duration 16 years)	History of CAD or coronary risk equivalents or candidates for lipid-lowering therapy	T1: 58 (SD 12) T2: 53 (SD 10)	T1: 0% T2: 11%

Ethnicity	Disease status and time/type of event	History of diabetes	Socioeconomic status	Current smoker	Mean BMI (kg/m^2) or BMI > 30 kg/m^2 (%)
T1: NR T2: NR	Prior MI > 6 months: T1: 61% T2: 55%	T1: 48% T2: 41%	T1: NR T2: NR	T1: 19% T2: 17%	T1: 13% T2: 10%
White: T1: 85.8% T2: 89.2% Black: T1: 8.4% T2: 6.6% Hispanic: T1: 3.4% T2: 2.9% Other: T1: 11.9% T2: 11.0%	CHD: T1: 46.0% T2: 48.0%	T1: 11.9% T2: 11.0%	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR
White: T1: 83% (assumed)[a] T2: 82%	CHD: T1: 9% (assumed)[a] T2: 8% No CHD and no risk factors: T1: 22% (assumed)[a] T2: 27%	T1: 4% T2: 2%	T1: NR T2: NR	T1: 13% T2: 15%	T1: 13% T2: 10%
T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	T1: 26.2 (SD 5.2) T2: 26.8 (SD 2.4)
White: T1: 87.0% (assumed)[a] T2: 87.0% (assumed)[a] T3: 89.2%	T1: NR T2: NR T3: NR	T1: NR T2: NR T3: NR	T1: NR T2: NR T3: NR	T1: NR T2: NR T3: NR	T1: 28.3 (SD 5.1) (assumed)[a] T2: 28.3 (SD 5.1) (assumed)[a] T1: 28.0 (SD 4.9)
T1: NR T2: NR	T1: NR T2: NR	T1: 0% T2: 0%	T1: NR T2: NR	T1: 18% T2: 0%	T1: NR T2: NR

continued

TABLE 3 *Summary of patient characteristics at baseline (continued)*

Study	Description	Exclusion criteria (brief)	Mean age (years)	Male
Cowell *et al.*, 2005[48]	Adult men and women (aged >18 years) with calcific aortic stenosis	Chronic liver disease, history of alcohol or drug misuse, severe mitral stenosis or aortic regurgitation, TC < 4.0 mmol/l	T1: 68 (SD 11) T2: 68 (SD 10)	T1: 68% T2: 72%
Davidson *et al.*, 2002[39]	Adult men and women (aged ≥ 18 years) with primary hypercholesterolaemia (LDL-c concentration between 3.77 and 6.50 mmol/l and TG level of ≤ 3.85 mmol/l after adequate lipid-lowering drug washout)	CHF; uncontrolled cardiac arrhythmias; UA; MI, CABG or angioplasty within 6 months of study entry; unstable/severe PAD within 3 months of entry; impaired renal function	T1: 56.4 (SD NR) (assumed)[a] T2: 56.4 (SD NR) (assumed)[a] T3: 58.8 (SD NR)	T1: 42% (assumed)[a] T2: 42% (assumed)[a] T3: 44%
Dobs *et al.*, 2000[44]	Adult men (aged 21–55 years) with type IIa or IIb hypercholesterolaemia	Fasting triglycerides > 350 mg/dl, homozygous familial hypercholesterolaemia, hyperlipidaemia types I, III, IV or V or secondary hypercholesterolaemia, active liver disease, and either MI, PTCA, CABG or UA within 4 months of screening	T1: 41.2 (SD 6.4) T2: 40.2 (SD 7.5)	T1: 100% T2: 100%
Dobs *et al.*, 2000[49]	Adult men (aged 21–50 years) with primary hypercholesterolaemial (LDL-c > 145 mg/dl and TG < 350 mg/dl	Liver aminotransferases and creatine kinase < 20% and < 50% above the upper limit of normal respectively	T1: NR T2: NR [overall, mean age 45.4 (SD 11.46) years]	T1: 100% T2: 100%

Ethnicity	Disease status and time/type of event	History of diabetes	Socioeconomic status	Current smoker	Mean BMI (kg/m^2) or BMI > 30 kg/m^2 (%)
T1: NR T2: NR	CHD: T1: 23.4% T2: 26.9% Cerebrovascular disease: T1: 11.7% T2: 14.1% PVD: T1: 6.5% T2: 16.7%	T1: 3.9% T2: 5.1%	T1: NR T2: NR	T1: 27.3% T2: 28.2%	T1: NR T2: NR
White: T1: 90% (assumed)[a] T2: 90% (assumed)[a] T3: 96% Black: T1: 5% (assumed)[a] T2: 5% (assumed)[a] T3: 1%	CHD: T1: 6% (assumed)[a] T2: 6% (assumed)[a] T3: 7%	T1: 3% (assumed)[a] T2: 3% (assumed)[a] T3: 9%	T1: NR T2: NR T3: NR	T1: 16% (assumed)[a] T2: 16% (assumed)[a] T3: 11%	T1: NR T2: NR T3: NR
White: T1: 93% T2: 80% Black: T1: 5% T2: 8% Hispanic: T1: 2% T2: 10% Oriental: T1: 0% T2: 3%	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR
T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR

continued

TABLE 3 *Summary of patient characteristics at baseline (continued)*

Study	Description	Exclusion criteria (brief)	Mean age (years)	Male
Goldberg *et al*., 2004[50]	Adult men and women (aged ≥ 18 years) with primary hypercholesterolaemia (LDL-c concentration between 3.77 and 6.50 mmol/l and TG level of ≤ 3.85 mmol/l after 6–8 weeks of lipid-lowering drug washout)	CHF; uncontrolled cardiac arrhythmias, unstable/severe PAD within 3 months of entry; MI, CABG or angioplasty within 3 months of study entry; impaired renal function	T1: NR T2: NR T3: NR (age range 22–81 years)	T1: 49% (assumed)[a] T2: 49% (assumed)[a] T3: 41%
Heart Protection Study Collaborative Group, 2002[34] and 2005[35]	Adult men and women (aged 40–80 years) with coronary disease, other occlusive arterial disease or diabetes	Chronic liver disease, abnormal liver function, severe liver disease or impaired renal function, severe heart failure	T1: NR T2: NR (age range 40–80 years)	T1: NR T2: NR (overall, 75% male)
Isaacsohn *et al*., 2003[27]	Adult men and women (aged 18–70 years) with average fasting TG levels of 300–900 mg/dl and LDL-c ≥ 1.9 mmol/l	Renal insufficiency, active liver disease, acute coronary insufficiency or vasospastic angina, and no MI; undergone PTCA or CABG within 3 months before study	T1: NR T2: NR (overall, 51 years)	T1: NR T2: NR (overall, 73% male)
Jones *et al*., 1998[40]	Adult men and women (aged 18–80 years) with hypercholesterolaemia (LDL-c concentration ≥ 4.2 mmol/l and TG level of ≤ 4.5 mmol/l	Primary hyperthyroidism, nephrotic syndrome, type 1 or uncontrolled type 2 diabetes, hepatic dysfunction; MI, CABG, angioplasty or severe or UA within 3 months before study	T1: NR T2: NR (overall, mean age 55 years)	T1: NR T2: NR (overall, 59% male)
Jones *et al*., 2003[28]	Adult men and non-pregnant women (aged ≥ 18 years) with hypercholesterolaemia (LDL-c concentration between 4.14 and 6.47 mmol/l and TG level of ≤ 4.52 mmol/l)	History of sensitivity to statins, history of heterozygous or homozygous familial hypercholesterolaemia or familial dysbeta-lipoproteinaemia, history of drug or alcohol abuse	T1: 58 (SD 12) (assumed)[a] T2: 58 (SD 12) (assumed)[a] T3: 58 (SD 12) (assumed)[a] T4: 58 (SD 12) (assumed)[a]	T1: 48% (assumed)[a] T2: 50% (assumed)[a] T3: 49% (assumed)[a] T4: 49% (assumed)[a]

Ethnicity	Disease status and time/type of event	History of diabetes	Socioeconomic status	Current smoker	Mean BMI (kg/m^2) or BMI > 30 kg/m^2 (%)
White: T1: 79% (assumed)[a] T2: 79% (assumed)[a] T3: 81% Black: T1: 4% (assumed)[a] T2: 4% (assumed)[a] T3: 5%	T1: NR T2: NR T3: NR	T1: NR T2: NR T3: NR	T1: NR T2: NR T3: NR	T1: NR T2: NR T3: NR	T1: NR T2: NR T3: NR
T1: NR T2: NR	T1: NR T2: NR (overall, 41% with previous MI, 24% other CHD, 35% no CHD)	T1: NR T2: NR (overall, 19% had diabetes)	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR
T1: NR T2: NR (overall, 93% white)	T1: NR T2: NR (overall, 3% with CVD)	T1: NR T2: NR (overall, 16% had diabetes)	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR
T1: NR T2: NR (overall, 90% white)	T1: NR T2: NR (overall, 17% had established CAD)	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR
White: T1: 86% (assumed)[a] T2: 85% (assumed)[a] T3: 86% (assumed)[a] T4: 86% (assumed)[a] Black: T1: 8% (assumed)[a] T2: 8% (assumed)[a] T3: 8% (assumed)[a] T4: 8% (assumed)[a]	CVD: T1: 18% (assumed)[a] T2: 20% (assumed)[a] T3: 20% (assumed)[a] T4: 20% (assumed)[a]	T1: 8% (assumed)[a] T2: 7% (assumed)[a] T3: 7% (assumed)[a] T4: 7% (assumed)[a]	T1: NR T2: NR T3: NR T4: NR	T1: NR T2: NR T3: NR T4: NR	T1: 35% (assumed)[a] T2: 36% (assumed)[a] T3: 34% (assumed)[a] T4: 34% (assumed)[a]

continued

TABLE 3 *Summary of patient characteristics at baseline (continued)*

Study	Description	Exclusion criteria (brief)	Mean age (years)	Male
Karalis *et al*., 2002[29]	Adult men and women (aged 18–80 years) with dyslipidaemia, with or without CHD	BMI > 32 kg/m^2, uncontrolled hyperthyroidism, nephrotic syndrome, renal dysfunction, type 1 or uncontrollled type 2 diabetes, hepatic dysfunction; MI, revascularisation procedure or severe or UA within 3 months before screening	T1: 61.3 (SD NR) T2: 61.5 (SD NR)	T1: 62% T2: 58%
Keech *et al*., 1994[43]	Adult men and women (aged 40–75 years) with a higher than average risk of CHD because of a history of MI angina pectoris, stroke, TIA, PVD, treated diabetes mellitus or treated hypertension	TC < 3.5 mmol/l; stroke, MI or hospital admission for UA within 6 months of study entry	T1: 63.4 (SD 7.6) T2: 63.7 (SD 7.3)	T1: 85% T2: 84%
Meredith, 2007[51]	Adult men and women who have undergone elective coronary angiography and found to have evidence of stable but discernible CAD and baseline hs-CRP > 3 mg/l	Hospitalised within 90 days with ACS, undergone coronary revascularisation within 90 days or known acute or long-term inflammatory process	T1: 70 (SD 10) T2: 65 (SD 11)	T1: 71% T2: 62%
Mohler, 2003[52]	Adult men and women (> 25 years) with stable intermittent claudication > 6 months	MI, coronary revascularisation, peripheral vascular surgery or PCI within 6 months; UA within previous 3 months; stroke or TIA within 6 months; DVT within previous 3 months	T1: 68 (SD NR) T2: 67 (SD NR)	T1: 79% T2: 77%
Ose *et al*., 1998[42]	Adult men and women (between 21 and 70 years) with hypercholesterolaemia (LDL-c ≥ 4.14 mmol/l and TG ≤ 3.95 mmol/l)	Uncontrolled hypertension, types I, III, IV or V hyperlipidaemia, homozygous familial hypercholesterolaemia and secondary hypercholesterolaemia, active liver disease or creatine kinase > 50% over upper normal limit; MI, acute coronary insufficiency, CABG within 3 months of study entry	T1: 51.6 (SD 11.7) T2: 50.1 (SD 12.0)	T1: 55.2% T2: 56.8%
Schneck, 2003[30]	Adult men and women (> 18 years) with hypercholesterolaemia and without active arterial disease within 3 months of study entry or uncontrolled hypertension	Heterozygous or homozygous familial hypercholesterolaemia or known type III hyperlipoproteinaemia	T1: 57.2 (SD 9.5) T2: 53.8 (SD 11.7)	T1: 51.1% T2: 68.3%

Ethnicity	Disease status and time/type of event	History of diabetes	Socioeconomic status	Current smoker	Mean BMI (kg/m^2) or BMI > 30 kg/m^2 (%)
White: T1: 95% T2: 92%	CHD: T1: 62% T2: 67% < two risk factors and no CHD: T1: 12% T2: 12%	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	T1: 26.9 (SD NR) T2: 27.4 (SD NR)
T1: NR T2: NR	CHD: T1: 81% T2: 85% Stroke: T1: 9% T2: 10%	T1: 3% T2: 3% (treated diabetes)	T1: NR T2: NR	T1: 15% T2: 14%	T1: 26.4 (SD 3.3) T2: 26.4 (SD 3.5)
T1: NR T2: NR	MI: T1: 20% T2: 25% Revascularisation: T1: 29% T2: 33%	T1: 11% T2: 17%	T1: NR T2: NR	T1: 20% T2: 21%	T1: NR T2: NR
White: T1: 95% T2: 91% Black: T1: 3% T2: 5%	T1: NR T2: NR	T1: 18% T2: 15%	T1: NR T2: NR	T1: 35% T2: 46%	T1: 27.1 (SD NR) T2: 27.4 (SD NR)
White: T1: 82.3% T2: 83.8% Hispanic: T1: 12.4% T2: 10.0% Multiracial: T1: 3.3% T2: 3.1% Other: T1: 2.0% T2: 3.1%	CHD and/or coronary revascularisations: T1: 20.1% T2: 16.1%	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR
White: T1: 86.7% T2: 95.1% Black: T1: 4.4% T2: 0%	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	T1: 27.8 (SD 4.1) T2: 27.9 (SD 4.5)

continued

TABLE 3 *Summary of patient characteristics at baseline (continued)*

Study	Description	Exclusion criteria (brief)	Mean age (years)	Male
Schwartz *et al*., 2001[53] and Olsson *et al*., 2005[54]	Adult men and women (> 18 years) with acute coronary syndrome (UA and non-Q-wave acute MI)	Serum TC > 7 mmol/l at screening; Q-wave acute MI within preceding 4 weeks; CABG within 3 months; PCI within 6 months; severe CHF	T1: 65 (SD 12) T2: 65 (SD 12)	T1: 64.5% T2: 65.9%
Sdringola, 2008[55]	Adult men and women (> 18 years) with documented CAD (including history of MI)	UA within 3 months of randomisation, symptomatic heart failure, left ventricular ejection fraction ≤ 35%, significant valve dysfunction; MI or revascularisation procedure within 6 months of randomisation or planned during study period; stroke or TIA within 3 months of screening	Median: T1: 70 (SD NR) T2: 64 (SD NR)	T1: 93% T2: 85%
Stein *et al*., 2007[31]	Adult men and women (> 18 years) with severe hypercholesterolaemia including heterozygous FH (LDL-c between 4.52 and 9.04 mmol/l and TG < 4.52 mmol/l)	Active arterial liver disease within 3 months of study entry, serum creatinine > 2.5 mg/dl, renal transplantation	T1: 55.7 (SD 13.7) T2: 55.8 (SD 13.7)	T1: 43.5% T2: 40.3%
Stein *et al*., 1998[41]	Adult men and women (between 21 and 70 years) with hypercholesterolaemia	Uncontrolled hypertension; types I, III, IV or V hyperlipidaemia; homozygous familial hypercholesterolaemia or secondary hypercholesterolaemia; MI, PTCA, CABG within 3 months of study entry	T1: 54.3 (SD 9.6) T2: 55.5 (SD 10.3)	T1: 64% T2: 55%
Vita *et al*., 2000[56]	Adult men and women (between 25 and 80 years) with angiographically documented CAD (diffuse luminal irregularities of ≥ one vessel with > 50% stenosis)	Hypertension, cigarette smoking within 1 month, diabetes mellitus, CABG within 6 months, coronary angioplasty within 2 weeks	T1: 55 (SD NR) T2: 55 (SD NR)	T1: 82% T2: 88%
Zeneca Pharmaceuticals, 2000[32] (unpublished study)	Adult men (aged 18–70 years) and postmenopausal women (aged 50–70 years) with LDL-c from 4.14 to < 6.21 mmol/l and TG < 3.39 mmol/l	Active liver disease or hepatic dysfunction, active arterial disease	T1: NR T2: NR (overall, mean age 55.4 years)	T1: NR T2: NR

Ethnicity	Disease status and time/type of event	History of diabetes	Socioeconomic status	Current smoker	Mean BMI (kg/m^2) or BMI > 30 kg/m^2 (%)
White: T1: 85.6% T2: 85.5% Black: T1: 3.3% T2: 2.8%	UA: T1: 47.2% T2: 45.5% Non-Q-wave MI: T1: 52.8% T2: 54.5%	T1: 22.2% T2: 24.1%	T1: NR T2: NR	T1: 27.9% T2: 27.8%	T1: NR T2: NR
T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	T1: 17% T2: 12%	T1: NR T2: NR
White: T1: 93.2% T2: 93.1%	CHD or > 20% 10-year CHD risk: T1: 22.7% T2: 26.1%	T1: 6.2% T2: 5.3%	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR
White: T1: 90% T2: 91% Black: T1: 6% T2: 3%	Angina pectoris: T1: 6% T2: 4% CAD: T1: 9% T2: 9% MI: T1: 12% T2: 11% Coronary vascular surgery: T1: 13% T2: 11%	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR
T1: NR T2: NR	Stenosis > 50%: T1: 53% T2: 46%	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR
T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR (overall, mean BMI 26 kg/m^2)

continued

TABLE 3 *Summary of patient characteristics at baseline (continued)*

Study	Description	Exclusion criteria (brief)	Mean age (years)	Male
Zeneca Pharmaceuticals, 2000[33] (unpublished study)	Adult men (aged 18–70 years) and postmenopausal women (aged 50–70 years) with LDL-c from 4.14 to < 6.21 mmol/l and TG < 3.39 mmol/l	Active liver disease or hepatic dysfunction, active arterial disease	T1: NR T2: NR (overall, mean age 57.5 years)	T1: NR T2: NR

ACS, acute coronary syndrome; BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CHD, coronary heart disease; CHF, congestive heart failure; CMR, cardiac magnetic resonance imaging; DVT, deep vein thrombosis; FH, familial hypercholesterolaemia; hs-CRP, high-sensitivity C-reactive protein; LDL-c, low-density lipoprotein cholesterol; MI, myocardial infarction; NR, not reported; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; PVD, peripheral vascular disease; TC, total cholesterol; TG, triglyceride; TIA, transient ischaemic attack; UA, unstable angina.

Cowell *et al.*[48] used numbered containers. The other 26 studies did not fully describe allocation concealment.

Seven studies blinded both participants and assessors to the assigned treatment groups or used a matching placebo. Sixteen studies did not clearly describe the method of blinding, but fifteen of these were described as double blind. Five studies were open blind.

Nineteen of the studies performed (modified) intention to treat (ITT) analysis. The remaining studies used a per protocol analysis; however, five of these were considered to be at high risk of bias as more than 10% of participants were excluded from the analysis or there were wide differences (more than 5%) in exclusion between groups. The majority of the studies did not adequately report compliance to study treatment; however, this appeared to be greater than 78%[38] for simvastatin 80 mg/day and greater than 86% for atorvastatin 80 mg/day.[53,54]

Overall, most of the information from the studies is at low or unclear risk of bias; however, information from nine of the 28 studies is at high risk of bias, sufficient to affect the interpretation of results (i.e. weakens confidence in the results). Therefore, the results should be interpreted with caution.

Assessment of clinical effectiveness

No studies were identified that assessed the efficacy of high-dose statins (simvastatin 80 mg/day, atorvastatin 80 mg/day, rosuvastatin 40 mg/day) compared with standard-dose statins (simvastatin 40 mg/day) in patients with recent (defined as less than 28 days) MI, unstable angina or revascularisation (CABG or PTCA) procedure. In the absence of such data we identified and included 28 RCTs (of which 15 were multiarm) of at least 6 weeks' duration with surrogate end-point data in adults over 18 years of age. A full list of the excluded publications with rationale is presented in Appendix 3. In brief, the treatment duration in the 28 included trials ranged from 6 weeks[27–33] to 5 years[34,35] with sample sizes ranging from 20[36] to 20,536.[34,35] Participants varied widely between trials but generally were at high risk of CVD (most studies generally excluded patients with MI, angina, coronary angioplasty or CABG within 3 or 6 months of study entry) with mean baseline LDL-c levels ranging from 2.84 mmol/l[36] to 6.38 mmol/l[42] and a mean age ranging from 40.2[44] to 75 years.[45]

Effectiveness results

The marginal posterior results of the percentage reductions in LDL-c (*Table 5*) show a hierarchy of the alternative treatments, with rosuvastatin 40 mg/day producing the greatest reduction (56%) and simvastatin 40 mg/day producing the smallest (37%).

Incorporating the relationship between changes in LDL-c and the RR of events (*Table 6*), the RRs per event are dose related with respect to the dose of simvastatin and, with the exception of fatal stroke, are statistically significant. In addition, the greatest effect on each event was with respect to rosuvastatin 40 mg/day.

The percentage reductions in LDL-c by statin and dose are similar to those reported in a recent review of the clinical evidence for rosuvastatin.[57] The authors reported percentage reductions from baseline as 58%, 53%, 42% and 37% for

Ethnicity	Disease status and time/type of event	History of diabetes	Socioeconomic status	Current smoker	Mean BMI (kg/m^2) or BMI > 30 kg/m^2 (%)
T1: NR	T1: NR	T1: NR	T1: NR	T1: NR	T1: NR
T2: NR	T2: NR	T2: NR	T2: NR	T2: NR	T2: NR (overall, mean BMI 25.5 kg/m^2)

a Data from these papers were derived from a pooled statin group. As patients were equally randomised it is assumed that the baseline data from the pooled statin groups would be similar to the baseline data for the statin intervention dose under consideration.

rosuvastatin 40 mg/day, atorvastatin 80 mg/day, simvastatin 80 mg/day and simvastatin 40 mg/day respectively.

Trial evidence

Included studies

A summary of the adverse event rates reported in the included trials is provided in *Table 7*. A formal mixed treatment meta-analysis was considered inappropriate because of insufficient (poor quality) data and low occurrence of the adverse events.

The most important clinically adverse events are related to the liver (elevated hepatic aminotransferase levels) or reactions of the skeletal muscle. The musculoskeletal events include myalgia (defined as proximal or diffuse muscle pain, tenderness or weakness), myopathy [defined as muscle pain, tenderness and weakness accompanied by elevated creatine kinase (CK) levels of greater than 10 times the normal upper limit] and rhabdomyolysis (characterised by profound CK elevations, muscle necrosis and renal failure).

Additional evidence

Literature searches were undertaken using berry-picking techniques[58] to identify existing systematic reviews and meta-analyses of drug-induced adverse events associated with statin therapy. Where available, post-marketing surveillance data were also sought.

Moderate-dose statins

Although the safety of statins (as a class) is well reported,[59] there are no specific systematic reviews and meta-analyses solely focusing on the adverse effects associated with moderate-dose statins (defined as all doses excluding the following: simvastatin 80 mg/day, atorvastatin 80 mg/day, rosuvastatin 20 mg/day, rosuvastatin 40 mg/day). Nevertheless, a meta-analysis[60] of 35 placebo-controlled trials (comprising 74,102 patients with follow-up ranging from 1.5 to 64.8 months) of atorvastatin (mainly 10–20 mg/day), fluvastatin (mainly 20–40 mg/day), pravastatin (mainly 40 mg/day), rosuvastatin (mainly 5–10 mg/day) and simvastatin (mainly 20–40 mg/day) found that statin therapy did not result in significant absolute increases in risks of myalgia [risk difference/100 patients (RD) 2.7; 95% confidence interval (CI) –3.2 to 8.7], CK elevations (RD 0.2; 95% CI –0.6 to 0.9), rhabdomyolysis (RD 0.4; 95% CI –0.1 to 0.9) or discontinuation because of any adverse events (RD –0.5; 95% CI –4.3 to 3.3). The absolute risk of aminotransferase elevations was significantly higher with statin therapy (RD 4.2; 95% CI 1.5 to 6.9).

In contrast, a meta-analysis[61] of 18 placebo-controlled trials involving 71,108 patients (trial duration 6–317 weeks) found that statins (mostly moderate-dose statins) have a 39% higher rate of any adverse effect [odds ratio (OR) 1.4; 95% CI 1.09 to 1.80; $p = 0.008$; number needed to harm 197) than placebo. However, serious adverse events (creatine phosphokinase greater than 10 times the upper normal limit) were infrequent and rhabdomyolysis was rare. Comparisons between simvastatin and atorvastatin suggested fewer total adverse events with simvastatin (OR 0.57; 95% CI 0.32 to 1.00; $p = 0.048$); however, patients receiving simvastatin had more creatine phosphokinase elevations (OR 2.32; 95% CI 1.05 to 5.15; $p = 0.038$).

TABLE 4 *Quality assessment*[a]

Study	Allocation sequence (randomisation)	Allocation concealment	Blinding	ITT analysis and loss to follow-up	Overall assessment
Aronow, 2003[45]	B (states 'randomised')	B (unclear)	B (unclear)	C (not ITT, exclusions > 10% and between-group difference > 5%)	C
Ballantyne *et al.*, 2003[46]	B (states 'randomised')	B (unclear)	B (described as DB)	A (states 'modified ITT')	B
Ballantyne *et al.*, 2003[37]	B (states 'randomised')	B (unclear)	B (described as DB)	A (states 'ITT')	B
Bauersachs *et al.*, 2007[47]	B (states 'randomised')	B (unclear)	B (described as DB)	C (not ITT, exclusions > 10%)	C
Bays *et al.*, 2004[38]	B (states 'randomised')	B (unclear)	B (described as DB)	A (states 'modified ITT')	B
Charles-Schoeman *et al.*, 2007[36]	A (states 'computer generated')	A (pharmacy controlled)	A (states 'neither patient nor doctors were aware of drug allocation')	A (appears to be ITT)	A
Cowell *et al.*, 2005[48]	A (states 'computer generated')	A (states 'numbered containers')	A (states 'matched placebo' and 'blinded study coordinator randomly assigned')	A (states 'ITT')	A
Davidson *et al.*, 2002[39]	A (states 'computer generated')	B (unclear)	B (described as DB)	A (states 'ITT')	B
Dobs *et al.*, 2000[44]	A (states 'computer generated')	B (unclear)	A (states 'matched … placebo'	C (not ITT, exclusions > 10%)	C
Dobs *et al.*, 2000[49]	B (states 'randomised')	B (unclear)	A (states 'matching placebo'	B (not ITT, exclusions < 10% and between-group difference < 5%)	B
Goldberg *et al.*, 2004[50]	A (states 'computer generated')	B (unclear)	B (described as DB)	A (states 'modified ITT')	B
Heart Protection Study Collaborative Group, 2002[34] and 2005[35]	A (states 'central telephone randomisation')	B (unclear)	A (states 'matching placebo')	A (states 'ITT')	B
Isaacsohn *et al.*, 2003[27]	B (states 'randomised')	B (unclear)	B (described as DB)	A (appears to be ITT)	B
Jones *et al.*, 1998[40]	B (states 'randomised')	B (unclear)	C (states 'open label')	A (states 'ITT')	C
Jones *et al.*, 2003[28]	B (states 'randomised')	B (unclear)	C (states 'open label')	A (states 'ITT')	C

Study	Allocation sequence (randomisation)	Allocation concealment	Blinding	ITT analysis and loss to follow-up	Overall assessment
Karalis *et al.*, 2002[29]	B (states 'randomised')	B (unclear)	C (states 'open label')	A (states 'modified ITT')	C
Keech *et al.*, 1994[43]	A (states 'computer generated')	B (unclear)	A (states 'matching placebo')	A (states 'ITT')	B
Meredith, 2007[51]	B (states 'randomised')	B (unclear)	B (described as DB)	B (not ITT, exclusions < 10%)	B
Mohler, 2003[52]	B (states 'randomised')	B (unclear)	B (described as DB)	A (appears to be modified ITT)	B
Ose *et al.*, 1998[42]	A (states 'computer generated')	B (unclear)	B (described as DB)	A (states 'ITT')	B
Schneck, 2003[30]	B (states 'randomised')	B (unclear)	B (described as DB)	A (states 'ITT')	B
Schwartz *et al.*, 2001[53,54]	B (states 'randomised')	B (unclear)	A (states 'matching placebo')	A (states 'modified ITT')	B
Sdringola, 2008[55]	B (states 'randomised')	B (unclear)	B (described as DB)	A (appears to be ITT)	B
Stein *et al.*, 2007[31]	B (states 'randomised')	B (unclear)	C (states 'open label')	A (states 'ITT')	C
Stein *et al.*, 1998[41]	A (states 'computer generated')	B (unclear)	B (described as DB)	A (states 'ITT')	B
Vita *et al.*, 2000[56]	B (states 'randomised')	B (unclear)	B (described as DB)	C (not ITT, exclusions > 10%)	C
Zeneca Pharmaceuticals, 2000[32] (unpublished study 4522IL/0008)	B (states 'randomised')	B (unclear)	B (described as DB)	B (not ITT, exclusions < 10% and between-group difference < 5%)	B
Zeneca Pharmaceuticals, 2000[33] (unpublished study 4522IL/0023)	B (states 'randomised')	B (unclear)	C (described as DB for rosuvastatin, placebo groups and open label for atorvastatin group)	C (not ITT, exclusions > 10% and between-group differences > 5%)	C

ITT, intention to treat; DB, double blind.
a See Appendix 4 for explanations of A, B and C.

TABLE 5 *Changes in LDL-c across statins*

Treatment	Mean (mmol/l)	SD	2.50%	Median	97.50%
Baseline LDL-c					
Placebo	3.99	0.18	3.64	3.99	4.35
Atorvastatin 80 mg/day	3.95	0.18	3.60	3.95	4.31
Rosuvastatin 40 mg/day	3.99	0.19	3.62	4.00	4.37
Simvastatin 40 mg/day	4.00	0.18	3.65	4.00	4.36
Simvastatin 80 mg/day	3.95	0.18	3.60	3.95	4.31
Percentage change from baseline					
Placebo	–0.57	0.89	–2.35	–0.56	1.16
Atorvastatin 80 mg/day	–52.09	1.39	–54.84	–52.07	–49.45
Rosuvastatin 40 mg/day	–56.16	2.06	–60.20	–56.15	–52.15
Simvastatin 40 mg/day	–36.70	1.35	–39.38	–36.68	–34.07
Simvastatin 80 mg/day	–44.72	1.41	–47.55	–44.73	–42.01
Post treatment					
Placebo	3.97	0.18	3.61	3.97	4.33
Atorvastatin 80 mg/day	1.91	0.10	1.71	1.91	2.12
Rosuvastatin 40 mg/day	1.75	0.11	1.53	1.75	1.98
Simvastatin 40 mg/day	2.53	0.13	2.28	2.53	2.78
Simvastatin 80 mg/day	2.21	0.11	1.98	2.21	2.43
Change from baseline					
Placebo	–0.02	0.04	–0.09	–0.02	0.05
Atorvastatin 80 mg/day	–2.04	0.11	–2.27	–2.04	–1.82
Rosuvastatin 40 mg/day	–2.24	0.14	–2.53	–2.24	–1.97
Simvastatin 40 mg/day	–1.47	0.09	–1.65	–1.47	–1.30
Simvastatin 80 mg/day	–1.75	0.10	–1.95	–1.74	–1.55
Difference from placebo in change from baseline					
Atorvastatin 80 mg/day	–2.02	0.11	–2.23	–2.02	–1.81
Rosuvastatin 40 mg/day	–2.22	0.14	–2.50	–2.22	–1.96
Simvastatin 40 mg/day	–1.45	0.08	–1.62	–1.45	–1.29
Simvastatin 80 mg/day	–1.72	0.10	–1.92	–1.72	–1.54

A systematic review[62] of cohort studies, randomised trials, voluntary notifications to national regulatory authorities and published case reports on the safety of statins also found a low incidence of myopathy (11 per 100,000 person-years) and rhabdomyolysis (estimated as 3 per 100,000 person-years and unlikely to exceed 7 per 100,000 person-years) in patients taking simvastatin, lovastatin, atorvastatin, pravastatin or fluvastatin. It is noteworthy that, although the majority of these adverse events are reversible with dose reduction or discontinuation of therapy,[63] symptoms generally return when restarting the same statin dose (95%) and frequently return when restarting a lower dose (55%).[64] No published post-marketing surveillance data for the UK are available for atorvastatin, rosuvastatin or simvastatin. Data from the US Food and Drug Administration's post-marketing database suggest that the rates of fatal and non-fatal rhabdomyolysis are less than one case (0.97) per million prescriptions (simvastatin, 0.83 per million prescriptions; atorvastatin. 0.3 per million prescriptions; rosuvastatin, data not available).[65] A more accurate estimate of the incidence of

TABLE 6 *Relative risk per event type obtained from the Bayesian model (treatment compared with placebo)*

Treatment	Mean RR	SD	2.50%	Median RR	97.50%
Non-fatal MI					
Atorvastatin 80 mg/day	0.475	0.057	0.361	0.476	0.581
Rosuvastatin 40 mg/day	0.423	0.066	0.287	0.424	0.546
Simvastatin 40 mg/day	0.623	0.042	0.539	0.623	0.701
Simvastatin 80 mg/day	0.552	0.050	0.454	0.553	0.644
Non-fatal stroke					
Atorvastatin 80 mg/day	0.658	0.053	0.552	0.658	0.761
Rosuvastatin 40 mg/day	0.624	0.059	0.509	0.624	0.738
Simvastatin 40 mg/day	0.754	0.038	0.679	0.755	0.828
Simvastatin 80 mg/day	0.708	0.045	0.618	0.709	0.795
Stroke death					
Atorvastatin 80 mg/day	0.828	0.186	0.483	0.821	1.212
Rosuvastatin 40 mg/day	0.811	0.205	0.432	0.803	1.234
Simvastatin 40 mg/day	0.876	0.134	0.625	0.871	1.154
Simvastatin 80 mg/day	0.853	0.159	0.558	0.847	1.180
CHD death					
Atorvastatin 80 mg/day	0.618	0.064	0.492	0.619	0.742
Rosuvastatin 40 mg/day	0.580	0.071	0.436	0.581	0.718
Simvastatin 40 mg/day	0.725	0.046	0.635	0.726	0.815
Simvastatin 80 mg/day	0.674	0.054	0.565	0.674	0.780

CHD, coronary heart disease; MI, myocardial infarction; RR, relative risk.

rhabdomyolysis attributed to statins may be obtained from Graham *et al*.[66] Prescription data were used to identify a cohort of 252,460 lipid-lowering drug users from 11 health plans across the USA between January 1998 and June 2001. Hospital data were then used to establish how many of the cohort were admitted to hospital with a diagnosis of rhabdomyolysis.

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 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)].

Intensive-dose statins

The safety profile associated with intensive-dose statin therapy is less clear because of the smaller number of clinical trials using intensive-dose treatments. To our knowledge there is no published evidence on adverse event rates associated with intensive-dose statin use in clinical practice and the following text summarises the event rates observed in the screened individuals enrolled in RCTs.

A meta-analysis of seven trials (involving 29,395 patients with CAD)[67] comparing intensive statin therapy with less intensive statin therapy found that more intensive regimens (atorvastatin 80 mg/day or simvastatin 80 mg/day) were associated with higher levels of aminotransferases (1.5% versus 0.4%; OR 4.14; 95% CI 2.30 to 7.44), myalgia (3.3% versus 2.8%; OR 1.26; 95% CI 0.98 to 1.63), myopathy (2.2% versus 1.8%; OR 1.91; 95% CI 0.11 to 32.13) and rhabdomyolysis (0.05% versus 0.04%; OR 0.97; 95% CI 0.29 to 3.24) than less intensive regimens (atorvastatin 10 mg/day, lovastatin 5 mg/day, pravastatin 40 mg/day, simvastatin 20 mg/day). Similar observations were reported in a meta-analysis by Silva *et al*.[68] This meta-analysis included four trials (all of which were included in the aforementioned meta-analysis) comprising 27,548

patients with ACS or stable CAD. Intensive-dose therapy with atorvastatin or simvastatin 80 mg/day was associated with a significant increase in the risk of any adverse event (OR 1.44; 95% CI 1.33 to 1.55; $p < 0.001$). Intensive-dose therapy was also associated with an increased risk of abnormalities on liver function testing (OR 4.48; 95% CI 3.27 to 6.16; $p < 0.001$) and elevations in CK (OR 9.97; 95% CI 1.28 to 77.92; $p = 0.028$).

In addition to these meta-analyses several other pooled analyses were identified. In an analysis of four RCTs[69] comparing simvastatin 80 mg/day ($n = 1586$) with simvastatin 40 mg/day ($n = 543$) for 36–48 weeks, the results showed that myopathy (0.6% versus 0.2% respectively) and consecutive elevations in liver function tests [alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than three times the upper limit of normal; 1.5% versus 0.7% respectively] were not significant ($p > 0.05$) between the intensive- and moderate-dose statins. Additional data from Waters[70] suggest that simvastatin 80 mg/day is associated with a low but definite risk (approximately 1 in 250) of myopathy. This finding is supported by the product information for simvastatin, which estimates the incidence of myopathy with a dose of 80 mg/day as 0.53% compared with 0.08% for a dose of 40 mg/day.[71]

A retrospective analysis of pooled safety data[72] from 49 short-term (treatment duration 2 weeks to 52 months) completed clinical trials of atorvastatin (atorvastatin 80 mg/day, $n = 4798$; atorvastatin 10 mg/day, $n = 7258$; placebo, $n = 2180$) showed that the discontinuation rates because of treatment-related adverse events were 1.8%, 2.4% and 1.2% respectively. Treatment-related myalgia was observed in 1.5%, 1.4% and 0.7% respectively, and no cases of rhabdomyolysis were reported in any group. Persistent elevations in hepatic aminotransferases greater than three times the upper normal limit were observed in 0.6%, 0.1% and 0.2% respectively.

Although the evidence for the long-term safety of rosuvastatin is limited, a rosuvastatin clinical trials database (comprising data from 33 phase II/III clinical trials)[73] suggests that rates of myopathy (< 0.03%), myositis (< 0.3%) and elevated ALT levels greater than three times the upper limit of normal (< 0.2%) are uncommon at doses of ≤ 40 mg/day. Although no deaths have been attributed to rosuvastatin (< 40 mg/day), one case of rhabdomyolysis has been found in a patient who received rosuvastatin 20 mg/day and concomitant gemfibrozil treatment. The product information for rosuvastatin indicates a higher risk of adverse events with the 40-mg dose than with lower doses (< 20 mg/day).[74] Although, overall, intensive-dose statins are generally well tolerated in clinical trials, the evidence suggests a higher rate of treatment discontinuation because of adverse effects. The meta-analysis by Josan *et al.*[67] found that more intensive regimens (atorvastatin 80 mg/day or simvastatin 80 mg/day) were associated with small non-statistically significant increases in rates of discontinuation compared with less intensive statins (atorvastatin 10 mg/day, lovastatin 5 mg/day, pravastatin 40 mg/day, simvastatin 20 mg/day) (7.8% versus 5.3%; OR 1.34; 95% CI 0.98 to 1.83). Similar but statistically significant findings were reported by Silva *et al.*[68] (adverse events requiring discontinuation of therapy: OR 1.28; 95% CI 1.18 to 1.39; $p < 0.001$).

Despite these findings, one randomised study (not included in the meta-analyses by Josan *et al.*[67] and Silva *et al.*[68]) of over 900 dyslipidaemic subjects showed that those who received an initial dose of atorvastatin 80 mg/day had a treatment-related discontinuation rate of 17% compared with a rate of 10–12% for doses of 10–40 mg/day.[75] In a pooled safety analysis of intensive- versus moderate-dose simvastatin[68] the treatment-related discontinuation rates were higher in the simvastatin 80 mg/day group (2.5%) than in the simvastatin 40 mg/day group (1.9%); however, the findings were not significant and data from the HPS study[34,35] suggest that drug-related discontinuation rates for simvastatin 40 mg/day (0.5%) were equal to those for placebo (0.5%). Evidence from a rosuvastatin clinical trials database suggests that treatment-related discontinuation rates were lower (2.9%) for patients receiving rosuvastatin 5–40 mg/day than for patients receiving placebo (4.3%).[73] However, in the 2-year open-label ASTEROID study ($n = 507$, all statin-naïve) discontinuation rates because of drug-related muscle pain or weakness for rosuvastatin 40 mg/day were 3.7%.[76]

It is noteworthy that adverse events may be more common in clinical practice as trial participants are usually younger, healthier and more closely monitored than patients in usual clinical practice. Most statin trials exclude over half of all screened patients because of co-morbidities (e.g. advanced age, renal failure, hepatic failure, hypothyroidism) or concomitant use of fibrates, macrolide antibiotics, antifungal agents, HIV protease inhibitors, verapamil or cyclosporine,

which may increase the risk of adverse events.[77] For example, screening data from the recent SPACE ROCKET trial[78] showed that there were specific contraindications to simvastatin 40 mg/day in 55% of 5000 contemporary UK ACS cases. Recently published data show an 11-fold increase in myopathy/myositis and defined premyositis giving a high risk of rhambdomyloysis.[79] In addition to the adverse events attributed to statin use, the discontinuation rates reported in clinical trials may not necessarily translate to discontinuation rates for high-dose statin regimens in general clinical practice.

Adherence to lipid modifications

There is a dearth of evidence illustrating differences in adherence according to either statin type or potency. Much of the published evidence examines adherence to statins as a class and does not provide data that can be used to determine adherence according to statin type and potency of dose. Nevertheless, the majority of patients for whom statins are prescribed in clinical practice either stop taking the drug altogether or take less than the prescribed dose.[80–83]

Although the adherence rates in the landmark secondary prevention trials (4S, simvastatin 20–40 mg/day;[84] CARE, pravastatin 40 mg/day;[85] LIPID, pravastatin 40 mg/day[86]) range from 81% to 94% at 5 years, observational cohort studies (data primarily from moderate-/low-dose statins) suggest that the level of adherence (deemed those taking ≥ 80% of therapy)[87] outside the clinical trial setting decreases with time and can fall below 50% after 2 years[81,88,89] or 5 years[90] with the greatest decline in the first 12 months.[90]

Numerous studies show that the number of patients continuing therapy falls sharply in the first months of treatment, followed by a more gradual decline. Observational data from a US Medicaid population (cohort of 35,501 patients aged over 65 years) showed that adherence rates declined from 79% to 56%, 50%, 35% and 42% at 3 months, 6 months, 12 months, 60 months and 120 months respectively.[88] A similar trend was observed by Caspard *et al.*[91] who found that the proportion of statin users remaining in treatment decreased from 80% at 6 months to a low point of 35% at 2 years in a cohort of 4776 patients (57% aged between 50 and 69 years) in a usual care setting in the USA. These findings are also consistent with those of other observational studies.[83,92]

Recent studies have reported differences in statin adherence rates among individuals treated for primary or secondary prevention. In a cohort study using linked population-based administrative data (143,505 patients aged 66 years or older who had at least one statin prescription), Jackevicius[81] showed that the 2-year adherence rates (defined as a statin being dispensed at least every 120 days) were slightly higher for ACS patients (40.1%) than for chronic CAD patients (36.1%) or primary prevention (25.4%). Similar trends were observed by Perreault *et al.*[93] who found that the adherence rate for individuals (aged 50–64 years) with CAD ($n = 4316$) fell from 71% after 6 months of treatment to 45% after 3 years; corresponding figures were 65% and 35% in the primary prevention cohort ($n = 13,642$). In a population-based, observational, longitudinal study of 31,455 elderly acute myocardial infarction (AMI) survivors Rasmussen *et al.*[94] showed that the adherence rate at 1 year was 87.5% with 13.2% discontinuing statin treatment at some point over the median 2.4-year follow-up period.

Ellis *et al.*[95] reported that the median time to discontinuation of statin therapy in secondary prevention was 3.7 years and the survival curves of subgroups according to statin type and potency showed that the median time for discontinuation was 3.9 years for simvastatin 0–10 mg/day, 2.2 years for simvastatin 10–20 mg/day and 1.0 year for simvastatin > 20 mg/day. Lachaine *et al.*[96] showed that although persistence with atorvastatin (63%) was greater than with simvastatin (61%) the difference was not statistically significant ($p = 0.09$). Huser *et al.*[97] also showed that, of the statins most widely used, persistence was higher for atorvastatin than for simvastatin (36% versus 26% respectively). In contrast, Perreault *et al.*[93] found that the adherence rates were significantly higher for simvastatin (77%, mean dose 17 mg/day) than for atorvastatin (69%, mean dose 16 mg/day). Studies have also reported that patients over 60 years were significantly better adherents than those under 45 years or over 75 years.[83,88,97]

In summary, much of the published data from the clinical practice setting focuses on adherence to moderate-/low-dose statins and consistently shows lower adherence than in clinical trials. Although adherence rates to intensive-dose statins have been reported in some clinical trials evaluated in the clinical review (> 78% for 12 weeks for simvastatin 80 mg/day and > 86% for 16 weeks for atorvastatin 80 mg/day), no studies

TABLE 7 *Adverse events*

Study	Intervention groups, dose, timings	Adverse event (treatment related) leading to drug discontinuation, no. (%) of patients	Aminotransferase elevations,[a] no. (%) of patients	Myalgia,[b] no. (%) of patients	Myositis,[c] no. (%) of patients	Myopathy,[d] no. (%) of patients	Rhabdomyolysis,[e] no. (%) of patients	Compliance with study treatments
Aronow, 2003[45]	T1: Simvastatin 40 mg/day ($n = 34$) T2: Placebo ($n = 35$)	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	NR
Ballantyne *et al.*, 2003[46]	T1: Atorvastatin 80 mg/day ($n = 464$) T2: Simvastatin 80 mg/day ($n = 453$)	T1: 28/464 (6.0) T2: 12/453 (2.6)	T1: Unclear T2: Unclear	T1: 15/464 (3.2) T2: 3/435 (0.7)	T1: 1/464 (0.2) T2: 0/453 (0)	T1: 0/464 (0) T2: 0/453 (0)	T1: NR T2: NR	NR
Ballantyne *et al.*, 2003[37]	T1: Atorvastatin 80 mg/day ($n = 62$) T2: Placebo ($n = 60$)	T1: NR T2: NR	T1: NR T2: 0/60 (0)	T1: NR T2: NR	T1: 0/62 (0) T2: 0/60 (0)	T1: NR T2: NR	T1: 0/62 (0) T2: 0/60 (0)	NR
Bauersachs *et al.*, 2007[47]	T1: Atorvastatin 80 mg/day ($n = 14$) T2: Placebo ($n = 14$)	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	NR
Bays *et al.*, 2004[38]	T1: Simvastatin 40 mg/day ($n = 154$) T2: Simvastatin 80 mg/day ($n = 156$) T3: Placebo ($n = 148$)	T1: NR T2: NR T3: 2/148 (1.4)	T1: 2/154 (1.3) T2: 4/156 (2.6) T3: 1/146 (0.7)	T1: NR T2: NR T3: NR	T1: NR T2: NR T3: 1/146 (0.7)	T1: 1/154 (0.6) T2: NR T3: 0/148 (0)	T1: 0/154 (0) T2: 0/156 (0) T3: 0/148 (0)	Mean % of patients with > 95% compliance (mean % of total doses taken) ranged from 78% to 82% in T1 and T2
Charles-Schoeman *et al.*, 2007[36]	T1: Atorvastatin 80 mg/day ($n = 11$) T2: Placebo ($n = 9$)	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: 1/9 (11.1)	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	NR

Study	Intervention groups, dose, timings	Adverse event (treatment related) leading to drug discontinuation, no. (%) of patients	Aminotransferase elevations,[a] no. (%) of patients	Myalgia,[b] no. (%) of patients	Myositis,[c] no. (%) of patients	Myopathy,[d] no. (%) of patients	Rhabdomyolysis,[e] no. (%) of patients	Compliance with study treatments
Cowell *et al.*, 2005[48]	T1: Atorvastatin 80 mg/day ($n = 77$) T2: Placebo ($n = 78$)	T1: 7/77 (9.1) T2: 4/78 (5.1)	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	T1: 0/77 (0) T2: 0/78 (0)	NR
Davidson *et al.*, 2002[39]	T1: Simvastatin 40 mg/day ($n = 65$) T2: Simvastatin 80 mg/day ($n = 67$) T3: Placebo ($n = 70$)	T1: NR T2: NR T3: NR	T1: 0/65 (0) T2: 1/67 (1.5) T3: 0/70 (0)	T1: NR T2: NR T3: NR	T1: 1/65 (1.5) T2: 0/67 (0) T3: 0/70 (0)	T1: NR T2: NR T3: NR	T1: 0/65 (0) T2: 0/67 (0) T3: 0/70 (0)	Mean compliance (mean % of total doses taken) ranged from 90% to 97% in T1 and T2
Dobs *et al.*, 2000[44]	T1: Simvastatin 40 mg/day ($n = 41$) T2: Placebo ($n = 40$)	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	NR
Dobs *et al.*, 2000[49]	T1: Simvastatin 80 mg/day ($n = 42$) T2: Placebo ($n = 39$)	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	NR
Goldberg *et al.*, 2004[50]	T1: Simvastatin 40 mg/day ($n = 90$) T2: Simvastatin 80 mg/day ($n = 87$) T3: Placebo ($n = 93$)	T1: NR T2: NR T3: 0/93 (0)	T1: 0/90 (0) T2: 0/87 (0) T3: 0/92 (0)	T1: NR T2: NR T3: NR	T1: NR T2: NR T3: 1/92 (1)	T1: 0/90 (0) T2: 0/87 (0) T3: 0/93 (0)	T1: 0/90 (0) T2: 0/87 (0) T3: 0/93 (0)	NR

continued

TABLE 7 *Adverse events (continued)*

Study	Intervention groups, dose, timings	Adverse event (treatment related) leading to drug discontinuation, no. (%) of patients	Aminotransferase elevations,[a] no. (%) of patients	Myalgia,[b] no. (%) of patients	Myositis,[c] no. (%) of patients	Myopathy,[d] no. (%) of patients	Rhabdomyolysis,[e] no. (%) of patients	Compliance with study treatments
Heart Protection Study Collaborative Group, 2002[34] and 2005[35]	T1: Simvastatin 40 mg/day ($n = 10,269$) T2: Placebo ($n = 10,267$)	T1: 493/10,269 (4.8%) T2: 524/10,267 (5.1%)	T1: NR T2: NR	T1: 3379/10,269 (32.9) T2: 3409/10,267 (33.2)	T1: 11/10,269 T2: 6/10,267	T1: 10/10,269 T2: 4/10,267	T1: 5/10,269 T2: 3/10,267	Average compliance 85% in T1 and average non-study statin use in placebo group was 17%
Isaacsohn *et al.*, 2003[27]	T1: Simvastatin 40 mg/day ($n = 90$) T2: Simvastatin 80 mg/day ($n = 87$) T3: Placebo ($n = 93$)	T1: 0/90 (0) T2: 0/87 (0) T3: 0/93 (0)	T1: 0/90 (0) T2: 0/87 (0) T3: 0/93 (0)	T1: NR T2: NR T3: NR	T1: 0/90 (0) T2: 0/87 (0) T3: 0/93 (0)	T1: 0/90 (0) T2: 0/87 (0) T3: 0/93 (0)	T1: NR T2: NR T3: NR	NR
Jones *et al.*, 1998[40]	T1: Atorvastatin 80 mg/day ($n = 10$) T2: Simvastatin 40 mg/day ($n = 61$)	T1: 0/10 (0) T2: 1/61 (1.6)	T1: 0/10 (0) T2: 0/61 (0)	T1: NR T2: NR	T1: 0/10 (0) T2: 0/61 (0)	T1: 0/10 (0) T2: 0/61 (0)	T1: NR T2: NR	NR
Jones *et al.*, 2003[28]	T1: Rosuvastatin 40 mg/day ($n = 158$) T2: Atorvastatin 80 mg/day ($n = 167$) T3: Simvastatin 80 mg/day ($n = 165$) T4: Simvastatin 40 mg/day ($n = 159$)	T1: 3/158 (1.9) T2: 6/167 (3.6) T3: 6/165 (3.6) T4: 3/159 (1.9)	T1: 0/158 (0) T2: 2/167 (1.2) T3: 1/165 (0.6) T4: 1/159 (0.6)	T1: reported as < 2% T2: 9/167 (5.4) T3: NR T4: reported as < 2%	T1: 0/158 (0) T2: 0/167 (0) T3: 0/165 (0) T4: 0/159 (0)	T1: 0/158 (0) T2: 0/167 (0) T3: 0/165 (0) T4: 0/159 (0)	T1: NR T2: NR T3: NR T4: NR	Compliance (mean of tablets taken) ranged from 90.5% to 95.3%

Study	Intervention groups, dose, timings	Adverse event (treatment related) leading to drug discontinuation, no. (%) of patients	Aminotransferase elevations,[a] no. (%) of patients	Myalgia,[b] no. (%) of patients	Myositis,[c] no. (%) of patients	Myopathy,[d] no. (%) of patients	Rhabdomyolysis,[e] no. (%) of patients	Compliance with study treatments
Karalis *et al.*, 2002[29]	T1: Atorvastatin 80 mg/day ($n = 207$) T2: Simvastatin 80 mg/day ($n = 207$)	T1: 17/207 (8.0) T2: 10/207 (5.0)	T1: 2/203 (< 1) T2: 2/187 (1)	T1: NR T2: NR	T1: 0/207 (0) T2: 0/207 (0)	T1: NR T2: NR	T1: NR T2: NR	T1: 91.6% T2: 91.5%
Keech *et al.*, 1994[43]	T1: Simvastatin 40 mg/day ($n = 206$) T2: Placebo ($n = 207$)	T1: NR T2: NR	T1: 0/206 (0) T2: 4/207 (1.9)	T1: 2/206 (1) T2: 2/207 (1)	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	Compliance defined as > 90% of scheduled treatment taken 8 weeks: T1: 93%, T2: 94%; 1 year: T1: 87%, T2: 89%; 2 years: T1: 83%, T2: 79%; 3 years: T1: 75%, T2: 76%
Meredith, 2007[51]	T1: Simvastatin 80 mg/day ($n = 35$) T2: Placebo ($n = 24$)	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	NR
Mohler, 2003[52]	T1: Atorvastatin 80 mg/day ($n = 120$) T2: Placebo ($n = 114$)	T1: 3/120 (2.5) T2: 2/114 (1.8)	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	NR
Ose *et al.*, 1998[42]	T1: Simvastatin 80 mg/day ($n = 355$) T2: Simvastatin 40 mg/day ($n = 229$)	T1: 12/355 (3.4) T2: 8/229 (3.5)	T1: NR T2: NR	T1: 17/355 (4.8) T2: 8/229 (3.5)	T1: 4/355 (1.1) T2: 1/229 (0.4)	T1: 3/355 (0.9) T2: 1/229 (0.4)	T1: NR T2: NR	NR

continued

TABLE 7 *Adverse events (continued)*

Study	Intervention groups, dose, timings	Adverse event (treatment related) leading to drug discontinuation, no. (%) of patients	Aminotransferase elevations,[a] no. (%) of patients	Myalgia,[b] no. (%) of patients	Myositis,[c] no. (%) of patients	Myopathy,[d] no. (%) of patients	Rhabdomyolysis,[e] no. (%) of patients	Compliance with study treatments
Schneck, 2003[30]	T1: Rosuvastatin 40 mg/day ($n = 45$) T2: Atorvastatin 80 mg/day ($n = 41$)	T1: 0/45 (0) T2: 1/41 (2.4)	T1: 0/45 (0) T2: 1/41 (2.4)	T1: 2/45 (4.4) T2: 1/41 (2.4)	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	NR
Schwartz *et al.*, 2001[53] and Olsson *et al.*, 2005[54]	T1: Atorvastatin 80 mg/day ($n = 1538$) T2: Placebo ($n = 1548$)	T1: NR T2: NR	T1: 38/1538 (2.5) T2: 9/1548 (0.6)	T1: NR T2: NR	T1: 0/1538 (0) T2: 0/1538 (0)	T1: NR T2: NR	T1: NR T2: NR	T1: 86% T2: 88%
Sdringola, 2008[55]	T1: Atorvastatin 80 mg/day ($n = 72$) T2: Placebo ($n = 73$)	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	Compliance by tablet count ≥ 90% in T1 and T2
Stein *et al.*, 2007[31]	T1: Rosuvastatin 40 mg/day ($n = 308$) T2: Simvastatin 80 mg/day ($n = 318$)	T1: 5/308 (1.6) T2: 5/318 (1.6)	T1: 1/308 (0.3) T2: 4/318 (1.3)	T1: 7/308 (2.3) T2: 15/318 (4.7)	T1: 0/308 (0) T2: 2/318 (0.6)	T1: NR T2: NR	T1: 0/308 (0) T2: 1/318 (0.3)	NR
Stein *et al.*, 1998[41]	T1: Simvastatin 80 mg/day ($n = 314$) T2: Simvastatin 40 mg/day ($n = 207$)	T1: 3/314 (1) T2: 2/207 (1)	T1: 6/314 (1.9) T2: 3/314 (1.4)	T1: 5/314 (1.6) T2: 3/207 (1.4)	T1: NR T2: NR	T1: 2/314 (0.6) T2: 0/207 (0)	T1: NR T2: NR	NR

Study	Intervention groups, dose, timings	Adverse event (treatment related) leading to drug discontinuation, no. (%) of patients	Aminotransferase elevations,[a] no. (%) of patients	Myalgia,[b] no. (%) of patients	Myositis,[c] no. (%) of patients	Myopathy,[d] no. (%) of patients	Rhabdomyolysis,[e] no. (%) of patients	Compliance with study treatments
Vita *et al.*, 2000[56]	T1: Simvastatin 40 mg/day ($n = 34$) T2: Placebo ($n = 26$)	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	T1: NR T2: NR	NR
Zeneca Pharmaceuticals, 2000[32]	T1: Rosuvastatin 40 mg/day ($n = 18$) T2: Atorvastatin 80 mg/day ($n = 13$) T3: Placebo ($n = 13$)	T1: NR T2: 1/13 (7.7) T3: NR	T1: 0/18 (0) T2: 0/13 (0) T3: 0/13 (0)	T1: 0/18 (0) T2: 1/13 (7.7) T3: 0/13 (0)	T1: 0/18 (0) T2: 0/13 (0) T3: 0/13 (0)	T1: NR T2: NR T3: NR	T1: NR T2: NR T3: NR	NR
Zeneca Pharmaceuticals, 2000[33]	T1: Rosuvastatin 40 mg/day ($n = 16$) T2: Placebo ($n = 17$)	T1: 0/16 (0) T2: NR	T1: 0/16 (0) T2: 0/17 (0)	T1: 1/16 (6.3) T2: 1/17 (5.9)	T1: 0/16 (0) T2: 0/17 (0)	T1: 0/16 (0) T2: 0/17 (0)	T1: NR T2: NR	NR

NR, not reported.
a Alanine aminotransferase and/or aspartate aminotransferase greater than three times the normal upper limit.
b Myalgia defined by study investigators as muscle complaints without serum creatine kinase (CK) elevations.
c Myositis defined by study investigators as CK elevation greater than 10 times the normal upper limit.
d Myopathy defined by study investigators as presence of myalgia in conjunction with CK elevations greater than 10 times the normal upper limit with no other etiology.
e Rhabdomyolysis defined by study investigators (fatal or non-fatal).

have reported adherence data in clinical practice for high-dose statins (atorvastatin 80 mg/day, rosuvastatin 40 mg/day, simvastatin 80 mg/day); however, adherence estimates in clinical practice are likely to be much lower than those reported in clinical trials. On the other hand, evidence suggests that regular cholesterol monitoring can influence compliance,[98,99] and follow-up lipid tests and physician visits are associated with improved adherence to statin therapy.[88] Personal interventions by health-care providers can improve compliance,[97] and being well informed by physicians before initiation of secondary prevention treatment can improve continuous use of statin therapy, contact with physicians and titration to higher doses.

As severe adverse event rates are extremely low (see clinical effectiveness review) we did not include these in the economic model. However, we used several scenarios exploring differing adherence rates (see Chapter 4, Scenarios) to reflect the potential greater rates of discontinuation with the higher-dose therapies caused by the less serious adverse events such as myopathy or myalgia. We also included an additional monitoring cost (see *Table 9*) for the higher doses.

Chapter 4
Economic evaluation

Markov model

An existing CVD model initially constructed to explore the cost-effectiveness of statin therapy versus no treatment[59] (Appendix 5), and subsequently modified to quantify treatment effects based on chemically induced changes in LDL-c,[100] was adapted to explore the cost-effectiveness of high-dose versus standard-dose statin therapy. The evaluation follows the NICE guidelines for economic evaluations,[101] thus a lifetime horizon was used with both costs and benefits discounted at 3.5%. The analysis was undertaken from the perspective of the UK NHS, hence only direct health-care costs were included.

Methods

The health states in the Markov model are shown in *Figure 1*. With all individuals starting in one of the three qualifying event health states, unstable angina, non-fatal MI or revascularisation, an annual cycle was used to model transitions to subsequent events. Where evidence was available, age-related transition probabilities were used to model the probabilities associated with the first year or subsequent year events. Individuals who did not experience an event in the current year moved to the corresponding 'post' health state, and subsequent year event rates were applied.

Markov models are useful for conditions which involve events that can occur more than once, probabilities that change according to the time since a previous event, and risks that continue or increase over time.[102] The Markov process does not hold a memory of clinical history, and only the costs and health consequences associated with the current health state are applied. To ensure that individuals do not move to a health state with smaller costs and a greater quality of life, transition restrictions may be applied. However, this does not always reflect natural clinical history, particularly in CVD in which it is possible for an individual to experience a severe event followed by a less severe event (e.g. a stroke followed by an MI or rehospitalisation for unstable angina).

To enable the model to capture the costs and benefits associated with major events in the clinical pathway for individuals with ACS, a number of combined health states were included in which transitions to future events were assumed to be the maximum value associated with the history of events. For example, if an individual with a history of stroke experienced an MI, they moved to a combined health state 'MI given history of stroke'. Transitions from the health state 'MI given history of stroke' would then be the maximum value of the transition from either the post stroke or the current year non-fatal MI health state. The costs

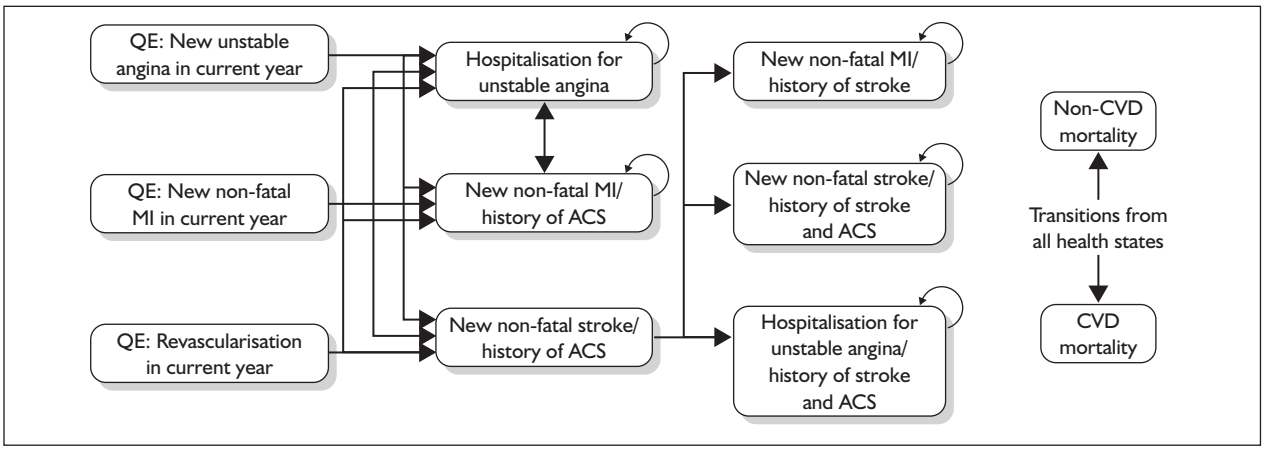

FIGURE 1 *Health states included in the Markov model. All health states have a 'post health state'. ACS, acute coronary syndrome; CVD, cardiovascular disease; MI, myocardial infarction; QE, qualifying event; revascularisation, coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA).*

and utilities were also adjusted to ensure that an individual experiencing a subsequent event did not have a lower ongoing cost or higher resultant utility than that associated with previous events.

Transitions between health states

The model was constructed with five alternative treatment arms: placebo, atorvastatin 80 mg/day, rosuvastatin 40 mg/day, simvastatin 40 mg/day and simvastatin 80 mg/day. Transitions for the placebo arm were obtained from individuals not receiving statin treatment. The RRs from the Bayesian mixed treatment meta-analysis (*Table 8*) were then applied to the baseline transitions to estimate the events in each arm of the model. The RRs for the different statins and events were sampled simultaneously from WinBUGS to preserve the properties of the joint posterior distribution.

UK-specific data were used where possible to ensure that event rates in the placebo arm matched the likely distribution in the UK. For individuals with a history of unstable angina or who had experienced an MI, the probabilities of further MIs, strokes and vascular deaths were derived from patients on the Nottingham Heart Attack Register (NHAR) and the Randomised Intervention Treatment for Angina (RITA-2) study.[59] The probabilities of subsequent strokes and vascular deaths for patients with a history of a stroke were derived from patients on the South London Stroke Register (SLSR).[59] Transitions from the qualifying revascularisation health state were taken from two large UK-based studies comparing coronary angioplasty with medical therapy, RITA-2 ($n = 1018$) and RITA-3 ($n = 1810$),[103,104] as in a recent UK evaluation.[105] The individual transition rates by age are provided in *Table 8*.

Costs

Health state costs

The first year costs (£3880) for the unstable angina health state include secondary care costs (100% hospitalisation, 50% revascularisation procedure, three outpatient appointments), primary care costs (three GP visits) and medications (see Appendix 6).[18] First year costs (£3996) for the MI health state include secondary care costs (100% hospitalisation, 50% revascularisation procedure, three outpatient appointments), primary care costs (three GP visits) and medications. First year costs (£5857) for the revascularisation health state include secondary

TABLE 8 *Age-related transitions between health states*

		Age (years)				
From	**To**	**55**	**65**	**75**	**85**	**Source**
Unstable angina	Unstable angina hospitalisation	5.8%	5.8%	5.8%	5.8%	Fox *et al.*, 2005[103]
	MI	5.0%	4.9%	4.7%	4.3%	Gray and Hapton, 2008[106]
	Stroke	0.2%	0.5%	1.0%	2.0%	Assumed same as MI to stroke
	Fatal CHD	3.9%	6.5%	10.5%	15.6%	Gray and Hapton, 2008[106]
	Fatal stroke	2.6%	4.3%	7.0%	10.3%	Gray and Hapton, 2008[106]
Post unstable angina	Unstable angina hospitalisation	2.0%	2.0%	2.0%	2.0%	Henderson *et al.*, 2008[104]
	MI	3.5%	6.3%	11.2%	18.5%	Gray and Hapton, 2008[106]
	Stroke	0.1%	0.1%	0.3%	0.7%	Assumed same as post MI to stroke
	Fatal CHD	0.6%	0.7%	0.9%	1.0%	Gray and Hapton, 2008[106]
	Fatal stroke	0.4%	0.5%	0.6%	0.7%	Gray and Hapton, 2008[106]
Revascularisation	Unstable angina hospitalisation	3.2%	3.2%	3.2%	3.2%	Henderson *et al.*, 2008[104]
	MI	3.8%	3.8%	3.8%	3.8%	Fox *et al.*, 2005[103]
	Stroke	0.1%	0.1%	0.1%	0.1%	Henderson *et al.*, 2008[104]
	Fatal CHD	3.1%	3.1%	3.1%	3.1%	Fox *et al.*, 2005[103]
	Fatal stroke	0.1%	0.1%	0.1%	0.1%	Assumed same as non-fatal stroke

TABLE 8 *Age-related transitions between health states (continued)*

		Age (years)				
From	**To**	**55**	**65**	**75**	**85**	**Source**
Post revascularisation	Unstable angina hospitalisation	2.1%	2.1%	2.1%	2.1%	Henderson *et al.*, 2008[104]
	MI	1.0%	1.0%	1.0%	1.0%	Fox *et al.*, 2005[103]
	Stroke	0.1%	0.1%	0.1%	0.1%	Assumed same as first year
	Fatal CHD	3.1%	3.1%	3.1%	3.1%	Fox *et al.*, 2005[103]
	Fatal stroke	0.1%	0.1%	0.1%	0.1%	Assumed same as non-fatal stroke
MI	Unstable angina hospitalisation	5.8%	5.8%	5.8%	5.8%	Assumed same as unstable angina to unstable angina hospitalisation
	MI	11.5%	10.2%	8.7%	7.3%	Gray and Hapton, 2008[106]
	Stroke	0.3%	0.7%	1.4%	2.6%	Gray and Hapton, 2008[106]
	Fatal CHD	2.0%	3.8%	6.8%	11.2%	Gray and Hapton, 2008[106]
	Fatal stroke	1.3%	2.5%	4.5%	7.4%	Gray and Hapton, 2008[106]
Post MI	Unstable angina hospitalisation	2.0%	2.0%	2.0%	2.0%	Assumed same as post unstable angina to unstable angina hospitalisation
	MI	1.8%	2.0%	2.0%	1.9%	Gray and Hapton, 2008[106]
	Stroke	0.1%	0.2%	0.5%	0.9%	Gray and Hapton, 2008[106]
	Fatal CHD	0.6%	1.0%	1.5%	2.1%	Gray and Hapton, 2008[106]
	Fatal stroke	0.4%	0.6%	1.0%	1.4%	Gray and Hapton, 2008[106]
Stroke	Unstable angina hospitalisation	2.9%	2.9%	2.9%	2.9%	Assumed 50% of MI to unstable angina hospitalisation
	MI	5.8%	5.1%	4.4%	3.6%	Assumed 50% of MI to MI
	Stroke	4.6%	4.8%	4.8%	4.5%	Wolfe *et al.*, 2002[107]
	Fatal CHD	1.1%	2.6%	5.9%	11.4%	Wolfe *et al.*, 2002[107]
	Fatal stroke	1.1%	2.6%	5.9%	11.4%	Wolfe *et al.*, 2002[107]
Post stroke	Unstable angina hospitalisation	1.0%	1.0%	1.0%	1.0%	Assumed 50% of post MI to unstable angina hospitalisation
	MI	0.9%	1.0%	1.0%	0.9%	Assumed 50% of post MI to MI
	Stroke	1.9%	2.2%	2.5%	2.5%	Wolfe *et al.*, 2002[107]
	Fatal CHD	0.5%	1.0%	2.1%	3.5%	Wolfe *et al.*, 2002[107]
	Fatal stroke	0.5%	1.0%	2.1%	3.5%	Wolfe *et al.*, 2002[107]

CHD, coronary heart disease; MI, myocardial infarction.

care costs (100% hospitalisation, three outpatient appointments), primary care costs (three GP visits) and medications. Subsequent year costs (£340) for all ACS patients include secondary care costs (one outpatient appointment), primary care costs (three GP visits) and medications. First year costs for non-fatal stroke (£8066) were obtained from the costs of acute events reported in Youman *et al.*[108] weighted by the distribution of severity of stroke.[59] The cost of non-fatal stroke for subsequent years (£2266) was based on the costs of ongoing care at home or in an institution weighted by the distribution of severity of stroke and discharge locations. The cost of fatal CHD events (£592) and the cost of non-cardiac fatal vascular events were obtained from Youman *et al.*[108] and Palmer *et al.*[109] respectively. It was assumed that only 50% of fatal cardiovascular events incur a cost.

A breakdown of the costs is provided in Appendix 6, and the mean health state values are provided in *Table 9*. Gamma distributions were used to explore

TABLE 9 *Health state costs (price year 2007)*

Health state	Base case, mean	Univariate sensitivity analyses		Source
		Minus 50%	Plus 50%	
Unstable angina year 1	£3880	£1940	£5820	*BNF*, 2008[18]
ACS year 2+	£340	£170	£510	*BNF*, 2008[18]
MI year 1	£3996	£1998	£5994	*BNF*, 2008[18]
Revascularisation year 1	£5857	£2928	£8785	*BNF*, 2008[18]
Stroke year 1	£8066	£296	£887	Ward *et al.*, 2007[59]
Stroke year 2+	£2266	£1844	£5532	Ward *et al.*, 2007[59]
Fatal CHD event	£592	£4033	£12,099	Ward *et al.*, 2007[59]
Fatal non-coronary vascular event	£3688	£1133	£3399	Ward *et al.*, 2007[59]
Monitoring cost for high-dose statin	£76			

ACS, acute coronary syndrome; CHD, coronary heart disease; MI, myocardial infarction.

uncertainty in the health state costs and costs were discounted at 3.5%.[101]

Monitoring costs

The safety profile for statin therapy is good with adverse events predominantly consisting of myopathy or myalgia. However, evidence suggests that there is a relationship between statin potency and the frequency of adverse events, which could increase non-adherence to medication. It was assumed that individuals on high potency statins would incur additional monitoring costs in the form of two additional GP visits per year with full blood counts conducted by the practice nurse (£76.00). The cost of monitoring was reduced in proportion to adherence (see Scenarios).

Treatment costs

The costs of statin treatment were taken from the *British National Formulary*[18] and are provided in *Table 10*. When generic alternatives for simvastatin became available there was a substantial decrease in the cost associated with this treatment. The cost for a pack of simvastatin 40 mg/day fell from £23.18 in 2004 to £1.31 in 2008.[59] When the patent for atorvastatin expires in 2011 the cost of this treatment is likely to fall considerably. We explored the effect on the results if it was assumed that the annual cost for atorvastatin 80 mg/day decreased to £90 per annum or if it decreased in line with that observed for simvastatin (i.e. to £20.78 per annum).

Health state utility values

The health state utility values (*Table 11*) were taken from a cardiovascular model used in a recent Health Technology Assessment (HTA) report.[100] These data were obtained from a literature review of published evidence on preference-based utility measures for the different health states modelled. The studies identified were evaluated based on the following criteria:

- data collected using the EuroQol 5 dimensions (EQ-5D) instrument as recommended for the NICE reference case
- preference-based utility scores obtained from the UK EQ-5D preference weights
- UK studies preferred to non-UK studies.

Unstable angina

The results from an RCT comparing care in a chest pain clinic observation unit ($n = 676$) with routine care in the emergency department of the Northern

TABLE 10 *Annual treatment costs*

Statin	Cost per pack of 28[18]	Annual cost
Atorvastatin 80 mg/day	£28.21	£367.74
Rosuvastatin 40 mg/day	£29.69	£387.03
Simvastatin 40 mg/day	£1.31	£17.08
Simvastatin 80 mg/day (assumed two times simvastatin 40 mg/day)		£34.15

TABLE 11 *Health state utility utilities*

Health state	First year	Subsequent years[a]	Source
Unstable angina	0.77	0.847	Goodacre *et al*., 2008[110]
Revascularisation	0.78	0.858	Serruys *et al*., 2001[111]
MI	0.76	0.836	Goodacre *et al*., 2008[110]
Stroke	0.629	0.692	Pickard *et al*., 2005[112]

MI, myocardial infarction.
a Assumed utility increases by 10% in subsequent years.

General Hospital in Sheffield suggested that the mean utility score measured using the EQ-5D at 6 months post diagnosis of unstable angina was 0.77.[59,110] It was assumed that 0.77 represents the HRQoL associated with the unstable angina health state. This was increased by 10% to 0.847 for the post event health state.

Revascularisation

The EQ-5D questionnaire was used to estimate utility values in 1205 patients randomly assigned to undergo either stent implantation or bypass surgery in the Arterial Revascularization Therapies Study (ARTS).[111] The mean utility value at baseline (3 months, 6 months and 12 months) was reported to be 0.68 (0.78, 0.86 and 0.87).[111] It has been assumed that 0.78 represents the HRQoL associated with the revascularisation health state. This was increased by 10% to 0.858 for the post event health state.

Myocardial infarction

The study by Goodacre *et al*. also collected EQ-5D data on individuals who had an MI (mean value was 0.76).[59,110] It was assumed that 0.76 represents the HRQoL associated with the MI health state. This was increased by 10% to 0.836 for the post event health state.

Stroke

A study ($n = 98$) by Pickard *et al*.[112] reported an increase in mean EQ-5D score from 0.31 (SD 0.38) at baseline to 0.629 (SD 0.33) at 6 months post stroke. These figures suggest that there is an initial large reduction in HRQoL and that the long-term HRQoL, although substantially lower than before the stroke, increases in the majority of individuals. It was assumed that 0.629 represents the HRQoL associated with the stroke health state. This was increased by 10% to 0.692 for the post event health state.

Subsequent major events

No evidence was found that could be used to model the effect on HRQoL for patients who have more than one cardiovascular event. An additional decrement of 10% was applied for subsequent major events such as MI or stroke. Uncertainty in the quality of life values was explored using beta distributions.

Health-related quality of life utility by age

A study by Kind *et al*.[113] using EQ-5D data collected from a sample ($n = 3395$) of the UK general population was used to inform changes in quality of life by age (*Table 12*). These data were used as the baseline HRQoL. It is acknowledged that by including a baseline utility adjusted for age there will be a small element of double counting as a proportion of individuals in the sample used in the Kind *et al*. study will have a history of ACS.

Scenarios

Based on the limited evidence available we used three different scenarios to examine the effects of possible reductions in adherence rates in clinical

TABLE 12 *Utility values by age*[113]

Age (years)	Utility
50	0.848
55	0.826
60	0.805
65	0.784
70	0.763
75	0.741

Utility = 1.060 − 0.004 × age.

practice. The RRs and treatment and monitoring costs were adjusted to account for the proportion of individuals who adhere to therapy.

Scenario 1

Adherence rates in statin clinical trials are reported to range between 80% and 90%. The effectiveness rates used in the current study are based on ITT analyses of changes in LDL-c values. It was assumed that adherence rates and discontinuation rates due to adverse events in clinical practice would be as observed in the clinical studies and no adjustments were made to the benefits or treatment or monitoring costs. The results generated for these analyses are applicable for individuals who tolerate the higher doses and adhere to treatment.

Scenario 2

It was assumed that adherence to statin therapy would be higher in individuals receiving simvastatin 40 mg/day than in those receiving the more potent doses (atorvastatin 80 mg/day, rosuvastatin 40 mg/day and simvastatin 80 mg/day). As in scenario 1 it was assumed that the ITT data for simvastatin 40 mg/day would reflect the benefits that would be achieved in clinical practice and that there would be an equal reduction in adherence rates for the three more potent statin doses. It was assumed that the proportion of individuals adhering to treatment decreased rapidly over the first 2 years (a reduction of 5% in each year), reducing more gradually over the next 3 years (a linear reduction of 5% over 3 years) until rates stabilised during the fifth year (*Table 13*). The benefits and treatment and monitoring costs were adjusted to reflect the proportions adhering to treatment.

Scenario 3

Based on the limited evidence base it was assumed that adherence rates are related to both brand of statin and dose. It was assumed that adherence rates were highest for the lower potency regimen of simvastatin 40 mg/day. Simvastatin 80 mg/day is not well tolerated in clinical practice and evidence suggests an 11-fold increase in rates of myopathy and myositis in patients receiving this dose compared with simvastatin 20 mg/day.[79] It was assumed that adherence rates would be lowest for this regimen. It has been hypothesised that rosuvastatin may be associated with low incidences rates of myopathy and myalgia, and recently published results show no significant difference in rates at any dose ratio when compared with atorvastatin (maximum doses being rosuvastatin 40 mg/day and atorvastatin 80 mg/day).[114,115] However, with no long-term data to support this it was assumed that adherence rates would be

TABLE 13 *Adherence rates used in scenarios 1, 2 and 3*

Treatment	1 year	2 years	3 years	4 years	5 years
Scenario 1					
Atorvastatin 80 mg/day	As per clinical trials				
Rosuvastatin 40 mg/day	As per clinical trials				
Simvastatin 40 mg/day	As per clinical trials				
Simvastatin 80 mg/day	As per clinical trials				
Scenario 2					
Atorvastatin 80 mg/day	95%	90%	88%	87%	85%
Rosuvastatin 40 mg/day	95%	90%	88%	87%	85%
Simvastatin 40 mg/day	As per clinical trials				
Simvastatin 80 mg/day	95%	90%	88%	87%	85%
Scenario 3					
Atorvastatin 80 mg/day	75%	70%	68%	67%	65%
Rosuvastatin 40 mg/day	73%	68%	66%	64%	63%
Simvastatin 40 mg/day	80%	75%	73%	72%	70%
Simvastatin 80 mg/day	70%	65%	63%	62%	60%

slightly lower for rosuvastatin 40 mg/day than for atorvastatin 80 mg/day. As in scenario 2, the proportion of individuals adhering to treatment decreased rapidly over the first 2 years, reducing more gradually over the next 3 years (a linear reduction of 5% over 3 years) until rates stabilised during the fifth year (*Table 13*). The benefits and treatment and monitoring costs were adjusted to reflect the proportions adhering to treatment.

Scenario 4

The adherence scenarios explored give an indication of the effects on the results if adherence is lower in clinical practice than observed in the RCTs, with the results generated for scenario 1 being a conservative estimate of the cost-effectiveness for individuals who adhere to treatment. To explore the effects of non-adherence, the RRs and treatment and monitoring costs were adjusted in proportion to the adherence rates modelled. This implies that individuals not adhering to treatment will not receive an alternative statin. However, it is likely that patients who do not tolerate the higher doses will be prescribed a lower-dose statin. Using the adherence rates for scenario 2 (*Table 13*), scenario 4 explores the cost-effectiveness of the treatments if it is assumed that individuals who do not adhere to the higher doses (atorvastatin 80 mg/day, rosuvastatin 40 mg/day and simvastatin 80 mg/day) switch to simvastatin 40 mg/day. The RRs and treatment costs were adjusted to reflect the proportions on each statin dose.

Sensitivity analyses

Sensitivity analyses were performed because there is always uncertainty in decision analysis. We used two methods to characterise this uncertainty: one-way sensitivity analyses and Monte Carlo simulations. One-way sensitivity analysis is a procedure in which the central estimates for key parameters in the model are varied one at a time. New results are generated from the model using the adjusted values and recorded. This process is repeated for key parameters in the model. One-way sensitivity analysis informs readers as to which variables drive the results generated by the model, but does not provide information on the overall uncertainty associated with the model. Monte Carlo simulations are used to create a probabilistic sensitivity analysis, which is a method of varying all variables simultaneously to assess the overall uncertainty in the model.[109] The individual simulations (5000) are generated using random numbers (0–1) to sample from the distributions. New results are generated by the model and each of the 5000 results stored. The recorded results are then used to illustrate the overall variability in the model. The 95% confidence intervals around the mean cost per QALY were estimated using jackknife techniques whereby the variance is estimated by sampling the residuals in the 5000 samples.[116]

Incremental cost-effectiveness ratio

The results are presented in terms of the incremental cost-effectiveness of each higher-dose statin compared with simvastatin 40 mg/day. The primary outcome is the incremental cost-effectiveness ratio (ICER). The ICER demonstrates the additional cost per QALY gained from treatment A compared with treatment B where treatment A is one of the higher-dose statins and treatment B is simvastatin 40 mg/day:

$$\text{ICER} = (\text{cost treatment A} - \text{cost treatment B}) / (\text{utility treatment A} - \text{utility treatment B})$$

Optimal treatment

Although the primary objective is to evaluate the cost-effectiveness of the higher-dose statins compared with simvastatin 40 mg/day, cost per QALY values may be difficult to interpret as the smallest value is not always associated with the optimal treatment. A hierarchy of interventions can be calculated by ranking all interventions in order of ascending health gain and initially comparing the two least effective treatments. If the resulting incremental cost per QALY is below a given cost per QALY threshold, the more effective treatment is selected as optimal. Similar comparisons are then iteratively conducted between the current optimal treatment and the next most efficacious treatment until the list is exhausted and the optimal treatment is found.

Net benefit

Results are also presented in terms of the 'net benefit' of the treatments. Because of the potential difficulties in interpreting cost per QALY values when more than two treatments are being compared, the use of net benefit is becoming more widespread. Although these results are analogous to those presented in the more traditional cost per QALY format, there is less scope for mistakes when interpreting the data as net benefit values can be directly compared across interventions. Net benefit is calculated using the formula $NB = \lambda \times QALY - cost$, where λ denotes the maximum cost that society is prepared to pay. When net benefit is positive the treatment is cost-

effective; when net benefit is negative the treatment is not cost-effective; and when net benefit is zero the cost per QALY is equal to the maximum cost per QALY that society is prepared to pay. The intervention with the highest net benefit is the most cost-effective at a given threshold.

Economic results

The following section describes the cost-effectiveness results for cohorts of 1000 individuals commencing treatment at the age of 60 years with ICERs generated using the costs and benefits accrued over a lifetime.

First, the results from the probabilistic sensitivity analyses (generated using 5000 Monte Carlo simulations) for each of the four different scenarios are presented. Results are compared in terms of the average numbers of events in each treatment arm. The cost-effectiveness of each of the individual higher-dose treatments is compared with that of simvastatin 40 mg/day and the results are described using ICERs and cost-effectiveness planes. The probabilistic sensitivity results are then used to identify a hierarchy in terms of the optimal treatment at a given cost per QALY threshold by ranking according to the benefits of the treatments. This is followed by a section describing the results in terms of the net benefit of the individual treatments using cost-effectiveness acceptability curves.

The penultimate set of analyses examines the potential differences in the ICERs and the net benefits of the treatments if the cost of atorvastatin 80 mg/day is reduced. Finally, a series of univariate sensitivity analyses are conducted to explore the effect of varying key parameters.

Probabilistic base-case analyses

For scenario 1 (*Table 14*), when assuming that the ITT results are representative of the benefits observed in clinical practice, simvastatin 80 mg/day is estimated to avoid on average 16 fatal CHD events, five fatal non-cardiac-related vascular events, 24 hospitalisations for unstable angina, 37 non-fatal MIs and three non-fatal strokes in comparison with simvastatin 40 mg/day. Atorvastatin 80 mg/day is estimated to avoid on average 33 fatal CHD events, 10 fatal non-cardiac-related vascular events, 51 hospitalisations for unstable angina, 78 non-fatal MIs and seven non-fatal strokes in comparison with simvastatin 40 mg/day. Rosuvastatin 40 mg/day is estimated to avoid on average 45 fatal CHD events, 14 fatal non-cardiac-related vascular events, 70 hospitalisations for unstable angina, 108 non-fatal MIs and nine non-fatal strokes in comparison with simvastatin 40 mg/day. The deaths from other causes are higher for the more potent statins because of the reduction in cardiovascular fatal events.

For scenario 2 (*Table 14*), when assuming that the ITT results are representative of the benefits associated with simvastatin 40 mg/day, but that the benefits associated with the more potent doses are reduced by equal amounts to take into account a potential reduction in adherence, simvastatin 80 mg/day is estimated to avoid on average two fatal CHD events, one fatal non-cardiac-related vascular event, four hospitalisations for unstable angina, five non-fatal MIs and less than one non-fatal stroke in comparison with simvastatin 40 mg/day. Atorvastatin 80 mg/day is estimated to avoid on average 17 fatal CHD events, five fatal non-cardiac-related vascular events, 27 hospitalisations for unstable angina, 40 non-fatal MIs and three non-fatal strokes in comparison with simvastatin 40 mg/day. Rosuvastatin 40 mg/day is estimated to avoid on average 27 fatal CHD events, eight fatal non-cardiac-related vascular events, 43 hospitalisations for unstable angina, 64 non-fatal MIs and six non-fatal strokes in comparison with simvastatin 40 mg/day.

For scenario 3 (*Table 14*), when assuming that adherence to therapy is reduced for all four treatment regimens with simvastatin 40 mg/day having the highest adherence rate and simvastatin 80 mg/day the lowest, simvastatin 80 mg/day is estimated to avoid on average one fatal CHD event, less than one fatal non-cardiac-related vascular event, two hospitalisations for unstable angina, three non-fatal MIs and less than one non-fatal stroke in comparison with simvastatin 40 mg/day. Atorvastatin 80 mg/day is estimated to avoid on average 17 fatal CHD events, five fatal non-cardiac-related vascular events, 27 hospitalisations for unstable angina, 39 non-fatal MIs and four non-fatal strokes in comparison with simvastatin 40 mg/day. Rosuvastatin 40 mg/day is estimated to avoid on average 21 fatal CHD events, seven fatal non-cardiac-related vascular events, 34 hospitalisations for unstable angina, 50 non-fatal MIs and five non-fatal strokes in comparison with simvastatin 40 mg/day.

TABLE 14 *The average number of events over a lifetime (for a cohort commencing high-dose statin therapy at the age of 60 years)*

	Simvastatin 40 mg/day	**Simvastatin 80 mg/day**	**Atorvastatin 80 mg/day**	**Rosuvastatin 40 mg/day**
Scenario 1				
Total number of fatal events in each arm (number of events avoided compared with simvastatin 40 mg/day)				
CHD	248	232 (16)	215 (33)	203 (45)
CVD	132	127 (5)	121 (10)	117 (14)
Other deaths	619	639 (–20)	662 (–43)	678 (–59)
Total number of non-fatal events in each arm (number of events avoided compared with simvastatin 40 mg/day)				
UA	228	204 (24)	177 (51)	159 (70)
MI	398	361 (37)	320 (78)	290 (108)
Stroke	55	51 (3)	48 (7)	45 (9)
Scenario 2				
Total number of fatal events in each arm (number of events avoided compared with simvastatin 40 mg/day)				
CHD	247	245 (2)	231 (17)	221 (27)
CVD	131	131 (1)	126 (5)	123 (8)
Other deaths	620	623 (–2)	642 (–22)	655 (–35)
Total number of non fatal events in each arm (number of events avoided compared with simvastatin 40 mg/day)				
UA	229	226 (4)	202 (27)	186 (43)
MI	398	392 (5)	357 (40)	333 (64)
Stroke	55	55 (0.3)	52 (3)	50 (6)
Scenario 3				
Total number of fatal events in each arm (number of events avoided compared with simvastatin 40 mg/day)				
CHD	271	269 (1)	254 (17)	249 (21)
CVD	139	138 (0.4)	134 (5)	132 (7)
Other deaths	589	591 (–2)	611 (–22)	617 (–28)
Total number of non fatal events in each arm (number of events avoided compared with simvastatin 40 mg/day)				
UA	265	263 (2)	238 (27)	231 (34)
MI	451	448 (3)	412 (39)	401 (50)
Stroke	60	60 (0.2)	56 (4)	56 (5)
Scenario 4				
Total number of fatal events in each arm (number of events avoided compared with simvastatin 40 mg/day)				
CHD	247	234 (13)	219 (28)	209 (39)
CVD	132	128 (4)	123 (9)	119 (12)
Other deaths	619	637 (–18)	656 (–37)	670 (–51)
Total number of non fatal events in each arm (number of events avoided compared with simvastatin 40 mg/day)				
UA	230	209 (21)	185 (45)	169 (61)
MI	398	366 (32)	330 (67)	305 (93)
Stroke	55	52 (3)	49 (6)	47 (8)

CHD, coronary heart disease; CVD, coronary vascular disease; MI, myocardial infarction; UA, unstable angina.

For scenario 4 (*Table 14*), using the adherence levels as in scenario 2 (i.e. assuming that the ITT results are representative of the benefits associated with simvastatin 40 mg/day, but that the benefits associated with the more potent doses are reduced by equal amounts to take into account a potential reduction in adherence) and assuming that all individuals who do not adhere to the higher-dose treatment receive simvastatin 40 mg/day, simvastatin 80 mg/day is estimated to avoid on average 13 fatal CHD events, four fatal non-cardiac-related vascular events, 21 hospitalisations for unstable angina, 32 non-fatal MIs and three non-fatal strokes in comparison with simvastatin 40 mg/day. Atorvastatin 80 mg/day is estimated to avoid on average 28 fatal CHD events, nine fatal non-cardiac-related vascular events, 45 hospitalisations for unstable angina, 67 non-fatal MIs and six non-fatal strokes in comparison with simvastatin 40 mg/day. Rosuvastatin 40 mg/day is estimated to avoid on average 39 fatal CHD events, 12 fatal non-cardiac-related vascular events, 61 hospitalisations for unstable angina, 93 non-fatal MIs and eight non-fatal strokes in comparison with simvastatin 40 mg/day.

For scenario 1, when comparing simvastatin 80 mg/day with simvastatin 40 mg/day, the avoided events provide an average 111 more QALYs (*Table 15*) over a lifetime of treatment. The total incremental costs are estimated to be £588,000, giving a cost per QALY of £5319. When comparing atorvastatin 80 mg/day with simvastatin 40 mg/day, the avoided events provide an average 232 more QALYs. The total incremental costs are estimated to be £4,050,000, giving a cost per QALY of £17,469. When comparing rosuvastatin 40 mg/day with simvastatin 40 mg/day, the avoided events provide an average 316 more QALYs. The total incremental costs are estimated to be £3,942,000, giving a cost per QALY of £12,484.

For scenario 2, when comparing simvastatin 80 mg/day with simvastatin 40 mg/day, the avoided events provide an average 23 more QALYs (*Table 15*) over a lifetime of treatment. The total incremental costs are estimated to be £827,000, giving a cost per QALY of £35,445. When comparing atorvastatin 80 mg/day with simvastatin 40 mg/day, the avoided events provide an average 129 more QALYs. The total incremental costs are estimated to be £3,795,000, giving a cost per QALY of £29,422. When comparing rosuvastatin 40 mg/day with simvastatin 40 mg/day, the avoided events provide an average 201 more QALYs. The total incremental costs are estimated to be £3,695,000, giving a cost per QALY of £18,372.

For scenario 3, when comparing simvastatin 80 mg/day with simvastatin 40 mg/day, the avoided events provide an average 10 more QALYs (*Table 15*) over a lifetime of treatment. The total incremental costs are estimated to be £597,000, giving a cost per QALY of £59,200. When comparing atorvastatin 80 mg/day with simvastatin 40 mg/day, the avoided events provide an average 125 more QALYs. The total incremental costs are estimated to be £2,739,000, giving a cost per QALY of £21,938. When comparing rosuvastatin 40 mg/day with simvastatin 40 mg/day, the avoided events provide an average 158 more QALYs. The total incremental costs are estimated to be £2,619,000, giving a cost per QALY of £16,592.

For scenario 4, when comparing simvastatin 80 mg/day with simvastatin 40 mg/day, the avoided events provide an average 97 more QALYs (*Table 15*) over a lifetime of treatment. The total incremental costs are estimated to be £506,000, giving a cost per QALY of £5226. When comparing atorvastatin 80 mg/day with simvastatin 40 mg/day, the avoided events provide an average 203 more QALYs. The total incremental costs are estimated to be £3,495,000, giving a cost per QALY of £17,217. When comparing rosuvastatin 40 mg/day with simvastatin 40 mg/day, the avoided events provide an average 276 more QALYs. The total incremental costs are estimated to be £3,393,000, giving a cost per QALY of £12,277.

The cost-effectiveness plane for scenario 1 (*Figure 2*) shows the individual results for each of the treatment regimens compared with simvastatin 40 mg/day, with each point representing the result of one of the Monte Carlo samples. As can be seen, a large proportion of the results for each regimen would be considered cost-effective when using a cost per QALY threshold of £20,000 per QALY: 98% for simvastatin 80 mg/day, 91% for rosuvastatin 40 mg/day and 66% for atorvastatin 80 mg/day.

The cost-effectiveness plane for scenario 2 (Appendix 6, *Figure 6*) shows that a proportion (21%) of the results for simvastatin 80 mg/day versus simvastatin 40 mg/day have a higher cost with a smaller benefit, and just 30% of results would be considered cost-effective when using a threshold of £20,000 per QALY. Using a threshold of £20,000 per QALY, 10% (56%) of the results for the comparison atorvastatin 80mg/day versus

TABLE 15 *Probabilistic base-case results (for a cohort of 1000 men aged 60 years, generated using 5000 simulations)*

	Simvastatin 40 mg/day	**Simvastatin 80 mg/day**	**Atorvastatin 80 mg/day**	**Rosuvastatin 40 mg/day**
Scenario 1				
Discounted benefits				
Life-years	11,686	11,851	12,033	12,158
QALYs	7546	7657	7778	7862
Incremental discounted QALYs		111	232	316
Discounted costs				
Total	£14,522,049	£15,110,134	£18,572,208	£18,463,934
Incremental total discounted costs		£588,085	£4,050,159	£3,941,885
Incremental cost-effectiveness ratio				
ICER		£5319	£17,469	£12,484
Confidence interval		£5229 to £5408	£17,330 to £17,604	£12,372 to £12,595
Scenario 2				
Discounted benefits				
Life-years	11,693	11,727	11,886	11,993
QALYs	7543	7566	7672	7744
Incremental discounted QALYs		23	129	201
Discounted costs				
Total	£14,511,140	£15,338,411	£18,306,366	£18,206,201
Incremental total discounted costs		£827,271	£3,795,226	£3,695,061
Incremental cost-effectiveness ratio				
ICER		£35,445	£29,422	£18,372
Confidence interval		£34,022 to £36,842	£29,136 to £29,706	£18,200 to £18,557
Scenario 3				
Discounted benefits				
Life-years	11,448	11,463	11,635	11,685
QALYs	7383	7393	7507	7540
Incremental discounted QALYs		10	125	158
Discounted costs				
Total	£15,232,422	£15,829,566	£17,971,442	£17,851,218
Incremental total discounted costs		£597,144	£2,739,020	£2,618,796
Incremental cost-effectiveness ratio				
ICER		£59,200	£21,938	£16,592
Confidence interval		£53,300 to £64,826	£21,699 to £22,186	£16,407 to £16,776

continued

TABLE 15 *Probabilistic base-case results (for a cohort of 1000 men aged 60 years, generated using 5000 simulations) (continued)*

	Simvastatin 40 mg/day	Simvastatin 80 mg/day	Atorvastatin 80 mg/day	Rosuvastatin 40 mg/day
Scenario 4				
Discounted benefits				
Life-years	11,688	11,833	11,991	12,101
QALYs	7545	7642	7748	7821
Incremental discounted QALYs		97	203	276
Discounted costs				
Total	£14,547,316	£15,053,288	£18,042,271	£17,940,003
Incremental total discounted costs		£505,972	£3,494,954	£3,392,687
Incremental cost-effectiveness ratio				
ICER		£5226	£17,217	£12,277
Confidence interval		£5138 to £5315	£17,081 to £17,353	£12,167 to £12,387

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.
The incremental values are high dose compared with simvastatin 40 mg/day.

simvastatin 40 mg/day (rosuvastatin 40 mg/day versus simvastatin 40 mg/day) would be considered cost-effective.

The cost-effectiveness plane for scenario 3 (Appendix 6, *Figure 7*) shows that 38% of the results for simvastatin 80 mg/day versus simvastatin 40 mg/day have a higher cost with a smaller benefit, and 30% of the results would be considered cost-effective when using a threshold of £20,000 per QALY. Using a threshold of £20,000 per QALY, 75% (90%) of the results for the comparison atorvastatin 80 mg/day versus simvastatin 40 mg/day (rosuvastatin 40 mg/day versus simvastatin 40 mg/day) would be considered cost-effective.

The cost-effectiveness plane for scenario 4 (Appendix 6, *Figure 8*) shows that a large proportion of the results for each regimen would be considered cost-effective when using a threshold

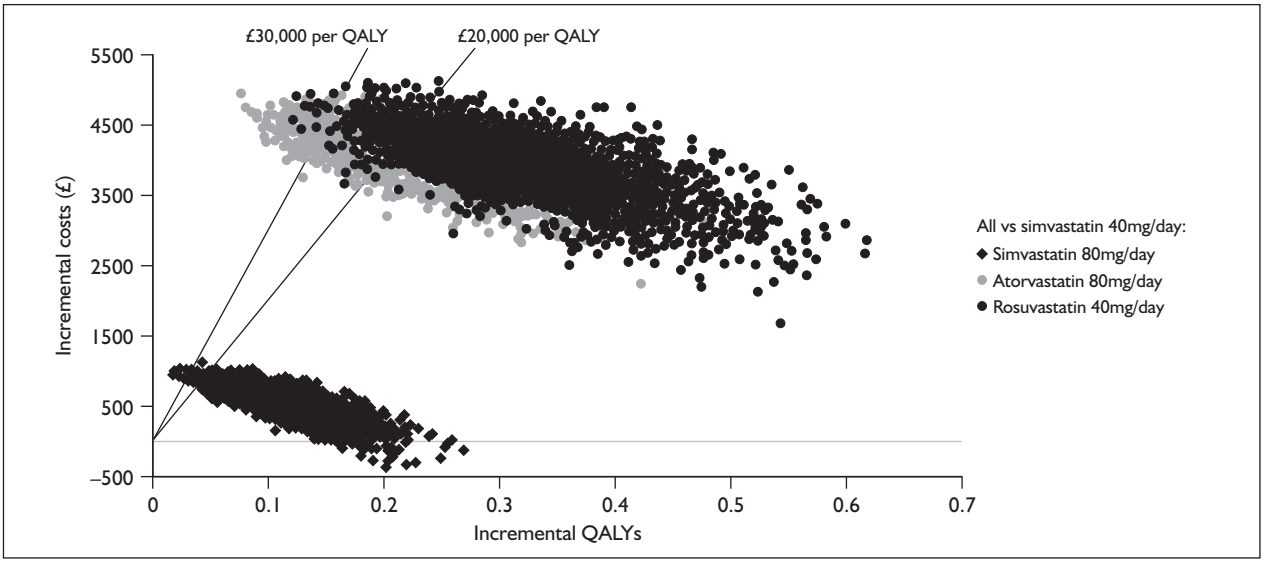

FIGURE 2 *Cost-effectiveness plane: scenario 1, generated using 5000 Monte Carlo simulations.*

of £20,000 per QALY: 99% for simvastatin 80 mg/day, 92% for rosuvastatin 40 mg/day and 68% for atorvastatin 80 mg/day.

Comparing all treatment regimens

The ICERs for all possible treatment comparisons for each scenario are provided in *Table 16*. For scenario 1, when ranking according to the benefits of the individual treatments, rosuvastatin 40 mg/day dominates atorvastatin 80 mg/day with greater QALYs gained (7.86 versus 7.78) at a smaller cost (£18,464 versus £18,572). The hierarchy of treatments shows a similar trend for each of the scenarios.

Net benefit

For scenario 1, when assessing the net benefit of the interventions, simvastatin 40 mg/day is the most cost-effective treatment if the maximum threshold is below £5000 per QALY (*Figure 3*). Simvastatin 80 mg/day is the most cost-effective treatment if the threshold is between £5000 and £16,000 per QALY and rosuvastatin 40 mg/day is the most cost-effective treatment if the threshold is greater than £15,000 per QALY. Atorvastatin 80 mg/day is never the most cost-effective treatment irrespective of the threshold. Similar results are observed for scenario 4 (Appendix 6, *Figure 11*). For scenarios 2 and 3 (Appendix 6, *Figures 9* and *10* respectively), simvastatin 40 mg/day is the most cost-effective treatment if the maximum threshold is below £18,000 per QALY. Rosuvastatin 40 mg/day is the

TABLE 16 *Hierarchy of treatments (per patient)*

	Cost	QALY	CER	ICER
Scenario 1				
Rosuvastatin 40 mg/day	£18,464	7.86	£2349	£16,344[a]
Atorvastatin 80 mg/day	£18,572	7.78	£2388	Dominated[b]
Simvastatin 80 mg/day	£15,110	7.66	£1973	£28,540[c]
Simvastatin 40 mg/day	£14,522	7.55	£1924	£5319
Scenario 2				
Rosuvastatin 40 mg/day	£18,206	7.74	£2351	£16,137[a]
Atorvastatin 80 mg/day	£18,306	7.67	£2386	Dominated[b]
Simvastatin 80 mg/day	£15,338	7.57	£2027	£28,091
Simvastatin 40 mg/day	£14,511	7.54	£1924	£35,445
Scenario 3				
Rosuvastatin 40 mg/day	£17,851	7.54	£2367	£13,683[a]
Atorvastatin 80 mg/day	£17,971	7.51	£2394	Dominated[b]
Simvastatin 80 mg/day	£15,830	7.39	£2141	£18,663
Simvastatin 40 mg/day	£15,232	7.38	£2063	£59,200
Scenario 4				
Rosuvastatin 40 mg/day	£17,940	7.82	£2294	£16,079[a]
Atorvastatin 80 mg/day	£18,042	7.75	£2329	Dominated[b]
Simvastatin 80 mg/day	£15,053	7.64	£1970	£28,150
Simvastatin 40 mg/day	£14,547	7.54	£1928	£5226

CER, cost-effectiveness ratio; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.
a Rosuvastatin 40 mg/day versus simvastatin 80 mg/day.
b Dominated = higher costs and lower benefits.
c Extendedly dominated.

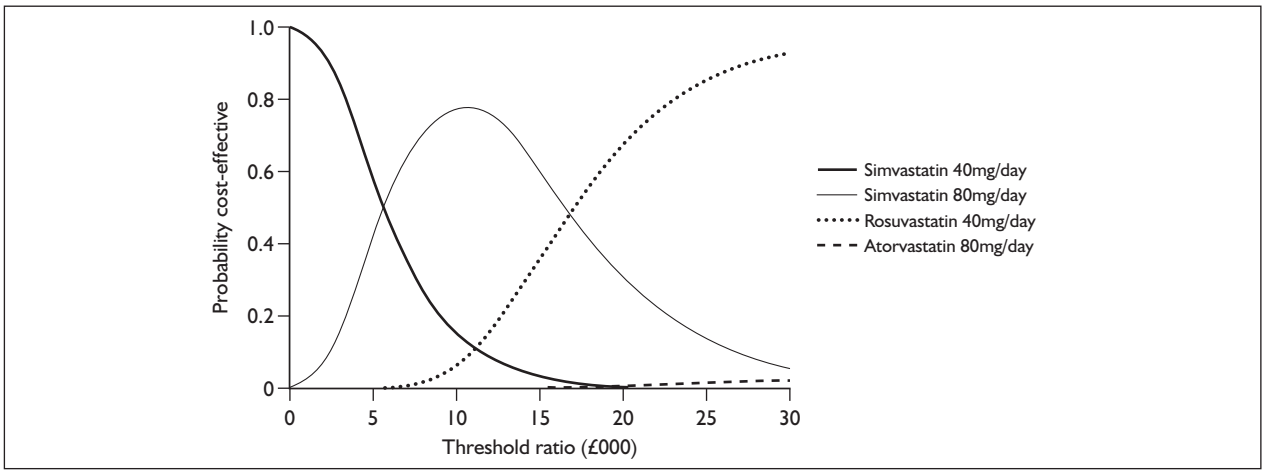

FIGURE 3 *Cost-effectiveness acceptability curve: scenario 1.*

most cost-effective treatment if the threshold is greater than this threshold. Simvastatin 80 mg/day and atorvastatin 80 mg/day are never the most cost-effective treatments irrespective of the threshold.

Cost of atorvastatin

The annual cost for atorvastatin 80 mg/day is currently £367.74 but when the patent expires in 2011 this cost is likely to fall substantially. When reducing the cost for atorvastatin 80 mg/day to £92 per annum, the cost per QALY (compared with simvastatin 40 mg/day) reduces to £3172 for scenario 1. The corresponding value for scenario 2 (scenario 3, scenario 4) is £7331 (£4739, £3155) per QALY.

If the cost of atorvastatin reduces in line with that observed for simvastatin when it came off patent, for scenario 1, assuming an annual cost for atorvastatin 80 mg/day of £20.78, when assessing the net benefit of the interventions the most cost-effective treatment is atorvastatin 80 mg/day (*Figure 4*). Assuming an annual cost of £92 for atorvastatin 80 mg/day, the most cost-effective treatment below a threshold of £4000 per QALY is simvastatin 40 mg/day (Appendix 6, *Figure 12*), whereas atorvastatin 80 mg/day is the most cost-effective treatment for thresholds between £5000 and £30,000 per QALY.

Univariate sensitivity analyses

A series of one-way sensitivity analyses (*Table 17*) were conducted to determine the effect on the results when varying key parameter variables. The results are robust to changes in values for the health state costs. However, if it is assumed that there are no additional monitoring costs associated

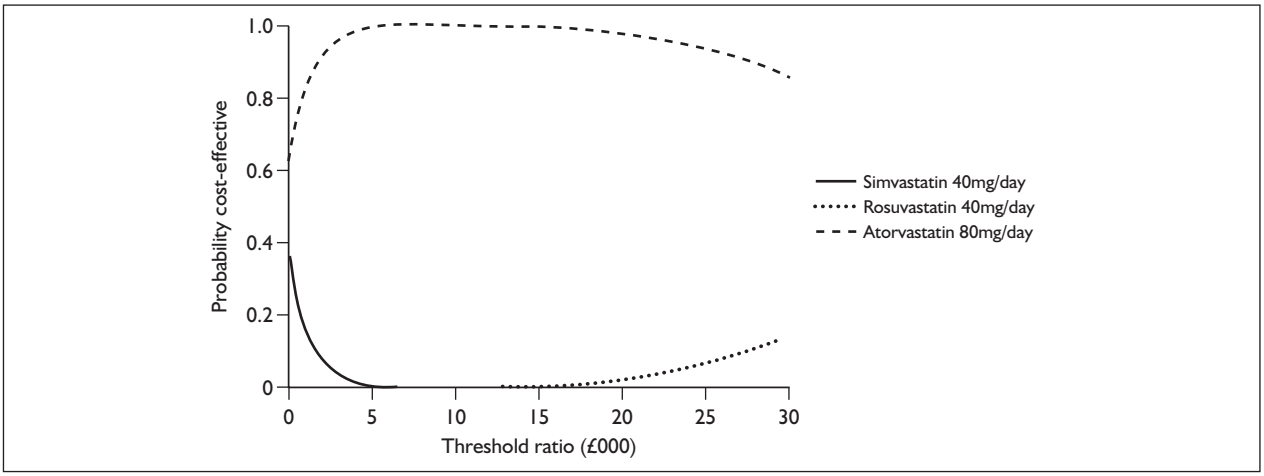

FIGURE 4 *Cost-effectiveness acceptability curve assuming lower cost for atorvastatin: scenario 1: atorvastatin 80 mg/day = £20.78 per annum.*

TABLE 17 *Results of the univariate sensitivity analyses*

Adherence scenario	Parameter	Incremental cost-effectiveness ratio		
		Simvastatin 80 mg/day vs simvastatin 40 mg/day	Atorvastatin 80 mg/day vs simvastatin 40 mg/day	Rosuvastatin 40 mg/day vs simvastatin 40 mg/day
Deterministic base case				
Scenario 1		£5494	£17,819	£12,783
Scenario 2		£33,135	£29,496	£18,502
Scenario 3		£63,083	£22,348	£16,949
Scenario 4		£5494	£17,819	£12,783
Undiscounted				
Scenario 1	0%	£3043	£13,144	£9026
Scenario 2	0%	£30,102	£23,403	£14,021
Scenario 3	0%	£63,083	£22,348	£16,949
Scenario 4	0%	£2996	£12,973	£8884
Baseline age of cohort				
Scenario 1	Age 50 years	£7007	£20,389	£14,848
Scenario 2	Age 50 years	£46,707	£34,716	£21,800
Scenario 3	Age 50 years	£77,004	£25,933	£19,903
Scenario 4	Age 50 years	£6963	£20,255	£14,733
Scenario 1	Age 70 years	£3996	£15,511	£10,851
Scenario 2	Age 70 years	£22,167	£24,637	£15,378
Scenario 3	Age 70 years	£50,867	£19,261	£14,337
Scenario 4	Age 70 years	£3891	£15,189	£10,589
Health state costs				
Scenario 1	Plus 50%	£3161	£15,480	£10,438
Scenario 2	Plus 50%	£31,076	£27,226	£16,209
Scenario 3	Plus 50%	£60,878	£20,055	£14,655
Scenario 4	Plus 50%	£3102	£15,267	£10,264
Scenario 1	Minus 50%	£7816	£20,148	£15,118
Scenario 2	Minus 50%	£35,184	£31,755	£20,784
Scenario 3	Minus 50%	£65,277	£24,631	£19,234
Scenario 4	Minus 50%	£7732	£19,908	£14,916
Health state utility values				
Scenario 1	Plus 20%	£4729	£15,347	£11,016
Scenario 2	Plus 20%	£28,523	£25,389	£15,933
Scenario 3	Plus 20%	£54,198	£19,201	£14,565
Scenario 4	Plus 20%	£4666	£15,150	£10,851
Scenario 1	Minus 20%	£4729	£15,347	£11,016
Scenario 2	Minus 20%	£28,523	£25,389	£15,933
Scenario 3	Minus 20%	£54,198	£19,201	£14,565
Scenario 4	Minus 20%	£6778	£21,991	£15,744

continued

TABLE 17 *Results of the univariate sensitivity analyses (continued)*

Adherence scenario	Parameter	Incremental cost-effectiveness ratio		
		Simvastatin 80 mg/day vs simvastatin 40 mg/day	**Atorvastatin 80 mg/day vs simvastatin 40 mg/day**	**Rosuvastatin 40 mg/day vs simvastatin 40 mg/day**
No additional monitoring costs for higher-dose therapies				
Scenario 1	Monitoring = zero	Dominates	£13,819	£9812
Scenario 2	Monitoring = zero	£1905	£23,404	£14,552
Scenario 3	Monitoring = zero	£6312	£17,542	£13,268
Scenario 4	Monitoring = zero	Dominates	£13,638	£9661
Using upper confidence interval from the MI RR to represent RR for UA				
Scenario 1		£5812	£18,251	£13,236
Scenario 2		£33,654	£30,053	£19,089
Scenario 3		£63,800	£22,924	£17,587
Scenario 4		£5743	£18,035	£13,059

MI, myocardial infarction; RR, relative risk; UA, unstable angina.
Dominates: greater benefits with lower costs.

with the more potent doses, the ICERs are reduced by approximately 20%. The ICERs decrease with starting age of treatment as would be expected, reflecting the higher risk of the older population and thus the potential to avoid events. When decreasing the utilities for all health states the ICERs increase by approximately 14% reflecting the decrease in benefits from events avoided. Increasing the utilities decreases the ICERs by approximately 25%. It was assumed that utility values for the post event health states increased by 10% in the base case and the results were robust to changes in this assumption (Appendix 6, *Table 22*).

Because there is no established link between reductions in LDL-c and unstable angina we assumed that the RR for MI was representative of the benefits for unstable angina. Using the upper confidence intervals for the RR of MI to represent the RR for unstable angina had little effect on the ICERs as these were applied for all statin doses.

Chapter 5
Discussion

The clinical review and the Bayesian mixed treatment meta-analysis demonstrated a clear dose–response relationship in terms of reductions in LDL-c, with rosuvastatin 40 mg/day achieving the greatest percentage reduction (56%), followed by atorvastatin 80 mg/day (52%), simvastatin 80 mg/day (45%) and simvastatin 40 mg/day (37%). These data are similar to those reported by Soran and Durrington.[57] When combined with the relationship between absolute reductions in LDL-c and RRs of events, the RRs for simvastatin 40 mg/day are also as expected when compared with those in a large meta-analysis of placebo-controlled trials.[59]

Although the safety of statins (as a class) is well reported,[59] there are no specific systematic reviews and meta-analyses of RCTs solely focusing on the adverse effects associated with moderate-dose statins (i.e. simvastatin 40 mg/day). The long-term RCT evidence for simvastatin 40 mg/day is limited. In the principal 4S trial,[84] two-thirds of patients received simvastatin 20 mg/day, whereas only one-third received simvastatin 40mg/day. In the HPS trial,[34] which used simvastatin 40 mg/day, there was a 6-week active treatment run-in period during which those experiencing adverse effects could drop out before randomisation. The safety profile associated with intensive-dose statin therapy is less clear because of the smaller number of RCTs using intensive-dose treatments. The evidence generally suggests a dose–response relationship in which increasing the dose leads to more adverse events. A meta-analysis of seven trials (involving 29,395 patients with CAD)[67] comparing intensive statin therapy with less intensive statin therapy found that more intensive regimens [atorvastatin 80 mg/day (six trials) or simvastatin 80 mg/day (one trial)] were associated with higher levels of aminotransferases (1.5% versus 0.4%; OR 4.14; 95% CI 2.30 to 7.44), myalgia (3.3% versus 2.8%; OR 1.26; 95% CI 0.98 to 1.63) myopathy (2.2% versus 1.8%; OR 1.91; 95% CI 0.11 to 32.13) and rhabdomyolysis (0.05% versus 0.04%; OR 0.97; 95% CI 0.29 to 3.24) than less intensive statin therapy (atorvastatin 10 mg/day, lovastatin 5 mg/day, pravastatin 40 mg/day, simvastatin 20 mg/day). Josan *et al.*[67] also showed that the more intensive regimens were associated with small statistically non-significant increases in rates of discontinuation (OR 1.34; 95% CI 0.98 to 1.83) compared with less intensive statins. Evidence for rosuvastatin 40 mg/day is very limited.[117] Although the product information for rosuvastatin indicates a higher risk of adverse events with the 40 mg/day dose than with lower doses (rosuvastatin < 20 mg/day),[74] recently published data[114,115] show that there was no significant difference in the adverse event rates at any dose ratio when compared with atorvastatin (maximum doses being rosuvastatin 40 mg/day and atorvastatin 80 mg/day).

Although documented serious adverse events are rare, individuals receiving the more potent doses should be screened for contraindications and monitored if symptoms are reported. The evidence suggests that long-term adherence to standard-dose statins is low in general clinical practice, with a large proportion of individuals discontinuing therapy during the first 12 months; however, there is evidence that adherence could be higher in individuals with a history of CVD and in those who receive regular monitoring.[88,94,98,99]

Although several meta-analyses of randomised statin trials have not detected any clinically meaningful effect of statins on cancer incidence,[6,118,119] data from epidemiological studies suggest an inverse association between serum cholesterol levels and incident cancer.[120] The recent results of a meta-regression analysis of data from 15 randomised clinical trials indicated that, although an inverse association between on-treatment LDL-c and incident cancer occurs, there was no evidence that statins themselves increased the risk of cancer.[121] Despite this, there is still concern that achieving low levels of LDL-c may increase the risk of cancer.[122–124] Long-term follow-up and registry data on adherence rates and adverse reactions to statins of all types and doses would be a useful contribution to the existing evidence base.

The economic results suggest that, if adherence levels in general practice are similar to those observed in clinical trials (scenario 1), all three higher-dose statins would be considered cost-effective compared with simvastatin 40 mg/day when using a threshold of £20,000 per QALY. When comparing all four treatment regimens,

atorvastatin 80 mg/day is dominated by rosuvastatin 40 mg/day with smaller benefits (7.86 versus 7.94 QALYs) and higher costs (£18,213 versus £18,116). Assessing the net benefit of the interventions, simvastatin 40 mg/day is the optimal treatment when using a threshold of £5000 per QALY, simvastatin 80 mg/day is the optimal treatment if the threshold is between £5000 and £16,000 per QALY and rosuvastatin 40 mg/day is the optimal treatment if the threshold is greater than £15,000 per QALY. However, simvastatin 80 mg/day is not well tolerated and a substantial proportion of patients are unlikely to adhere to this treatment. Recently published results show that the incidence of myopathy in individuals receiving simvastatin 80 mg/day was 26 times higher than incidence rates in those receiving simvastatin 20 mg/day. With defined premyositis also increased, simvastatin 80 mg/day cannot be recommended.[79]

Although this analysis shows that atorvastatin 80 mg/day is never the most cost-effective alternative at any tested threshold, when the patent for atorvastatin expires in 2011 it is probable that there will be a substantial decrease in the cost of this treatment. If the cost of atorvastatin decreases in line with that observed for simvastatin, atorvastatin 80 mg/day will be the most cost-effective treatment at all thresholds. If the cost of atorvastatin reduces to 25% of the current cost, atorvastatin 80 mg/day will be the most cost-effective treatment for thresholds between £5000 and £30,000 per QALY.

The results reported above are generated using the unadjusted effectiveness rates obtained from the clinical trials, which typically report adherence rates in the region of 80–90%. If it is assumed that the RCT adherence rates are representative of adherence to simvastatin 40 mg/day, but that the level of adherence to the more potent doses is lower in general practice (scenario 2), using a threshold of £30,000 per QALY all three higher-dose statins would be considered cost-effective compared with simvastatin 40 mg/day, and using a threshold of £20,000 per QALY rosuvastatin 40mg/day would be considered cost-effective. As in scenario 1, when comparing all four treatment regimens, atorvastatin 80 mg/day is again dominated by rosuvastatin 40 mg/day. If adherence rates are adjusted to reflect the trends in the limited evidence available for the different statins (scenario 3), compared with simvastatin 40 mg/day, atorvastatin 80 mg/day and rosuvastatin 40 mg/day remain cost-effective using a threshold of £20,000 per QALY but simvastatin 80 mg/day would not be considered cost-effective using a threshold of £30,000 per QALY.

It is likely that an individual with a history of a recent acute cardiovascular event would be offered an alternative if they did not tolerate the more potent doses. In scenario 4 we used the same levels of adherence as in scenario 2 and assumed that individuals who do not adhere to the higher-dose statins receive simvastatin 40 mg/day. The results generated using these assumptions are comparable with the results for scenario 1.

In general, the results are reasonably robust to changes in the majority of parameter values and are driven by the differences in the adherence rates modelled and the monitoring costs associated with the more potent doses. However, there is evidence that adherence could be higher in individuals with a history of a recent cardiovascular event and in those who receive regular monitoring. Thus, within the limitations of the evidence available, the results for scenario 1 and scenario 2 could be considered the most accurate representations of the cost-effectiveness of the different interventions for individuals who adhere to treatment.

There are several major limitations in the evidence base used to estimate the benefits associated with the treatment regimens, which may have implications when interpreting the results generated by the economic model. First, the individuals enrolled in the RCTs used in the mixed treatment meta-analysis were screened before randomisation and some studies excluded individuals who had recently experienced an ACS episode. Consequently, when examining the dose–response rates to the treatments, we are assuming that these will be generalisable to individuals with ACS.

Second, the data used in the mixed treatment comparison came from studies having a duration of 6 weeks, 12 weeks, 24 weeks/6 months, 9 months, 1 year, 3 years or 5 years. Although at least one of the included studies for simvastatin 40 mg/day, simvastatin 80 mg/day and atorvastatin 80 mg/day was of at least 6 months in duration, the data for rosuvastatin 40 mg/day were obtained from studies having a duration of 12 weeks or less. Consequently, although we accounted for heterogeneity using a Bayesian random-effects model, we did not postulate plausible statistical models to link the data across time periods. Indeed, data were available only for placebo and simvastatin 40 mg/day beyond 1 year, and there

were no data available on rosuvastatin 40 mg/day beyond 12 weeks. If the effectiveness of the treatments decreases over the long term it is likely that the benefits of rosuvastatin are overestimated, particularly as the economic evaluation extrapolates the results over a lifetime. In addition, the current model will also underestimate the uncertainty associated with the effectiveness of treatment beyond 1 year.

Third, the link between changes in LDL-c and RRs of events was derived predominantly from individuals who were not receiving the more potent doses of statins.[6] Although the analysts reported that their findings were independent of characteristics such as baseline LDL-c values or cardiovascular risk, we are extrapolating beyond the evidence base used. Although our economic results suggest that atorvastatin 80 mg/day is dominated by rosuvastatin 40 mg/day, clinical data supporting the assumption that rosuvastatin-induced reductions in LDL-c (and its greater potential to increase HDL-c) will translate into corresponding reductions in clinical events are limited.

Cardiovascular disease is a complex field and the economic model focuses on the following major events: hospitalisation for unstable angina, MI, stroke, fatal CHD and fatal non-cardiac vascular events. Other analysts have constructed models that include health states such as heart failure and revascularisation procedures, which were not included in the current evaluation.[105] Heart failure was not included as the evidence for and against prescribing statins for people with heart failure is limited, conflicting and unclear. Although several studies (i.e. post hoc subgroup analyses in prospective RCTs; subgroup analysis of the evidence of statin use in large heart failure trials of different medications and medical devices; retrospective observational studies and prospective RCTs of statins in non-ischaemia) lend support for a beneficial effect of statins in heart failure,[125] there are concerns that the routine use of statins may be harmful in such patients. First, non-RCT evidence suggests that lower cholesterol levels are associated with a worse prognosis in heart failure patients.[125,126] Second, statins in heart failure may adversely affect mitochondrial function through inhibition of ubiquinone (coenzyme Q10) levels, thus affecting cardiac muscle function. Finally, statins may decrease selenoproteins, which could result in decreased myocardial function.[125,126] In addition, the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA)[127] is the first prospective randomised placebo-controlled clinical outcome trial with statins (rosuvastatin 10 mg/day) focused specifically on older patients (at least 60 years of age) with systolic heart failure. Over a median follow-up of 33 months there were no significant differences in the primary end point or in all-cause mortality, the rate of coronary events, the effects on New York Heart Association class or the rate of newly diagnosed diabetes. Other large clinical trials (GISSI-HF)[128] are also under way to further clarify the effects of statin treatment in heart failure.

Although data show that statins reduce the number of revascularisation procedures, the current model does not include this as a subsequent event. As revascularisations are considered to be a treatment as opposed to a cardiac event, to avoid double counting costs and utility we chose to model potential reductions in subsequent procedures by including these in the hospitalisation for unstable angina and MI health states. We assume that by reducing the number of cardiac events we also take into account potential reductions in revascularisation procedures due to statin treatment.[13,16]

Finally, we assume that the relationship between reductions in LDL-c and the RR of any stroke reported by the cholesterol trialist collaborators is representative of the relationship between reductions in LDL-c and the RR of non-fatal stroke.[6] As the RRs for fatal strokes are generally not significant,[59] it is possible that we are underestimating the benefits in terms of the number of non-fatal strokes avoided.

Chapter 6
Conclusion

The Bayesian mixed treatment meta-analysis demonstrated a clear dose–response relationship in terms of reductions in LDL-c, with rosuvastatin 40 mg/day achieving the greatest percentage reduction (56%), followed by atorvastatin 80 mg/day (52%), simvastatin 80 mg/day (45%) and simvastatin 40 mg/day (37%). Although the literature suggests that serious adverse events are rare for all statins, incidence rates are likely to be higher for individuals receiving the more potent doses. Adherence rates in general clinical practice are lower than those reported in clinical trials, may be correlated with less severe adverse event rates such as for myalgia, and are likely to vary by statin type and dose.

Using a threshold of £20,000 per QALY, if it is assumed that the benefits and adherence rates observed in the clinical trials are generalisable to a clinical setting, or if it is assumed that individuals who do not tolerate the higher-dose statins are prescribed simvastatin 40 mg/day, then simvastatin 80 mg/day, atorvastatin 80 mg/day and rosuvastatin 40 mg/day would all be considered cost-effective compared with simvastatin 40 mg/day in individuals with ACS. However, because of high incidence rates of myopathy/myalgia in individuals receiving simvastatin 80 mg/day, adherence is likely to be poor and simvastatin 80 mg/day cannot be recommended.

With current treatment costs and existing evidence our results show that rosuvastatin 40 mg/day is potentially the most cost-effective treatment. However, these results are based on the assumption that the larger benefits in LDL-c measurements will produce an equivalent reduction in cardiovascular event rates. Although data on event rates supporting this assumption are beginning to emerge, the evidence base for atorvastatin 80 mg/day is more robust. If the cost of atorvastatin decreases when the patent ends in 2011, atorvastatin 80 mg/day will be the most cost-effective treatment.

Chapter 7

Recommendations for further research

Large long-term RCTs reporting effects in terms of clinical events are required to determine the optimum statin use for subgroups. These will include head-to-head studies comparing higher-dose statins with lower-dose statins, studies of rosuvastatin and studies comparing high-dose statin monotherapy with combination therapies such as low-dose statins combined with alternative lipid modifications. Studies recruiting high-risk groups typically excluded from RCTs, such as individuals with recent ACS events or heart failure, diabetics and Asian people, should be considered. Long-term registry data are required to determine adherence rates and adverse event profiles for individual statins and doses when used in general clinical practice. Studies exploring the effects of interventions designed to increase adherence to statin therapy in general clinical practice and in subgroups are required.

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Matt Stevenson and Eva Kaltenthaler are guarantors.

Contribution of authors

All authors were involved in the design of this review. AR developed the search strategy, undertook searches and organised the retrieval of papers. AP and RR screened the search results, screened retrieved papers against inclusion criteria, abstracted the data, and appraised the quality of the papers. JS performed the Bayesian analysis, and RA conducted the economic evaluation. AP and RA co-ordinated the review.

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220. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG *et al*., the 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.

221. 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**:113–19.

222. Jukema JW, Bruschke AVG, Van Boven JS, 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.

223. 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.

224. The 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/day) plus two additional atherosclerotic risk factors. *Am J Cardiol* 1993;**72**:1031–7.

225. Anon. Effect of simvastatin on coronary atheroma: the Multicentre Anti-Atheroma Study (MAAS). *Lancet* 1994;**344**:633–8.

226. 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.

227. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, *et al*.; CARDS investigators. 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**:685–96.

228. The Diabetes Atorvastin 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.

229. Mohler ER. Therapy insight: peripheral arterial disease and diabetes – from pathogenesis to treatment guidelines. *Nature Clin Pract Cardiovasc Med* 2007;**4**:151–62.

Appendix 1

Example of MEDLINE search strategy

Search terms
1. Coronary Disease/
2. Myocardial Infarction/
3. myocardial infarc$.tw.
4. Angina, Unstable/
5. unstable angina.tw.
6. angina unstable.tw.
7. acute coronary syndrome.tw.
8. Angioplasty, Transluminal, Percutaneous Coronary/
9. ptca.tw.
10. percutaneous transluminal coronary angioplasty.tw.
11. Coronary Artery Bypass/
12. cabg.tw.
13. coronary artery bypass graft.tw.
14. revascularisation.tw.
15. revascularization.tw.
16. or/1–15
17. Simvastatin/
18. simvastatin.tw.
19. atorvastatin.tw.
20. rosuvastatin.tw.
21. randomized controlled trial.pt.
22. controlled clinical trial.pt.
23. randomized controlled trials/
24. clinical trial.pt.
25. exp clinical trial/
26. (clin$adj25 trial$).ti,ab.
27. 17 or 18 or 19 or 20
28. 21 or 22 or 23 or 24 or 25 or 26
29. 27 and 28
30. 16 and 29

Appendix 2

QUOROM trial flow chart (clinical effectiveness)

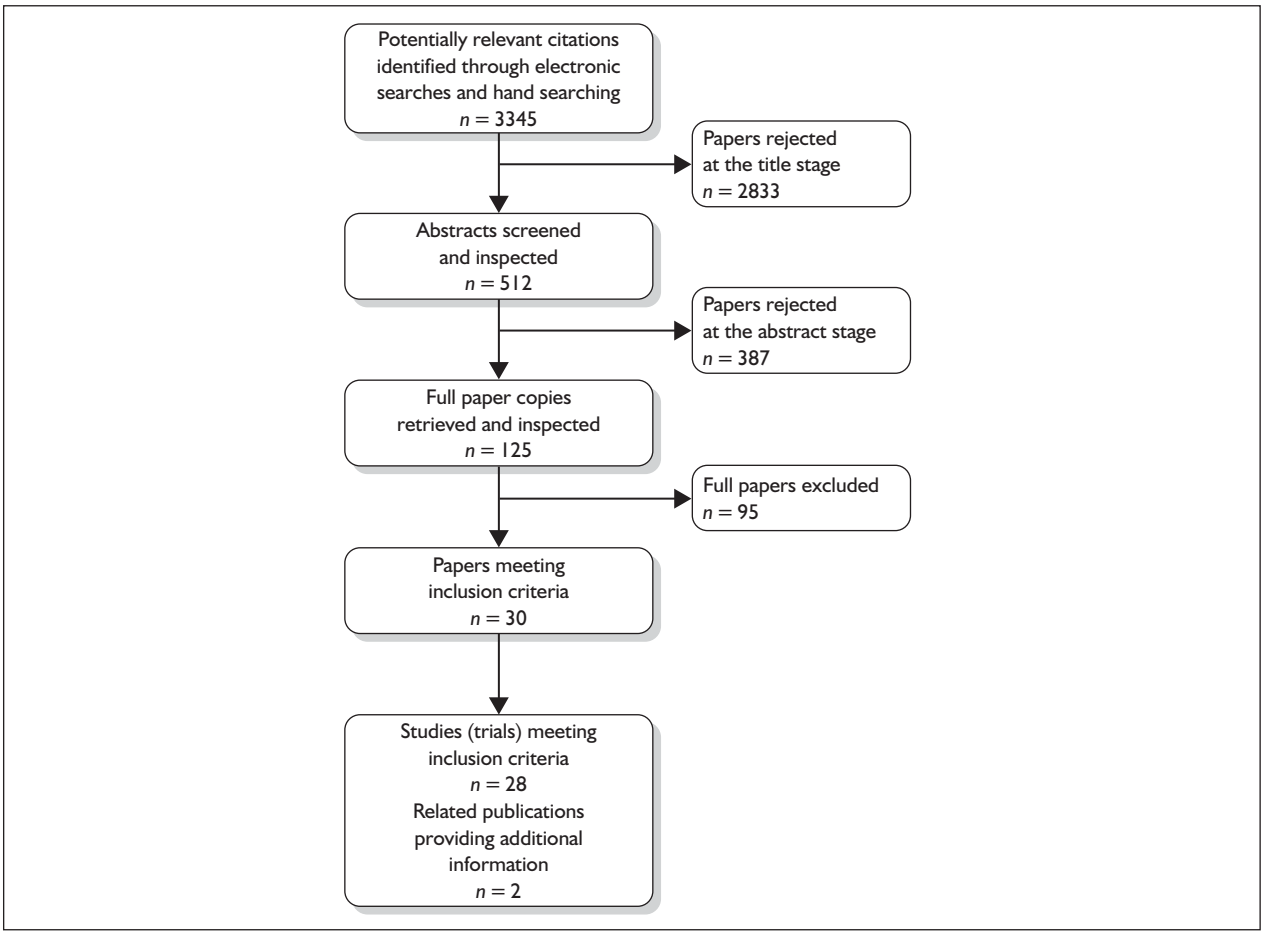

FIGURE 5 *QUOROM trial flow chart.*

Appendix 3

List of excluded studies with rationale

Study	Reason for exclusion
Amarenco *et al*., 2007[129]	Dose titration (SPARCL trial)
Anon, 1998[130]	Letter/comment/editorial
Anon, 2004[131]	Letter/comment/editorial
Anon, 2001[132]	Letter/comment/editorial
Anon, 2004[133]	Letter/comment/editorial
Anon, 2004[134]	Letter/comment/editorial
Asztalos *et al*., 2007[135]	Does not provide any additional data to the STELLAR trial[136]
Ballantyne *et al*., 2001[136]	Dose titration (4S trial)
Barrett-Connor, 2004[137]	Letter/comment/editorial
Bestehorn *et al*., 1997[138]	Dose titration (CIS trial)
Bunch, 2002[139]	Not RCT
Burton *et al*., 2003[140]	Dose titration (SCAT trial)
Cannon *et al*., 2004[14]	Wrong comparator (pravastatin 40 mg/day; PROVE-IT TIMI 22 trial)
Chello *et al*., 2007[141]	No LDL outcomes
Chhatriwalla, 2006[142]	No comparator (ASTEROID study)
Chonchol *et al*., 2007[143]	Dose titration (4S trial)
Coccia *et al*., 2007[144]	Treatment duration 3 weeks
Colivicchi *et al*., 2002[145]	Incorrect comparator (conventional medical treatment including dose titration of statin or other lipid therapy)
Correia *et al*., 2003[146]	Treatment duration 5 days
Correia *et al*., 2003[147]	Subgroup results of Correia *et al.*, 2003[146]
Correia *et al*., 2002[148]	Subgroup results of Correia *et al.*, 2003[146]
Crouse *et al*., 1999[149]	Incorrect comparator (atorvastatin 40 mg/day)
Dallinga-Thie, 2006[150]	Dose titration
Dane-Stewart *et al*., 2003[151]	Dose titration
Davidson *et al*., 2000[69]	Pooled analysis of included and excluded studies
Davidson *et al*., 1997[152]	Crossover study with washout
Deedwania *et al*., 2007[152]	Incorrect comparator (pravastatin 40 mg/day; SAGE trial)
de Lemos *et al*., 2004[26]	Incorrect comparator (atorvastatin 10 mg/day; A to Z trial)
de Sauvage Nolting *et al.*, 2002[153]	Not RCT
Diabetes Atorvastin Lipid Intervention (DALI) Study Group, 2001[154]	Dose titration (DALI study)
Ferrier, 2002[155]	Crossover study with washout
Gaspardone, 2002[156]	Not RCT
Heart Protection Study Collaborative Group, 2004[157]	Does not provide any additional data to the HPS trial[34]

continued

Study	Reason for exclusion
Heart Protection Study Collaborative Group, 2003[158]	Does not provide any additional data to the HPS trial[34]
Heart Protection Study Collaborative Group, 2007[159]	Does not provide any additional data to the HPS trial[34]
Horng, 2007[160]	Review
Houslay *et al*. 2006[161]	Does not provide any additional data to the SALTIRE study[48]
Johnston, 2004[162]	Letter/comment/editorial
Jones *et al*., 2005[75]	Incorrect comparator (atorvastatin 10, 20, 40 mg/day; NASDAC study)
Jukema, 2005[163]	Dose titration (RADAR study)
Kinlay *et al*., 2004[164]	Does not provide any additional data to the MIRACL trial[53]
Koh *et al*., 2004[165]	Incorrect comparator (simvastatin 20 mg/day)
LaRosa *et al*., 2005[23]	Incorrect comparator (atorvastatin 10 mg/day; TNT trial)
Leiter, 2007[166]	Dose titration (POLARIS trial)
Masumi *et al*., 2008[167]	Does not provide any additional data to the STELLAR trial[28]
Meade, 1999[168]	Does not provide any additional data to the HPS trial[34]
Miettinen *et al*., 1997[169]	Dose titration (4S trial)
Miller *et al*., 2001[170]	Crossover study of simvastatin 80 mg/day and 40 mg/day and placebo
Mitropoulos *et al*., 1997[171]	Does not provide any additional data to the Oxford Cholesterol Study[43]
Mizia-Stec *et al*., 2006[172]	Incorrect comparator (simvastatin 20 mg/day)
Mulder *et al*., 2007[173]	Dose titration/switching
Nakamura, 1997[174]	Incorrect intervention (atorvastatin 10 mg/day; J-CLAS trial)
Nissen, 2004[25]	Incorrect comparator (pravastatin 40 mg/day; REVERSAL trial)
Nissen, 2006[76]	No comparator
Olivotti *et al*., 2002[175]	Does not provide any additional data to the MIRACL trial[53]
Olsson *et al*., 2002[176]	Review
Olsson *et al*., 2001[177]	Pooled analysis of individual included unpublished studies – 4522IL/0008[32] and 4522IL/0023[33]
Olsson *et al*., 2007[178]	Does not provide any additional data to the MIRACL trial[53]
Ose *et al*., 2000[179]	Pooled analysis of individual included studies – Stein *et al*., 1998,[41] Ose *et al*.,1998[42] for 24 weeks; however, extension results not reported separately
Pearson *et al*., 2007[180]	Pooled analysis of individual included studies – Davidson *et al*., 2002,[39] Goldberg *et al*., 2004,[50] Bays *et al*., 2004[38]
Pedersen, 1995[181]	Dose titration (4S trial)
Pedersen *et al*., 2004[182]	Incorrect comparator (simvastatin 20 mg/day; IDEAL trial)
Pedersen *et al*., 2000[183]	Dose titration (4S trial)
Pedersen *et al*., 2005[24]	Incorrect comparator (simvastatin 20 mg/day; IDEAL trial)
Pedersen *et al*., 1999[184]	Incorrect intervention/comparator
Pedersen *et al*., 1998[185]	Dose titration (4S trial)
Pedersen, 1994[186]	Dose titration (4S trial)
Pedersen *et al*., 1996[187]	Dose titration (4S trial)
Pitt *et al*., 1999[188]	Incorrect comparator (angioplasty followed by usual care; AVERT trial)
Pitt, 1999[189]	Incorrect comparator (angioplasty followed by usual care; AVERT trial abstract)
Pyorala *et al*., 1997[190]	Dose titration (4S trial)
Pyorala *et al*., 2004[191]	Dose titration (4S trial)

Study	Reason for exclusion
Rensing *et al*., 1999[192]	Foreign language, dose titration (CIS trial)
Riahi *et al*., 2006[193]	Crossover study with no washout
Rosenson *et al*., 2001[194]	Dose titration (CHRIS trial)
Sakamoto *et al*., 2006[195]	Dose titration and switching
Schaefer *et al*., 2004[196]	Dose titration
Schaefer *et al*., 2002[197]	Dose titration
Scheen, 2006[198]	Foreign language, incorrect comparator (simvastatin 20 mg/day; IDEAL trial)
Schwartz *et al*., 1998[199]	Does not provide any additional data to the MIRACL trial[53]
Schwartz *et al*., 2005[200]	Does not provide any additional data to the MIRACL trial[53]
Sillesen *et al*., 2007[201]	Dose titration (abstract, SPARCL trial)
Smilde *et al*., 2001[202]	Dose titration (ASAP trial)
Stein *et al*., 2000[203]	Crossover study with no washout (simvastatin 80 mg/day and 40 mg/day and placebo)
Szramka *et al*., 2007[204]	Crossover study
Teo *et al*., 2000[205]	Dose titration (SCAT trial)
Terry *et al*., 2007[206]	Dose titration (CATZ trial)
Tonstad and Holme, 2002[207]	Review
van der Harst *et al*., 2005[208]	Treatment duration 28 days and no useable data
Van Wijk, 2003[209]	Dose titration
Van Wissen *et al*., 2003[210]	Dose titration (ASAP trial)
van Wissen *et al*., 2005[211]	Not RCT (extension study of ASAP trials)
Waters *et al*., 2002[212]	Does not provide any additional data to the MIRACL trial[53]
Verri, 2004[213]	Dose titration
Wierzbicki *et al*., 1999[214]	Crossover and dose titration study with washout

Appendix 4

Quality assessment criteria

Allocation sequence (randomisation)	Allocation concealment	Blinding	Intention to treat analysis and loss to follow-up	Overall assessment
A – Adequate sequence generation is reported (such as computer-generated random numbers and random number tables; inadequate approaches will include the use of alternation, case record numbers, birth dates or days of the week)	A – Adequate measures to conceal allocations. Concealment will be deemed adequate when randomisation is centralised or pharmacy controlled or when the following are used: serially numbered containers, on-site computer-based systems in which assignment is unreadable until after allocation, other robust methods to avoid foreknowledge of the allocation sequence by clinicians and patients	A – Participants and investigators were blinded. Method of blinding will be considered appropriate if studies report that neither the person administering the treatment nor the study participant could identify the intervention being assessed, or if in the absence of such a statement the use of active placebos, identical/matching placebos or dummies is mentioned	A – Studies with intention to treat analysis in which exclusions were less than 10% and differences in exclusion between groups were less than 5% (with adequate reporting of withdrawals and dropouts)	A – All criteria met (all 'A'); low risk of bias
B – Did not specify one of the adequate reported methods in A but mentioned randomisation method	B – Unclearly concealed trials in which the authors either did not report an allocation concealment approach at all or reported an approach that did not fall into one of the categories in A	B – Unclear (study described as single blind or double blind when the method of blinding used was partially reported or inappropriate)	B – Studies without intention to treat analysis but exclusions were less than 10% and differences in exclusion between groups were less than 5% (with adequate reporting)	B – One or more criteria partly met (at least one criterion is 'B', but none is 'C'); moderate risk of bias
C – Other methods of allocation that appear to be biased	C – Inadequately concealed trials. Inadequate approaches will include the use of alternation, case record numbers, days of the week, open random number lists and serially numbered envelopes, even if opaque	C – No blinding at all, i.e. open-label studies	C – No intention to treat analysis performed, no reporting of exclusions (withdrawals and dropouts), exclusions of 10% or more, or wide differences in exclusion between groups (more than 5%)	C – One or more criteria not met (at least one criterion is 'C'); high risk of bias

Appendix 5

Synopsis of placebo-controlled RCTs included in the NICE HTA meta-analysis[59]

Of the 25 studies ($n = 35,721$ for statins; $n = 35,432$ for placebo) included in the meta-analysis used in the current evaluation, three of the four fluvastatin studies (FLARE,[215] FLORIDA,[216] LIPS[217]) used the maximum dose of 80 mg/day whereas the LiSA study[218] increased the starting dose of 40 mg/day to 80 mg/day 6 weeks after randomisation if the decrease in LDL-c was less than 30%. All but two of the pravastatin studies used the maximum dose of 40mg/day (CAIUS,[219] CARE,[220] PLAC-I,[221] REGRESS[222]). In the remaining two studies (PLAC-II[223] and PMSG[224]) the dose could be increased to 40 mg/day in participants whose LDL-c levels had not responded to the starting dose of 20 mg/day. Two[34,45] of the six simvastatin studies used 40 mg/day throughout whereas the MAAS study[225] used a dose of 20 mg/day throughout. The remaining three studies (4S,[186] CIS,[138] SCAT[205]) used a starting dose of 20 mg/day, which could be increased to 40 mg/day if this was necessary to achieve an adequate reduction in LDL-c. By contrast, the atorvastatin studies generally used doses well below the maximum dose of 80 mg/day: the ASCOT-LLA[226] and CARDS[227] studies used a fixed dose of 10 mg/day. Only the small DALI[228] ($n = 145$ on atorvastatin) and Mohler[229] ($n = 240$ on atorvastatin) studies used a dose of 80 mg/day: each had two treatment arms, one on a fixed dose of 10 mg/day and the other on 80 mg/day. Assuming that atorvastatin 10 mg/day, fluvastatin 80 mg/day, pravastatin 40 mg/day and simvastatin 20/40 mg/day provide similar benefits, the results can be used to represent the effectiveness achieved through standard statin treatment compared with no treatment.

Appendix 6

Additional tables for economic evaluation

TABLE 18 *Unit costs included in the annual health state costs*[18]

	Mean value	Upper limit	Lower limit	Alpha	Beta	
Unstable angina hospital: EB05Z	£1059.00	£448.00	£1521.33	£311.79	3	Gamma
Revasc. hospital mixture of HRG codes (see below)	£5011.81	£1099.75	£12,044.01	£300.00	17	Gamma
MI hospital: EB107	£1290.88	£803.86	£1985.92	£248.48	5	Gamma
First outpatient	£137.28	£62.15	£175.52	£100.00	1	Gamma
Subsequent appointment	£91.37	£39.28	£123.13	£75.00	1	Gamma
GP visits year 1	£102.00	Constant				
GP visits years 2+	£91.37	Constant				
Fatal CHD (Palmer inflated[109])	£591.52			300	2	Gamma
Fatal stroke (Youman inflated[108])	£3688.23			280	13	Gamma
First year stroke (Youman inflated[108])	£8066.18			350	23	Gamma
Subsequent year stroke (Youman inflated[108])	£2266.16			300	8	Gamma
90% of patients receive Glytrin Spray, isorbide mononitrate, one of verapamil, atenolol or diltiazem, and aspirin	0.9			50	450	Beta
60% of patients receive clopidogrel	0.6			400	600	Beta
90% of patients receive rampiril (ACE) – 10% non-tolerant	0.9			100	900	Beta
10% of patients (those who do not tolerate rampiril) receive ARB	0.1			1 minus ramipril		
Glytrin Spray® (Sanofi-Synthelabo)	£10.47	Constant				
Isosorbide mononitrate	£11.24	Constant				
Verapamil (non-proprietary)	£41.98	Constant				
Atenolol	£30.24	Constant				
Aspirin	£6.65	Constant				
Ramipril (non-proprietary)	£75.09	Constant				
ARB	£210.27	Constant				
Clopidogrel	£460.27	Constant				

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CHD, coronary heart disease; MI, myocardial infarction.
BNF accessed 6 June 2008.[18]

TABLE 19 *Breakdown of health state costs*

	Cost
First year unstable angina	
Hospitalisation (EB05Z)	£529.56
50% of individuals have revascularisation	£2505.90
3×outpatient visits per annum	£320.03
All patients visit the GP 3×per annum for monitoring and prescribing of medication	£102.00
90% of patients receive Glytrin Spray, isosorbide mononitrate, one of verapamil, atenolol or diltiazem and aspirin	£58.02
60% of patients receive clopidogrel	£276.16
Ramipril (ACE inhibitor)×0.9	£67.58
ARB×0.1	£21.03
Total	£3880.28
Subsequent year, all CHD	
1×outpatient visit	£91.37
All patients visit the GP 3×per annum for monitoring and prescribing of medication	£102.00
90% of patients receive Glytrin Spray, isosorbide mononitrate, one of verapamil, atenolol or diltiazem and aspirin	£58.02
Ramipril (ACE inhibitor)×0.9	£67.58
ARB×0.1	£21.03
Total	£340.00
First year MI costs	
Hospitalisation (EB10Z)	£645.44
50% revascularisation	£2506.00
Outpatient and treatment costs (as unstable angina)	£844.82
Total	£3996.26
First year revascularisation costs	
Weighted revascularisation cost	£5011.81
Outpatient and treatment costs (as unstable angina)	£844.82
Total	£5856.63

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CHD, coronary heart disease; MI, myocardial infarction.

TABLE 20 *Weighted estimation of revascularisation costs*

Code	Description	Number	Unit cost
EA31Z	Percutaneous coronary intervention (0–2 stents)	18,187	2585
EA32Z	Percutaneous coronary intervention (0–2 stents) and catheterisation	5275	2864
EA33Z	Percutaneous coronary intervention with 3 stents	1616	3212
EA34Z	Percutaneous coronary intervention with 3 stents and catheterisation	794	3759
EA35Z	Other transluminal percutaneous interventions	494	2039
EA14Z	Coronary artery bypass graft (first time)	5151	8800
EA15Z	Coronary artery bypass graft (first time) with cardiac catheterisation	82	8617
EA16Z	Coronary artery bypass graft (first time) with percutaneous coronary intervention, pacing, EP or RFA +/– catheterisation	264	10,456
	Percutaneous coronary intervention	0.67	70,142
	Coronary artery bypass graft	0.23	20,600
	Weighted costs for revascularisation procedure		5012

EP, electrophysiology; RFA, radiofrequency ablation.

TABLE 21 *Monitoring costs for higher-dose statins*

Tests and additional GP visits for high-dose statins	Annual cost	Unit cost
Bloods $\times 2$[a]	£8	£4.00
GP appointment $\times 2$[b]	£68	£34.00
Total	£76.00	

a Phlebotomy code 839.
b Assumed 10-minute consultation.

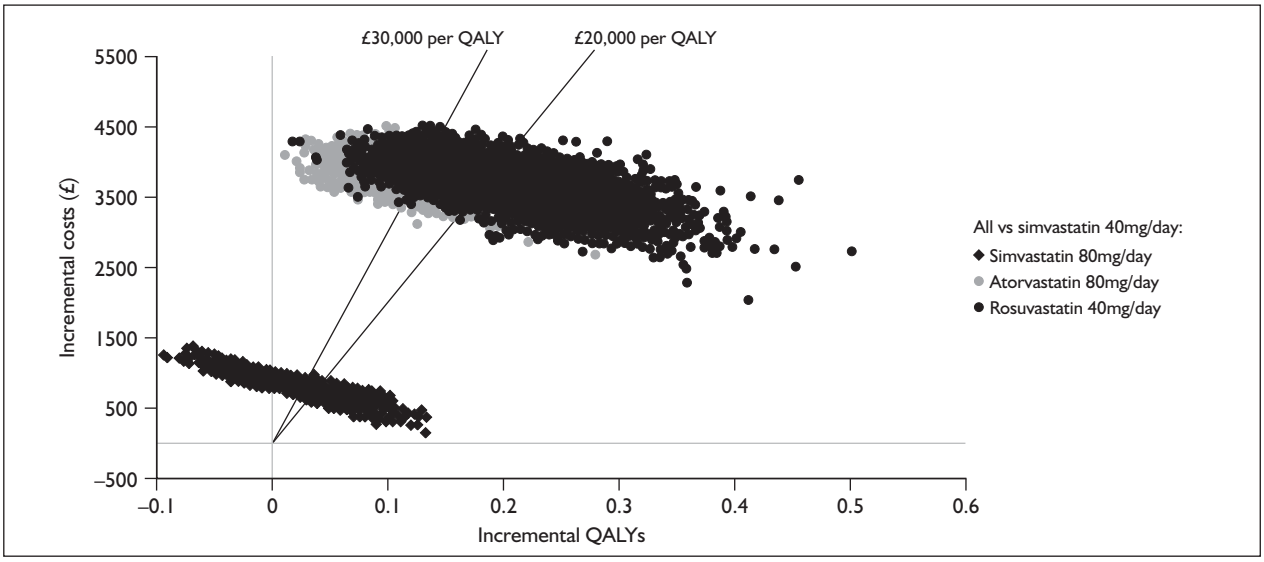

FIGURE 6 *Cost-effectiveness plane: scenario 2: generated using 5000 Monte Carlo simulations.*

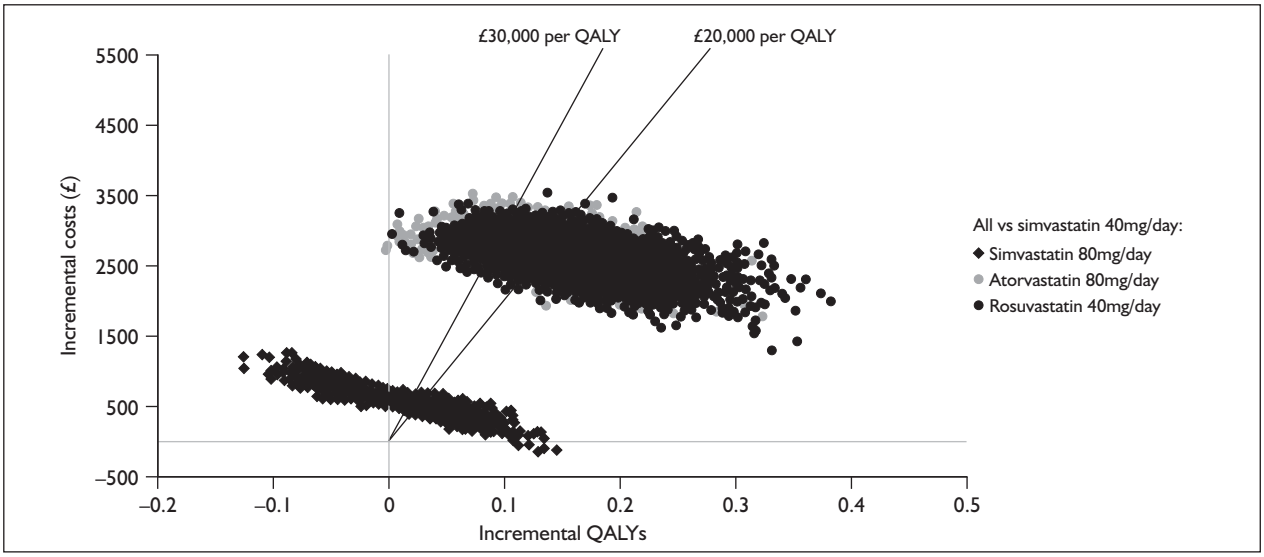

FIGURE 7 *Cost-effectiveness plane: scenario 3: generated using 5000 Monte Carlo simulations.*

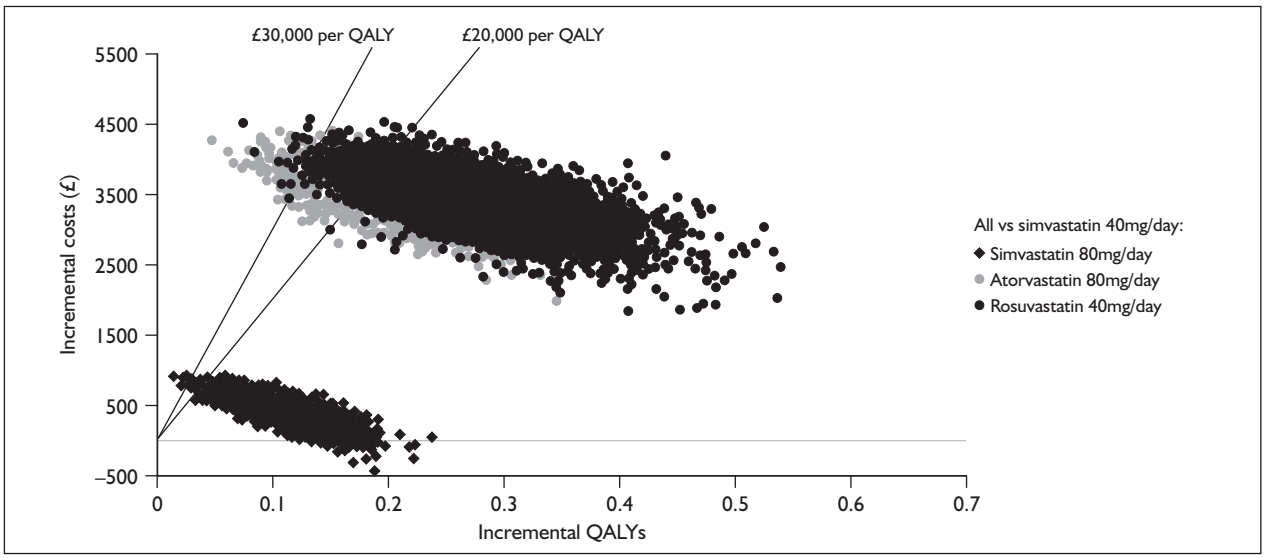

FIGURE 8 *Cost-effectiveness plane: scenario 4: generated using 5000 Monte Carlo simulations.*

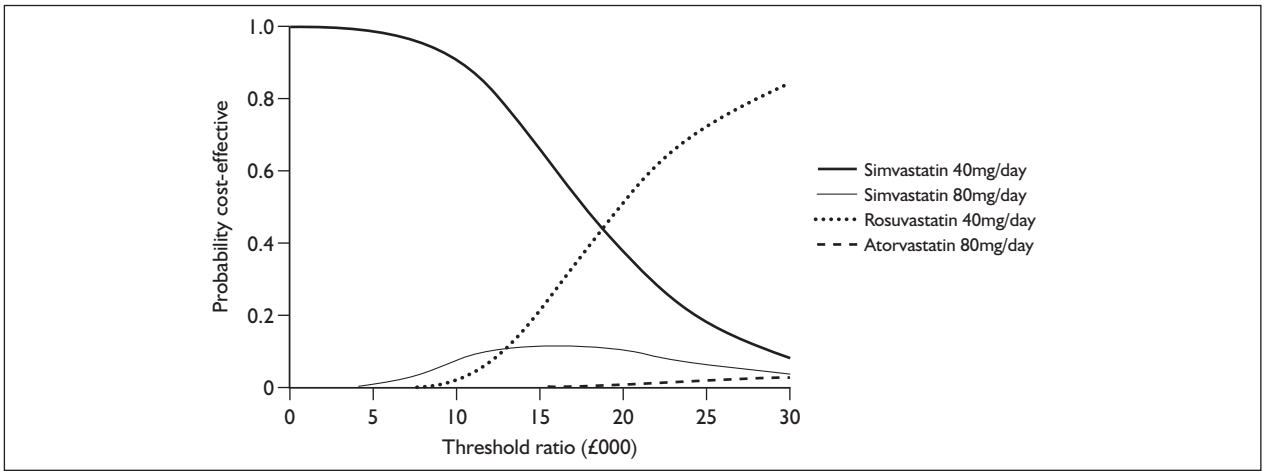

FIGURE 9 *Cost-effectiveness acceptability curve: scenario 2.*

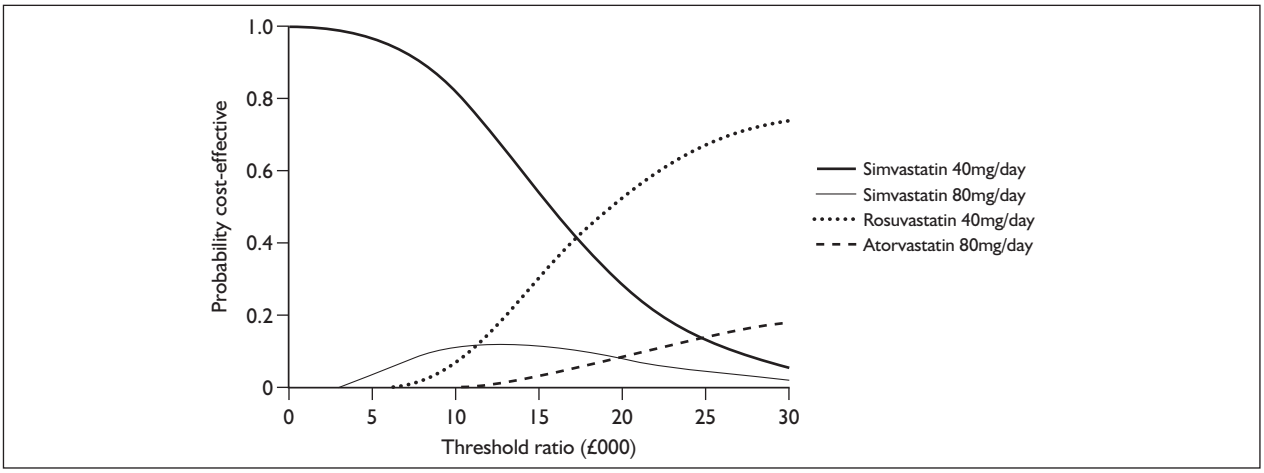

FIGURE 10 *Cost-effectiveness acceptability curve: scenario 3.*

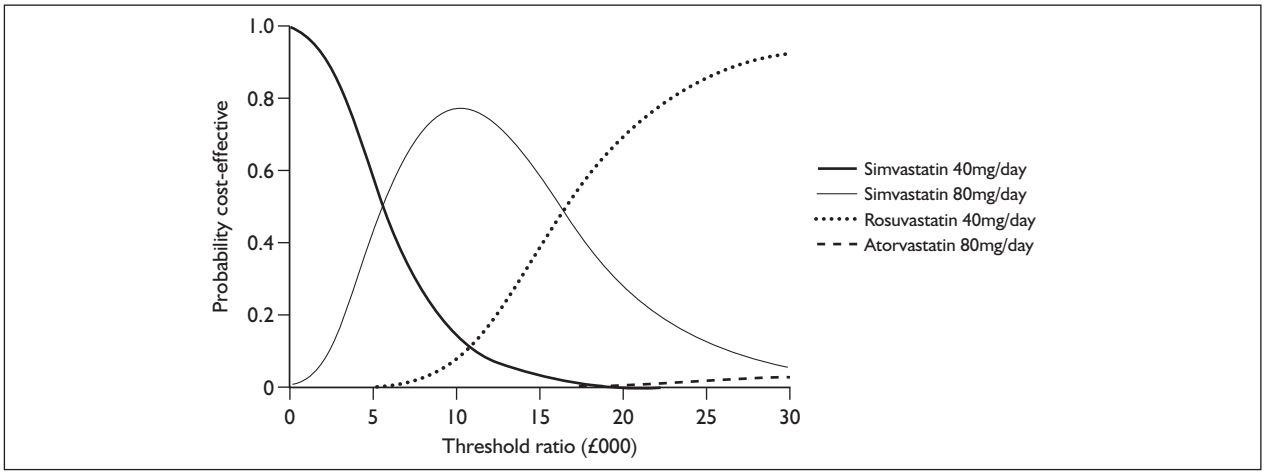

FIGURE 11 *Cost-effectiveness acceptability curve: scenario 4.*

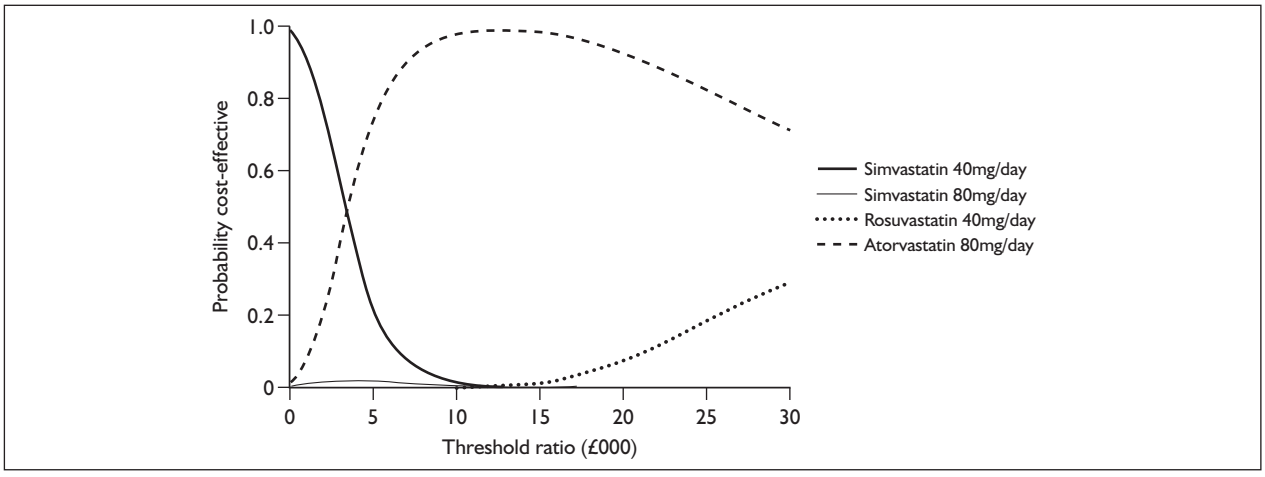

FIGURE 12 *Cost-effectiveness acceptability curve: scenario 1: atorvastatin 80 mg/day = £92 per annum.*

TABLE 22 *Additional univariate sensitivity analyses*

Adherence scenario	Parameter	Incremental cost-effectiveness ratio: Simvastatin 80 mg/day vs simvastatin 40 mg/day	Incremental cost-effectiveness ratio: Atorvastatin 80 mg/day vs simvastatin 40 mg/day	Incremental cost-effectiveness ratio: Rosuvastatin 40 mg/day vs simvastatin 40 mg/day
Deterministic base case				
Scenario 1		£4519	£15,623	£11,913
Scenario 2		£28,403	£25,885	£17,635
Scenario 3		£52,212	£19,590	£16,065
Scenario 4		£5226	£17,217	£12,277
First year UA utility used for post UA health state				
Scenario 1		£5780	£18,773	£13,483
Scenario 2		£34,382	£30,933	£19,437
Scenario 3		£65,789	£23,410	£17,759
Scenario 4		£5700	£18,516	£13,268
First year MI utility used for post MI health state				
Scenario 1		£5513	£17,822	£12,754
Scenario 2		£33,282	£29,585	£18,524
Scenario 3		£63,846	£22,594	£17,122
Scenario 4		£5443	£17,611	£12,582
First year revascularisation utility used for post revascularisation health state				
Scenario 1		£5850	£19,000	£13,646
Scenario 2		£33,015	£29,395	£18,439
Scenario 3		£67,013	£23,712	£17,991
Scenario 4		£5773	£18,755	£13,440
First year stroke utility used for post stroke health state				
Scenario 1		£5476	£17,758	£12,739
Scenario 2		£33,015	£29,395	£18,439
Scenario 3		£62,873	£22,277	£16,895
Scenario 4		£5404	£17,533	£12,552
All post event health state utility values equal first year utility values				
Scenario 1		£6200	£20,112	£14,430
Scenario 2		£37,329	£33,271	£20,875
Scenario 3		£71,127	£25,206	£19,118
Scenario 4		£6119	£19,854	£14,216
All patients start in UA qualifying event				
Scenario 1		£4536	£16,434	£11,537
Scenario 2		£26,764	£26,761	£16,699
Scenario 3		£56,128	£20,651	£15,497
Scenario 4		£4462	£16,139	£11,315

continued

TABLE 22 *Additional univariate sensitivity analyses (continued)*

Adherence scenario Parameter	Incremental cost-effectiveness ratio		
	Simvastatin 80 mg/day vs simvastatin 40 mg/day	**Atorvastatin 80 mg/day vs simvastatin 40 mg/day**	**Rosuvastatin 40 mg/day vs simvastatin 40 mg/day**
All patients start in revascularisation qualifying event			
Scenario 1	£5402	£16,133	£11,726
Scenario 2	£36,891	£27,591	£17,273
Scenario 3	£61,741	£20,676	£15,817
Scenario 4	£5383	£16,068	£11,659
All patients start in MI qualifying event			
Scenario 1	£6794	£21,792	£15,763
Scenario 2	£38,218	£35,367	£22,365
Scenario 3	£73,510	£26,525	£20,155
Scenario 4	£6662	£21,417	£15,442

MI, myocardial infarction; UA, unstable angina.

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We look forward to hearing from you.

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