Health Technology Assessment 2008; Vol. 12: No. 21

Ezetimibe for the treatment of hypercholesterolaemia: a systematic review and economic evaluation

R Ara, I Tumur, A Pandor, A Duenas, R Williams, A Wilkinson, S Paisley and J Chilcott

May 2008

Health Technology Assessment
NHS R&D HTA Programme
www.hta.ac.uk

How to obtain copies of this and other HTA Programme reports.
An electronic version of this publication, in Adobe Acrobat format, is available for downloading free of charge for personal use from the HTA website (http://www.hta.ac.uk). A fully searchable CD-ROM is also available (see below).

Printed copies of HTA monographs cost £20 each (post and packing free in the UK) to both public **and** private sector purchasers from our Despatch Agents.

Non-UK purchasers will have to pay a small fee for post and packing. For European countries the cost is £2 per monograph and for the rest of the world £3 per monograph.

You can order HTA monographs from our Despatch Agents:

– fax (with **credit card** or **official purchase order**)
– post (with **credit card** or **official purchase order** or **cheque**)
– phone during office hours (**credit card** only).

Additionally the HTA website allows you **either** to pay securely by credit card **or** to print out your order and then post or fax it.

Contact details are as follows:

HTA Despatch
c/o Direct Mail Works Ltd
4 Oakwood Business Centre
Downley, HAVANT PO9 2NP, UK

Email: orders@hta.ac.uk
Tel: 02392 492 000
Fax: 02392 478 555
Fax from outside the UK: +44 2392 478 555

NHS libraries can subscribe free of charge. Public libraries can subscribe at a very reduced cost of £100 for each volume (normally comprising 30–40 titles). The commercial subscription rate is £300 per volume. Please see our website for details. Subscriptions can only be purchased for the current or forthcoming volume.

Payment methods

Paying by cheque
If you pay by cheque, the cheque must be in **pounds sterling**, made payable to *Direct Mail Works Ltd* and drawn on a bank with a UK address.

Paying by credit card
The following cards are accepted by phone, fax, post or via the website ordering pages: Delta, Eurocard, Mastercard, Solo, Switch and Visa. We advise against sending credit card details in a plain email.

Paying by official purchase order
You can post or fax these, but they must be from public bodies (i.e. NHS or universities) within the UK. We cannot at present accept purchase orders from commercial companies or from outside the UK.

How do I get a copy of *HTA on CD*?

Please use the form on the HTA website (www.hta.ac.uk/htacd.htm). Or contact Direct Mail Works (see contact details above) by email, post, fax or phone. *HTA on CD* is currently free of charge worldwide.

The website also provides information about the HTA Programme and lists the membership of the various committees.

Ezetimibe for the treatment of hypercholesterolaemia: a systematic review and economic evaluation

R Ara,* I Tumur, A Pandor, A Duenas, R Williams, A Wilkinson, S Paisley and J Chilcott

School of Health and Related Research (ScHARR), University of Sheffield, UK

* Corresponding author

Declared competing interests of authors: none

Published May 2008

This report should be referenced as follows:

Ara R, Tumur I, Pandor A, Duenas A, Williams R, Wilkinson A, *et al*. Ezetimibe for the treatment of hypercholesterolaemia: a systematic review and economic evaluation. *Health Technol Assess* 2008;**12**(21).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE and *Science Citation Index Expanded (SciSearch®)* and *Current Contents®*/Clinical Medicine.

NIHR Health Technology Assessment Programme

The Health Technology Assessment (HTA) Programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA Programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

The HTA Programme is needs-led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, the public and consumer groups and professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA Programme then commissions the research by competitive tender.

Secondly, the HTA Programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Thirdly, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

The final reports from HTA projects are peer-reviewed by a number of independent expert referees before publication in the widely read journal series *Health Technology Assessment*.

Criteria for inclusion in the HTA journal series

Reports are published in the HTA journal series if (1) they have resulted from work for the HTA Programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this issue of the journal was commissioned and funded by the HTA Programme on behalf of NICE as project number 05/22/01. The protocol was agreed in June 2006. The assessment report began editorial review in December 2006 and was accepted for publication in January 2008. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme or the Department of Health.

ISSN 1366-5278

Published by Gray Publishing, Tunbridge Wells, Kent, on behalf of NCCHTA.
Printed on acid-free paper in the UK by St Edmundsbury Press Ltd, Bury St Edmunds, Suffolk.

T

Abstract

Ezetimibe for the treatment of hypercholesterolaemia: a systematic review and economic evaluation

R Ara,* I Tumur, A Pandor, A Duenas, R Williams, A Wilkinson, S Paisley and J Chilcott

School of Health and Related Research (ScHARR), University of Sheffield, UK

* Corresponding author

Objectives: To review the clinical and cost-effectiveness of ezetimibe as a combination therapy or monotherapy for the treatment of primary hypercholesterolaemia in the UK.

Data sources: Twelve electronic databases were searched from inception to June 2006. Searches were supplemented by hand-searching relevant articles, sponsor and other submissions of evidence to the National Institute of Health and Clinical Excellence and conference proceedings.

Review methods: A systematic review and meta-analysis (where appropriate) of the clinical efficacy evidence was undertaken following recommended guidelines. A Markov model was developed to explore the costs and health outcomes associated with ezetimibe treatment.

Results: No published clinical outcome trials (>12 weeks) were identified. In the absence of clinical end-point data from trials, 13 (of which five were multi-arm) phase III multi-centre randomised controlled trials (RCTs) (of varying methodological quality) of short-term duration (12–48 weeks) with surrogate end-point data were included. For patients not adequately controlled with a statin alone, a meta-analysis of six studies showed that a fixed-dose combination of ezetimibe and statin treatment was associated with a statistically significant reduction in low-density lipoprotein cholesterol (LDL-c) and total cholesterol (Total-c) compared with statin alone ($p < 0.00001$). Four studies (not eligible for meta-analysis) that titrated (either forced or stepwise) the statin doses to LDL-c targets generally showed that the co-administration of ezetimibe and statin was significantly more effective in reducing plasma LDL-c concentrations than statin monotherapy ($p < 0.05$ for all studies). For patients where a statin is not considered appropriate, a meta-analysis of seven studies demonstrated that ezetimibe monotherapy significantly reduced LDL-c levels compared with placebo ($p < 0.00001$). There were no statistically significant differences in LDL-c-lowering effects across different subgroups. Ezetimibe therapy (either in combination with a statin or monotherapy) appeared to be well tolerated compared to statin monotherapy or placebo, respectively. No ezetimibe studies reported data on health-related quality of life (HRQoL). There was a wide range in the economic results depending on the treatment strategies evaluated. When comparing ezetimibe monotherapy with no treatment in individuals with baseline LDL-c values of 3.0–4.0 mmol/l, the results range from £21,000 to £50,000 per quality-adjusted life-year (QALY). Results for individuals with baseline LDL-c values over 5.0 mmol/l are below £30,000 per QALY. When comparing the costs and benefits of adding ezetimibe to ongoing statin treatment compared with maintaining statin treatment at the current dose, the majority of results are above values generally considered to be cost-effective (range £19,000 to £48,000 per QALY). Based on the evidence available, when comparing the costs and benefits associated with adding ezetimibe to ongoing statin treatment compared with a switch to a more potent statin, the results are governed by the difference in the cost of the treatment regimens compared and results range from £1500 to £116,000 per QALY.

Conclusions: The short-term RCT clinical evidence demonstrated that ezetimibe was effective in reducing LDL-c when administered as monotherapy or in combination with a statin. However, when used as a monotherapy, ezetimibe is less effective than statins in lowering LDL-c. Given the limitations in the effectiveness data, there is great uncertainty in the economic results. These suggest that ezetimibe could be a cost-effective treatment for individuals with high baseline LDL-c values, for patients with diabetes and for individuals with heterozygous familial hypercholesterolaemia. Long-term clinical outcome studies are needed to allow more precise cost-effectiveness estimates to be calculated.

Contents

Glossary and list of abbreviations

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

Glossary

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

Angina, stable Pain or discomfort in the chest or adjacent areas caused by insufficient blood flow to the heart muscle. This chest pain is relieved by rest or medication within a short period (usually 15 minutes).

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.

Anorexia nervosa An eating disorder characterised by low body weight (less than 85% of normal weight for height and age), a distorted body image and an intense fear of gaining weight.

Apo-lipoprotein Major protein component of lipoproteins.

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

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

Cardiovascular Pertaining to the heart and blood vessels.

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

Coronary arteries The arteries which 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 somewhat in their size (8–11 nm in diameter) and contents that carry cholesterol from the body's tissues to the liver.

Homozygous Possessing two identical forms of the same gene.

Hypercholesterolaemia High blood cholesterol.

Hyperlipidaemia High blood lipids.

continued

Glossary *continued*

Hypertriglyceridaemia High blood triglycerides.

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.

Monogenic hypercholesterolaemia Hypercholesterolaemia caused by **a** single genetic defect only.

Myalgia Diffuse muscle pain, tenderness and weakness.

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

Myopathy Muscle pain, tenderness or weakness associated with abnormal elevations in creatinine kinase levels (>10 times the upper limit of normal).

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.

Obstructive jaundice Increased blood bilirubin causing yellow skin due to the blockage of the bile ducts.

Polygenic hypercholesterolaemia Hypercholesterolaemia caused by a number of genes combined with dietary and other factors.

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.

Sitosterolaemia Rare autosomal recessive disease characterised by increased intestinal absorption of plant sterols, decreased hepatic excretion into bile and elevated concentrations in plasma phytosterols.

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 The sum of all the cholesterol in the blood.

Triglycerides Glyceride 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

ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
CAD	coronary artery disease
CEAC	cost-effectiveness acceptability curve
CHD	coronary heart disease
CI	confidence interval
CK	creatine kinase
CPK	creatine phosphokinase
CTTC	Cholesterol Treatment Trialists' Collaborators
CV	cardiovascular
CVD	cardiovascular disease
DM	diabetes mellitus
FH	familial hypercholesterolaemia
GMF	General Medical Services Framework
HDL-c	high-density lipoprotein cholesterol
HeFH	heterozygous familial hypercholesterolaemia
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
IHD	ischaemic heart disease
ITT	intention-to-treat
LDL-c	low-density lipoprotein cholesterol
LS	least-squares
LYG	life-year gained
MI	myocardial infarction
MSD/SP	Merck Sharp and Dohme Limited/Schering-Plough Limited
NICE	National Institute for Health and Clinical Excellence
NSF	National Service Framework
OR	operational research
PCT	Primary Care Trust
PSM	problem structuring methods
QALY	quality-adjusted life-year
QOF	Quality and Outcomes Framework
QoL	quality of life
QUOROM	Quality Of Reporting Of Meta-analyses
RCT	randomised controlled trial
RR	relative risk
SCA	Strategic Choice Approach
SD	standard deviation
Str	stroke
TG	triglycerides
TIA	transient ischaemic attack
Total-c	total cholesterol
UKPDS	United Kingdom Prospective Diabetes Study
ULN	upper limit of normal
VLDL-c	very low-density lipoprotein cholesterol
WHO	World Health Organization

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

Objectives

To review the evidence for the clinical and cost-effectiveness of ezetimibe (in its licensed indication) as combination therapy or monotherapy for the treatment of primary (heterozygous familial and non-familial) hypercholesterolaemia in the UK.

Methods

In all, twelve electronic bibliographic databases covering the biomedical, scientific, and grey literature were searched from inception to June 2006 (supplemented by contact with experts in the field). Data relating to study design, baseline patient characteristics, clinical or surrogate outcomes, 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.

A new Markov model was developed, to assess the costs and health outcomes associated with ezetimibe treatment. Several treatment regimens were explored including: ezetimibe monotherapy versus no treatment for individuals in whom statin therapy is contraindicated or those who do not tolerate statins; ezetimibe plus a statin compared with the same statin; ezetimibe plus a statin compared with a switch to a more potent statin. The model utilised the established relationship linking changes in low-density lipoprotein cholesterol (LDL-c) and cardiovascular events to estimate the cardiovascular events avoided through lipid lowering therapies.

Results

Clinical effectiveness results

No published clinical outcome trials (>12 weeks) examining the cardiovascular benefit of ezetimibe were identified. In the absence of clinical end-point data from trials, 13 (of which five were multi-arm) Phase III multi-centre RCTs (of varying methodological quality) of short-term duration (12–48 weeks) with surrogate end-point data [such as LDL-c and total cholesterol (Total-c)] were included. Although all the included studies involved patients with primary hypercholesterolaemia (mean baseline LDL-c levels ranging from 3.36 to 6.50 mmol/l), the populations were not fully representative of the population specified in the inclusion criteria, that is, individuals whose lipids were not adequately controlled with current statin treatment or those who are intolerant of statins. The clinical evidence is derived from a population that required a washout or discontinuation of all ongoing lipid regulating drug therapy prior to randomisation and initiation of study treatments.

For patients whose condition is not adequately controlled with a statin alone

Fixed-dose studies

A meta-analysis of six studies showed that the combination of ezetimibe and statin treatment was associated with a statistically significant reduction in LDL-c and Total-c compared with statin alone ($p < 0.00001$). No RCTs were identified that compared ezetimibe plus statin with statin plus other lipid lowering therapy (nicotinic acid, bile acid resins or fibrates).

Titration studies

Four studies (not eligible for meta-analysis) that titrated (either forced or stepwise) the statin doses to LDL-c targets generally showed that the co-administration of ezetimibe and statin was significantly more effective in reducing plasma LDL-c concentrations than statin monotherapy ($p < 0.05$ for all studies). No RCTs were identified that compared ezetimibe plus statin with statin plus bile acid resins or fibrates. One study reported that low–moderate doses of atorvastatin/rosuvastatin plus niacin achieved similar marked LDL-c reductions compared with the highest doses of rosuvastatin monotherapy or ezetimibe/simvastatin.

For patients in whom a statin is considered inappropriate, or is not tolerated

A meta-analysis of seven studies demonstrated that ezetimibe monotherapy significantly reduced LDL-c levels compared with placebo ($p < 0.00001$). This effect was generally consistent across all trials. No RCTs were identified that directly compared

ezetimibe with other lipid-regulating drug (nicotinic acid, bile acid resins or fibrates) therapy.

Subgroup analyses
There were no statistically significant differences in LDL-c-lowering effects across different subgroups such as people with or without existing coronary heart disease (CHD) or other vascular disease, people with or without diabetes, different ethnic groups and patients with or without heterozygous familial hypercholesterolaemia (HeFH).

Safety and tolerability
Ezetimibe therapy (either in combination with a statin or monotherapy) appeared to be well tolerated compared to statin monotherapy or placebo, respectively. The low frequency of adverse events may be attributed to the relatively short periods of the included studies (the majority were 12 weeks). Long-term adverse events are unknown.

Quality of life
No ezetimibe studies reported data on health related quality of life (HRQoL).

Cost-effectiveness results

Two full studies and one abstract were identified in the systematic review for economic evaluations. The studies described country-specific adaptations of a core model. The results ranged from £7700 per life year when comparing ezetimibe co-administered with current statin with current statin in adults with a history of CHD in Germany, to £50,700 per life year when comparing ezetimibe co-administered with current statin treatment with current statin treatment titrated by one dose for adults with diabetes and no history of CHD in Spain. The abstract, which provided insufficient detail for review, reported results to be £8000 per QALY (Quality Adjusted Life Year) for patients aged 65 years with a history of CVD when comparing ezetimibe plus current statin with titration of current statin treatment in Scotland.

Industry submission

Two cost-effectiveness models were presented by the industry submission. The first (referred to as the Cook model) is an adaptation of the model used in the studies identified in the literature search. The second (referred to as the Basic model) was built and submitted to lend credence to the results generated by the more complex model. The Cook model uses the Framingham equations to predict annual changes in coronary risk based on changes in Total-c and HDL-c. The Basic model utilises published evidence on the link between chemically induced reductions in LDL-c and reductions in CV events. Effectiveness rates are derived from meta-analyses of published data. Several treatment regimens are used and the base case evaluates the cost-effectiveness of ezetimibe plus current weighted statin therapy compared with current weighted statin therapy titrated by one dose. The results range from £8800 per QALY for South Asian males aged 60 years at high risk of a CHD event to £122,000 per QALY for females aged 80 years with no history of CVD. However, several key errors were identified and the results are not considered to be robust.

ScHARR economic evaluation

There is a wide range in the results depending on the treatment strategies compared. When comparing ezetimibe monotherapy with no treatment in individuals with baseline LDL-c values of 3.0–4.0 mmol/l, the results range from £21,000 to £50,000 per QALY. Results for individuals with baseline LDL-c values over 5.0 mmol/l are below £30,000 per QALY.

When comparing the costs and benefits of adding ezetimibe to ongoing statin treatment compared with maintaining statin treatment at the current dose, the majority of results are above values generally considered to be cost-effective (range £19,000 to £48,000 per QALY). Based on the evidence available, when comparing the costs and benefits associated with adding ezetimibe to ongoing statin treatment compared with a switch to a more potent statin, the results are governed by the difference in the cost of the treatment regimens compared and results range from £1,500 to £116,000 per QALY.

Limitations of the cost-effectiveness estimates

There are several major limitations associated with the economic evaluation:

- A lack of robust long-term data on clinical effectiveness evidence derived from patients who fail to achieve lipid goals on statin treatment or patients who are intolerant of statins.
- The need to translate changes in surrogate outcomes to reductions in cardiovascular events and the need to extrapolate well beyond the RCT evidence underpin all analyses and increase the uncertainty in the results generated.
- It is uncertain if the proportional reduction in event rates per mmol/L in LDL-c derived from patients receiving statin treatment is generalisable to patients receiving either ezetimibe monotherapy or ezetimibe in combination with a statin.

- The lack of direct evidence of ezetimibe plus a low-dose statin versus a more potent-dose statin increases the uncertainty associated with the effectiveness of the treatments.
- Although the short-term safety profile appears to be good, long-term adverse event data associated with ezetimibe treatment are not available.

Conclusions

The short-term RCT clinical evidence demonstrated that ezetimibe was effective in reducing LDL-c when administered as monotherapy or in combination with a statin. However, when used as a monotherapy, the ability of ezetimibe to lower LDL-c is less effective than that of statins. Given the lack of detailed effectiveness data, there is a great deal of uncertainty in the cost-effectiveness of ezetimibe. The results suggest that depending on the comparator, ezetimibe could be a cost-effective treatment for individuals with high baseline LDL-c values, for patients with diabetes and for individuals with HeFH. Further research is urgently required to allow more precise estimates of cost-effectiveness to be calculated.

Generalisability of findings

There is a major concern regarding the generalisability of the results of the short-term RCT effectiveness evidence into routine clinical practice. The current evaluation explores the costs and benefits associated with adding ezetimibe treatment to ongoing treatment for individuals not achieving adequate lipid control. Due to inclusion and exclusion criteria and the washout periods, the populations in the RCTs may not be representative of the target population.

Recommendations for future research

Further research is required in the following areas:

- Long-term clinical outcome trials involving patients who are intolerant of statins, patients in whom statins are contraindicated and patients who fail to achieve lipid control on statin monotherapy. Studies exploring the long-term effectiveness and safety profile of ezetimibe using combinations of lipid-lowering treatments are also required.
- Lifetime adherence to combination therapies in the relatively healthy younger and asymptomatic patients with no history of CVD.
- To establish if reductions in lipids to predetermined targets provide additional reductions in cardiovascular events.
- Research on short- and long-term changes in HRQoL associated with primary or subsequent cardiovascular events is also required to reduce uncertainty in cost-effectiveness estimates for cardiovascular interventions.

Chapter 1
Background

Description of health problem

Introduction

Cardiovascular disease (CVD) is a disease of the heart and blood vessels, which can lead to cardiovascular events such as myocardial infarction (MI), angina and stroke (Str). The most common form of CVD is coronary heart disease (CHD). Other forms of CVD are Str, transient ischaemic attack (TIA) and peripheral arterial disease. CVD is the most common cause of death in the UK and is a major cause of illness, disability and reduced quality of life.[1,2]

High levels of cholesterol in the blood (hypercholesterolaemia) are associated with an increased risk of CHD and Str.[3] Serum cholesterol is an important determinant of cardiovascular (CV) risk. The increased risk is due mainly to raised low-density lipoprotein cholesterol (LDL-c). Lowering the concentration of total cholesterol (Total-c) and LDL-c, and raising high-density lipoprotein cholesterol (HDL-c) can reduce the risk of CV events, morbidity and mortality. The absolute risk for an individual depends on a range of CV risk factors such as smoking, diabetes and hypertension, and treatment decisions are generally based on overall risk.

Primary hypercholesterolaemia is associated with an underlying genetic defect; this can be due to a single genetic defect (monogenic) or, much more commonly, to the interaction of a number of genes (polygenic) with dietary and other factors.[4] The various forms of hypercholesterolaemia (including other primary dyslipidaemia) are summarised in *Table 1*. The majority of people with hypercholesterolaemia have plasma cholesterol concentrations that are only mildly or moderately elevated, and they exhibit no clinical symptoms. Severe hypercholesterolaemia can cause xanthomas (lesions on the skin containing cholesterol and fats) and arcus corneae (cholesterol deposits in the eyes). In people with very severe forms of the condition, such as heterozygous familial hypercholesterolaemia (HeFH), onset of CHD is not uncommon during the second and third decades of life. Secondary hypercholesterolaemia has other causes or is induced by drug therapy [e.g. kidney disease (nephrotic syndrome), hypothyroidism, anorexia nervosa, obstructive jaundice, family history and diabetes mellitus (DM)].

Although the difference between 'normocholesterolaemia' and 'hypercholesterolaemia' is arbitrary, various UK (and international) guidelines stipulate target lipid levels for people with or at risk of CVD (see *Table 6*). For the purpose of this assessment, the targets for Total-c and LDL-c, as set by revised JBS2,[3] will be regarded as optimal targets [there are no definite targets for HDL-c and triglycerides (TG)] for people who require lipid-regulating treatment.

Epidemiology

Blood lipid levels in the UK

Lipid levels vary in an individual from day to day; additionally, levels vary across different populations.[6,8] The variation in blood cholesterol may be accounted for by random (biological), methodological, genetic and environmental factors.[6] Due to these differences, there are no fixed 'normal ranges' for blood lipids; however, the average level of blood cholesterol within a population is an important determinant of CHD risk of the population.[9]

In England (data not available for Wales), the mean serum cholesterol level in adults is approximately 5.6 mmol/l.[10] This is much higher than the World Health Organization (WHO) recommended theoretical minimum of 3.8 mmol/l.[11] Of the average serum Total-c, two-thirds is LDL-c (about 3.6 mmol/l), one-quarter is HDL-c (around 1.5 mmol/l) and the remainder is other lipid particles. Cholesterol values are fairly similar in males and females, although in women there are higher HDL-c levels contributing to the Total-c. In women, cholesterol and LDL-c levels increase after the menopause, and the mean level is then slightly higher than in men (*Table 2*).

Regional and socio-economic variations in blood Total-c levels are small for either sex. However, the prevalence of low HDL-c levels (<1.0 mmol/l) varies substantially by income (high-level earners tend to have greater levels of HDL-c, most notably

TABLE 1 *Various forms of primary dyslipidaemia*[5,6]

Dyslipidaemia	WHO phenotype	Diagnosis	Estimated prevalence (population)[a]	
			%	Ratio[6,7]
Hypercholesterolaemia (mainly)	Type IIa: raised LDL	Monogenic hypercholesterolaemia		
		Familial hypercholesterolaemia	0.2	1:500 (heterozygous) 1:10^6 (homozygous)
		Familial defective apo-B	0.2	1:1000 (heterozygous) 1:4×10^6 (homozygous)
		Polygenic hypercholesterolaemia	20–80	42:1000
Combined hypercholesterolaemia and hypertriglyceridaemia				
Triglycerides 2.0 to 10.0 mmol/l	Type IIb: raised VLDL and LDL	Familial combined (if relatives have same pattern, otherwise only combined) hyperlipidaemia	10+	5:1000
Triglycerides 5.0 to 20.0 mmol/l (cholesterol typically 7.0 to 12.0 mmol/l)	Type III: raised chylomicrons remnants and IDL	Type III or remnant particle size	0.02	0.1:1000
Triglycerides >10.0 mmol/l	Type V: raised chylomicrons and VLDL; or type I: raised chylomicrons	Lipoprotein lipase deficiency	0.1	1:1000
Raised triglycerides alone	Type IV	Familial or sporadic hypertriglyceridaemia	1	–
Hypoβlipoproteinaemia	None: low HDL	Often undiagnosed and associated with low HDL	10–25	50:1000
Hypoβlipoproteinaemia	None: low LDL and frequently VLDL	Familial, e.g. truncated apo-B	0.01–0.1	–

HDL, high-density lipoprotein cholesterol; IDL, intermediate-density lipoprotein cholesterol (VLDL remnants); LDL, low-density lipoprotein cholesterol; VLDL, very low-density lipoprotein cholesterol.
[a] Among European adults.

in women) but not by region.[12] Of the minority ethnic groups in England (Black Caribbean, Indian, Pakistani, Chinese and Irish), the mean serum Total-c (including LDL-c) in both men and women is marginally lower than in the general population. However, ethnic variations in the prevalence of low HDL-c (<1.0 mmol/l) is considerable, with the highest rates for both sexes found in the Pakistani and Bangladeshi communities. In contrast, Black Caribbean males and females have a relatively low prevalence of low HDL-c.[13]

The prevalence of raised cholesterol levels according to different definitions is summarised in *Table 3*. In general, raised cholesterol levels increase with age and tend to be higher in men than women. However, levels are greater in women after the age of 65 years. Overall, approximately 27% of people in England (data not available for Wales) have a serum cholesterol level ⩾6.5 mmol/l and about 70% ⩾5.0 mmol/l.

Aetiology, pathology and prognosis

Aetiology

Genetic predisposition, concomitant diseases (e.g. DM and chronic renal failure), certain medications (e.g. anabolic steroids, beta-blockers, corticosteroids and oral contraceptives), diet and lifestyle (e.g. smoking, physical inactivity) influence the total serum cholesterol level.[14] Of these, dietary fat and cholesterol intake

TABLE 2 *Blood lipid levels in England 2003 by age and sex[12] (data not available for Wales)*

	Age (years)							
	16–24	**25–34**	**35–44**	**45–54**	**55–64**	**65–74**	**75+**	**Total**
Male								
Total-c (mmol/l)[a]								
Mean	4.5	5.3	5.8	5.9	5.8	5.5	5.3	5.5
10th percentile	3.4	4.0	4.3	4.6	4.5	4.0	3.9	4.0
90th percentile	5.7	6.7	7.2	7.3	7.2	7.1	6.6	7.0
LDL-c (mmol/l)[b]								
Mean	–	–	3.5	3.7	3.6	3.7	3.6	3.6
10th percentile	–	–	–	–	–	–	–	–
90th percentile	–	–	–	–	–	–	–	–
HDL-c (mmol/l)								
Mean	1.3	1.4	1.4	1.4	1.4	1.4	1.4	1.4
10th percentile	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
90th percentile	1.8	1.7	1.8	1.8	1.8	1.8	1.9	1.8
Triglycerides (mmol/l)[b]								
Mean	–	–	1.7	1.8	2.1	1.7	1.5	1.8
10th percentile	–	–	–	–	–	–	–	–
90th percentile	–	–	–	–	–	–	–	–
Female								
Total-c (mmol/l)[a]								
Mean	4.6	5.0	5.4	5.8	6.3	6.2	6.1	5.6
10th percentile	3.7	3.9	4.2	4.5	4.9	4.8	4.6	4.1
90th percentile	5.8	6.1	6.6	7.2	7.7	7.8	7.8	7.2
LDL-c (mmol/l)[b]								
Mean	–	–	3.2	3.5	3.8	3.9	3.9	3.6
10th percentile	–	–	–	–	–	–	–	–
90th percentile	–	–	–	–	–	–	–	–
HDL-c (mmol/l)								
Mean	1.6	1.6	1.6	1.7	1.7	1.7	1.6	1.6
10th percentile	1.2	1.1	1.1	1.2	1.2	1.2	1.2	1.2
90th percentile	2.0	2.0	2.0	2.2	2.3	2.3	2.1	2.1
Triglycerides (mmol/l)[b]								
Mean	–	–	1.2	1.3	1.5	1.6	1.5	1.4
10th percentile	–	–	–	–	–	–	–	–
90th percentile	–	–	–	–	–	–	–	–

[a] Including those taking lipid-regulating drugs (6.2%).
[b] Interpret with caution: values are based on very small sample sizes.

(saturated fatty acids) are the major determinants of the serum Total-c and LDL-c levels in populations. Approximately 50% of the inter-individual variation in plasma LDL-c is attributable to genetic predisposition.[15] The most common and the most severe form of genetically predetermined hypercholesterolaemia is familial hypercholesterolaemia. HeFH is an autosomal codominant inherited disorder of lipoprotein metabolism, characterised by mutations of the LDL-c receptor, resulting in high levels of LDL-c. Currently, 800–1000 mutations have been identified at a single locus on chromosome 19 that causes genetically inherited primary hypercholesterolaemia.[16] These mutations cause a variety of defects in LDL receptor function, including impaired synthesis, transport to the cell surface, binding and clustering at the cell surface and degradation. Cholesterol normally circulates in the body for 2.5 days, after which it is cleared by the liver. In familial hypercholesterolaemia, the half-life of an LDL particle is almost doubled to 4.5 days. This leads to markedly elevated LDL-c levels, with the other forms of cholesterol remaining normal. Each first-degree relative of an individual with familial hypercholesterolaemia

TABLE 3 *Total-c levels in England 2003 according to different definitions[10] (data not available for Wales)*

	Gender	Age (years)			
		16–44	45–64	65+	All (16+)
Total-c (mmol/l)					
% ⩾6.5	Male	15.9	37.8	40.4	26.5
	Female	8.1	36.9	54.6	26.5
	Total	12.0	36.9	48.4	26.5
% ⩾5.0	Male	57.6	85.8	81.9	69.9
	Female	50.4	84.5	91.7	69.3
	Total	54.0	85.2	87.3	69.9
Cholesterol ratio					
Total: HDL ⩾5.0	Male	20.6	31.1	23.1	24.3
	Female	6.9	13.6	17.0	11.0
	Total	13.7	22.3	19.6	17.5
Total: HDL ⩾7.0	Male	1.8	2.7	1.3	2.0
	Female	0.5	0.9	1.2	0.8
	Total	1.1	1.8	1.2	1.4

TABLE 4 *Modifiable and non-modifiable risk factors for CVD[18]*

Lipid risk factors	Non-lipid risk factors	
	Preventable risk factors	Non-preventable risk factors
Elevated serum triglycerides	Type 2 diabetes	Family history of premature CVD
Non-HDL cholesterol (VLDL + LDL)	High blood pressure	Increasing age
Low HDL cholesterol	Lack of physical activity	Male gender
	Overweight and obesity	Race/ethnicity
	Tobacco smoking	
	Alcohol consumption	
	Atherogenic diet	

(FH) has a 50:50 chance of also being affected by this condition, with males and females equally affected.[17] *Table 4* provides a list of other modifiable and non-modifiable risk factors for CVD.

A further discussion of the relationship between cholesterol and CVD is provided in the section 'Key issues' (p. 13).

Pathophysiology

The main physiological systems involved in the absorption, metabolism and storage of cholesterol and triglycerides are the small intestine, liver, adipose tissue and peripheral cells. These lipids are transported together with phospholipids within plasma by lipoproteins. Dietary cholesterol and triglycerides are carried by chylomicrons and endogenously synthesised triglycerides by LDL-c. Cholesterol is transported out to the periphery by LDL-c and returned to the liver by HDL-c. Other factors which influence elevated plasma cholesterol levels include age, hormonal changes, diet, exercise and concomitant disease. Elevated concentrations of the plasma cholesterol promote atheroma formation in the walls of arteries, a condition known as atherosclerosis.

Atherosclerosis begins when a fatty streak develops on an arterial wall. This fatty streak is formed when monocytes congregate on the arterial wall in response to lipoprotein oxidation or other influences. When monocytes leave the bloodstream and migrate to the intima, they become macrophages. Macrophages then phagocytise oxidised LDL-c and die, thereby contributing to the lipid component of the fatty streak. Before they die, macrophages also secrete multiple growth factors that serve as the principal mitogens for connective tissue cells, such as fibroblasts and smooth muscle cells. Collagen is another principal contributor to atherosclerotic plaque, and its production leads to the formation of hard fibrous plaques, usually in the third decade of life.

In response to increased plaque volume, arterial remodelling occurs, which results in an outward expansion of the coronary arteries. The arteries expand in an effort to overcome the effects of the blockage, allowing blood to flow through the stenosed vessel segment. This expansion continues until the artery reaches its maximum point of flexibility and can no longer accommodate the continued growth of the plaque. This threshold generally occurs when the arterial stenosis reaches 40%. As the plaque ages, an increasing amount of fibrous tissue accumulates, leading to the formation of a fibrous cap, which is vulnerable to rupture.

Prognosis

A number of complications may occur if a high cholesterol level in blood is left untreated. As mentioned in the previous section, it can cause atherosclerosis, a slowly progressing formation and accumulation of plaque deposits within the intima of arteries, resulting in narrowing or blocking of arteries. These progressive arterial stenoses eventually lead to ischaemic vascular disease or coronary artery disease (CAD), and the rupture of a plaque can cause an MI (also called heart attack).

Table 5 presents the estimates of the risk of death according to serum cholesterol level in patients with hypercholesterolaemia. Raised serum cholesterol is a major risk factor for CHD. However, when it is used on its own, it is a relatively poor predictor of who will go on to have a CHD event – only 42% of those who will suffer a CHD event over 15 years will have a serum cholesterol greater than 6.5 mmol/l.[9]

People with HeFH generally have more than a 50% cumulative risk of fatal or non-fatal CHD in men and at least a 30% cumulative risk in women.[19]

TABLE 5 *Estimates of the risk of death according to serum cholesterol level in patients with hypercholesterolaemia*[8]

Serum cholesterol (mmol/l)	Risk of death before age of 60 years (per 1000)[a]
<5	25
5–6	30
6–7	43
7–8	55
8–9	74
>9	130
HeFH	500

[a] Death up to 60 years of age in men is chosen because of limited data on cholesterol in older age groups, on morbidity and on women. Combined CHD death and non-fatal symptomatic CHD is probably 2–3 times that of CHD death.[8]

Impact of health problem

Significance for patients in terms of ill-health (burden of disease)

In the UK, CVD (CHD, Str and other vascular diseases) accounted for nearly 216,000 deaths in 2004; about half (49%) of these were from CHD and about one-quarter (28%) from Str.[1] CVD is one of the main causes of premature death (death in people aged under 75 years). In 2004, it caused about 60,000 premature deaths in the UK, accounting for 32% of premature deaths in men and 24% in women.[1] CVD is also a significant cause of morbidity (approximately 2.7 million people have or have had CHD in the UK),[1] and can have a major impact on quality of life (QoL). CHD has been estimated to be the leading cause of disability in Europe, accounting for 10.5% of total disability-adjusted life-years.[2] Mortality and morbidity rates associated with CVD vary by socio-economic group (higher in manual social classes), geographic area (CHD is highest in the north of England and Wales and lowest in the south of England, particularly in the north and south Thames regions; Str is highest in the Yorkshire region and lowest in the Oxford region) and ethnic group (CHD is high among people from the Indian subcontinent and Str is particularly high in people of black Caribbean origin).[1]

Cholesterol is a key component in the development of atherosclerosis (the accumulation of fatty deposits on the inner lining of arteries). Mainly as a result of this, cholesterol increases the risks of CVD. In 2002, the World Health Report[11] estimated that high cholesterol causes 18% of global cerebrovascular disease (mostly non-fatal events) and 56% of global ischaemic heart disease (IHD). In the UK, the British Heart Foundation[20] and the National Heart Forum[21] suggest that high blood cholesterol is the single biggest modifiable risk factor for CHD (greater than the individual risk from physical inactivity, smoking, high blood pressure and obesity) with about 46% of CHD deaths (in people under 75 years of age) attributed to raised serum cholesterol. These data are similar to those reported for the US population.[22,23]

Significance for the NHS

CVD is a major public health concern that imposes a substantial burden, both to the NHS and to the wider economy as a whole. In 2004, CVD cost the NHS about £15.7 billion

(representing 21% of overall NHS expenditure), with CHD and cerebrovascular disease accounting for 22% (£3.45 billion) and 30% (£4.69 billion) of the total, respectively. Hospital inpatient care was the largest component of CVD-related healthcare costs, representing £9.93 billion. Moreover, when the economic costs of CVD in terms of lost productivity due to CVD mortality and CVD-related incapacity and cost of informal care of incapacitated patients in the community are taken into account, the overall cost of CVD to the UK economy was estimated to be £29.1 billion.[24] On the evidence currently available, it is not possible to establish what proportion of the overall cost of CVD is directly attributable to primary hypercholesterolaemia.

Current service provision

Management of disease and national guidelines

The management of hypercholesterolaemia is constantly evolving. The main aim of treatment is to prevent or reduce the risk and complications of CVD.[25] Although blood cholesterol is an important risk factor for CHD, cholesterol lowering is only one of a number of methods of reducing the risk of CVD.[9] Dietary and lifestyle modifications (e.g. weight loss, smoking cessation, aerobic exercise) are an integral part of risk management. If these are unsuccessful or the patient is at high risk, more aggressive therapy, including lipid-regulating drug therapy, is initiated.[26]

The UK guidelines published in the National Service Framework (NSF) for CHD in 2000[27] advocate that patients with clinical evidence of CHD or those with a 10-year risk greater than 30% should be prescribed lipid-regulating drug therapy (combined with advice on diet and lifestyle), with the aim of reducing serum Total-c to less than 5 mmol/l (or a reduction of 20–25% if that produces a lower concentration) and LDL-c to below 3 mmol/l (or a reduction of about 30% if that produces a lower concentration). The recommended target Total-c and LDL-c levels are broadly similar to the guidelines issued by the NSF for CHD in Wales,[28] the Scottish Intercollegiate Guidelines Network (SIGN),[29,30] the Clinical Resources Efficiency Support Team (CREST) Guidelines in Northern Ireland[31] and the New General Medical Services (GMS) contract.[32]

More recent guidance, published in 2004, from six Joint British Societies (JBS2)[3] recommends lower treatment thresholds [Total-c less than 4.0 mmol/l **and** LDL-c below 2.0 mmol/l in all people with CVD or at high risk (CVD risk ⩾20% over 10 years)]. Although the lipid targets in the NSF for CHD[27] have been superseded by new scientific evidence, they have been maintained as an audit standard for the management of cholesterol in patients with, or at risk of, CVD.[3] In the USA, the revised NCEP ATP III guidelines[33] propose an optional lower LDL-c target of <1.8 mmol/l for people at very high risk. The UK, European and US guidelines for best practice are summarised in *Table 6*. It is noteworthy that although lowering cholesterol has been shown to reduce the risk of CV events, the optimal guideline targets are based on expert consensus agreement and have not been tested *a priori* by clinical trials.[6] These guidelines may not be appropriate for people with FH.

At present, statins are the cholesterol-regulating drugs of choice for both primary and secondary prevention of CVD.[3,27–31,33,35,36] In comparison with other lipid-regulating agents (e.g. anion-exchange resins, nicotinic acid or fibrates), statins are the most effective drugs for lowering surrogate end-points (Total-c by approximately 20–30% and LDL-c by about 25–50%)[37] and reducing coronary events, all CV events and total mortality.[3,38] In 2006, the National Institute for Health and Clinical Excellence (NICE) issued guidance on the use of statins for the prevention of cardiovascular events to clinicians within the NHS in England and Wales.[39] The guidance recommends statin therapy for all adults with clinical evidence of CVD and as part of the management strategy for the primary prevention of CVD for adults who have a 20% or greater 10-year risk of developing CVD.

If targeted lipid levels (Total-c and LDL-c) are not achieved in people who are tolerant of statins, additional strategies may include increased dosage of the statin, changing to a more potent statin or combination therapy with statins and fibrate or nicotinic acid.[3,38] If this fails or when people are intolerant of statins, other lipid-regulating drug therapies may be utilised in some people (*Table 7*). As noted earlier, target guidelines are based on expert consensus, and therefore the benefits of titrating, switching or combination therapy to reach an optimum goal are unknown. Individuals at very high risk who are resistant to medical therapy may require plasma apheresis.[26]

Current service cost

Statins represent the largest drug spend in the NHS budget, costing £578 million in England[43]

TABLE 6 *Target lipid levels of consensus guidelines in the UK, Europe and USA*

Guideline	Published	Population/risk group	Key lipid targets	
			Total-c (mmol/l)	**LDL-c (mmol/l)**
UK				
Joint British Societies-2 (JBS2)	2005[3]	Established atherosclerotic disease; CHD, Str or peripheral arterial disease; CVD risk ⩾20% over 10 years; DM	Optimal target <4.0 or 25% reduction (whichever is greater) Audit standard <5.0	Optimal target <2.0 or a 30% reduction (whichever is greater) Audit standard <3.0
National Service Framework for CHD (England)	2000[27]	Diagnosed CHD/other occlusive vascular disease; without diagnosed CHD/other occlusive arterial disease but CHD risk >30% over 10 years	<5.0 or 30% reduction (whichever is greater)	<3.0 or 30% reduction (whichever is greater)
National Assembly for Wales	2001[28]	With CHD; high risk of developing CHD	<5.0 or a reduction by 2 mmol/l	<3.0
Scottish Intercollegiate Guidelines Network (SIGN)	1999,[29] 2000[30]	With CHD (MI); CHD risk >30% over 10 years	<5.0	–
Clinical Resource Efficiency Support Team (CREST)	2000[31]	With CHD; without diagnosed CHD but CHD risk >30% over 10 years	<5.0	<3.0
General Medical Services Contract	2006[32]	With CHD; Str/transient ischaemic attack; DM	<5.0	–
Europe				
European Society of Cardiology	2003[35]	Without CVD; asymptomatic but at high risk of atherosclerotic CVD (including diabetes); established atherosclerotic CVD	<5.0 (in general) <4.5 (in clinically established CVD and diabetes)	<3.0 (in general) <2.5 (in clinically established CVD and diabetes)
USA				
National Cholesterol Education Program (ATP III)	2002,[36] 2004[33]	Established CHD and CHD risk equivalents (diabetes and multiple CHD risk factors with 10-year risk for CHD >20%) (all high risk); multiple (2+) risk factors, 10-year CHD risk <20% (moderately high risk); none or 1 risk factor (lower risk)	–	<1.8 (optional in very high-risk patients) <2.6 (high risk) <3.4 (moderate to moderately high risk) <4.2 (lower risk) (All lipid-lowering drug therapy should be sufficient to achieve at least 30–40% reduction in LDL-c levels)

and £40 million in Wales in 2005.[44] The estimated cost of statins in England in 2006 is approximately £389 million (data not available for Wales), based on prescribing rates (*Table 8*).

Ezetimibe is a comparatively new intervention and has only been available in England and Wales since April 2003. Although prescribing rates for ezetimibe are small in comparison with statins, the current prescribing growth rate is high (see the section 'Impact on the NHS', p. 69). The impact of the current growth rate on the future number and type of patients who will receive ezetimibe as monotherapy or combination therapy is uncertain.

TABLE 7 *Comparative features of other lipid-regulating drugs*[7,40]

Drug class, agents and daily dose[38]	Main indication and use	Lipid/lipoprotein effects	Adverse effects	Contraindications	Comments
Anion-exchange resins[a]	Hypercholesterolaemia	LDL-c: decreased by 15–30% HDL-c: increased by 5–15% TG: no change or increase	Gastrointestinal dysfunction (e.g. constipation, nausea and flatulence)	Hypertriglyceridaemia, peptic ulcer, haemorrhoids	Poor tolerability and unpalatability often limit use[41] However, useful, when tolerated, in moderate or higher dose as adjunct to statins and other therapies, for greater reduction of LDL-c (e.g. FH)[6]
Fibrates[b]	Hypertriglyceridaemia, mixed hyperlipidaemia	LDL-c: decreased by 5–20% (may be increased in patients with high TG) HDL-c: increased by 10–20% TG: decreased by 20–50%	Myositis-like syndrome, increased bile lithogenicity, pruritus, urticaria, impotence, headache, vertigo, dizziness, fatigue, hair loss	Renal or hepatic impairment, gall bladder disease, pregnancy, breast-feeding, cirrhosis (Never use gemfibrozil with statin)	Not a first-line therapy for isolated hypercholesterolaemia as they have only a moderate effect on LDL-c levels. People with mixed hyperlipidaemia may be prescribed statin plus fibrate.[6] Fibrates may be considered first-line therapy in those with severe hypertriglyceridaemia[38] or familial dysbetalipoproteinaemia[6]
Nicotinic acid and analogues[c]	Combined mixed dyslipidaemia	LDL-c: decreased by 5–25% HDL-c: increased by 15–35% TG: decreased by 20–50%	Gastrointestinal disturbances, vasodilatation, flushing, rash, itching, headaches	Pregnancy, breast-feeding, peptic ulcer (acipimox). Caution in patients with gout, diabetes, liver disease	Rarely prescribed in the UK due to adverse-effects;[42] however, modified/extended release preparations have been developed and appear to be better tolerated and may have a useful role in high-risk people with difficult to control dyslipidaemia[6]

[a] Colestyramine (12–24 g/day; maximum 36 g/day); colestipol hydrochloride (5–10 g/day; maximum 30 g/day).
[b] Bezafibrate (400–600 mg/day); ciprofibrate (100 mg/day); fenofibrate (160–267 mg/day); gemfibrozil (1200 mg/day).
[c] Nicotinic acid (standard release, 300 mg/day–6 g/day; modified release, 375 mg/day–2 g/day); acipimox (500–750 mg/day).

TABLE 8 *Lipid-regulating prescribing rates[a] for 2005 in England[43] (data not available for Wales)*

Selected lipid-regulating drug		Dose (mg)	% of patients	Annual cost[b] (£000)	% of all lipid-regulating drug
Statins[c]	Atorvastatin	10	19.75	120,234	
		20	11.75	97,752	
		40	6.18	58,857	
		80	1.34	12 731	
		All	39.02	289,574	
	Fluvastatin	20	0.48	2,061	
		40	0.73	3,111	
		80	0.32	1,747	
		All	1.53	6,919	
	Pravastatin	10	1.04	1,347	
		20	1.87	3,221	
		40	3.66	6,643	
		All	6.57	11,211	
	Rosuvastatin	5	0.001	15	
		10	3.21	19,536	
		20	0.57	3,444	
		40	0.11	1,093	
		All	3.89	24,087	
	Simvastatin	10	9.32	6,000	
		20	19.90	16,679	
		40	18.89	27,446	
		80	0.88	7,185	
		All	48.99	57,310	
	All	–	–	389,101	94.90
Ezetimibe	Ezetimibe monotherapy	10	97.57	17,391	
	Ezetimibe in combination with simvastatin (single tablet)	10/20	1.27	287	
		10/40	0.99	261	
		10/80	0.18	49	
	All	–	–	17,988	1.90
Nicotinic acid	All	–	–	517	0.07
Cholestyramine	All	–	–	2,045	0.21
Fibrates	All	–	–	14,285	2.37

[a] Data for all lipid-regulating drugs not shown.
[b] Total costs according to prescribed doses, prescribing rates as per 2005 and costs as per 2006.
[c] Includes both generic and non-generic drugs.

The literature suggests that 72% of individuals on statins are at target in the UK.[45] It is uncertain at the moment what proportion of the individuals who are not at target on current medications will receive ezetimibe in the future. Future prescribing rates are likely to be influenced by (1) evidence from long-term studies demonstrating effectiveness in terms of hard clinical outcomes, (2) evidence of long-term adverse event rates, (3) the rate of effectiveness in reducing lipids in clinical practice and (4) identification of subgroups likely to benefit from ezetimibe treatment.

Variation in services and/or uncertainty about best practice

As ezetimibe is a relatively new treatment, there is a dearth of evidence on variations in prescribing rates. It is likely that variation in ezetimibe prescribing rates could be correlated with variations in statin prescribing rates. Statin

prescribing has been shown to vary between[46,47] and within countries,[48,49] between health authorities and GPs[48,50–52] and between patients on the basis of gender,[48,49,53–55] demographics,[48,56] ethnicity[57] and deprivation.[58] Despite the widespread variation, there has been an exponential rise in the number of people with CVD being treated with statins, from 49.4% in 2002 to 71.5% in 2004–5. However, about one-third (33.2%) of patients fail to reach the NSF targets of lowering cholesterol below 5 mmol/l.[59] Other UK studies in patients with CHD or at high CHD risk suggest a figure of around 50%.[60–63]

A survey evaluating statin prescribing in UK general practice[64] found that the success in lowering Total-c levels to less than 5 mmol/l was achieved at the first dose of statin in 65% of patients with CHD. However, only 46% achieved a cholesterol reduction of 25%. After dose titration or switching of statin therapy, 78% of patients with CHD reached the 5 mmol/l or less target and 56% achieved a 25% reduction in Total-c. The authors suggested that these modest improvements in achieving targets may reflect caution and a reluctance to use high doses or (switch to) newer statins that provide greater cholesterol reduction in UK general practice.[64] Other studies have also found that the failure to achieve target levels may be due to either the use of suboptimal doses of statins[65] or observed reductions in clinical practice are less than those projected by package insert guidelines.[66] Moreover, with all statins, the greatest proportion of LDL-c lowering occurs at the initial dose and each subsequent doubling of the statin dose produces, on average, an additional 6% incremental reduction in LDL-c beyond that achieved by the starting dose[67] (e.g. a three-step titration, equivalent to increasing the dose from 10 to 80 mg simvastatin, will result in approximately an additional 18% reduction in LDL-c).

Prescription cost analyses[43] and data from the Primary Care Data Quality audit[59] show that the average statin dose prescribed in the UK is less than that used in clinical trials. Initiation of statins at evidence-based doses (e.g. MRC/BHF Heart Protection Study, 40 mg simvastatin in high-risk individuals) may be more common in secondary care than in primary care, but the reason for this is unknown.[68] A reluctance to prescribe statins at the higher maximum doses in clinical practice and the failure to titrate statins may be due to a variety of reasons. For physicians, patient compliance, fear of adverse effects (higher doses of statins are associated with an increased risk of serious adverse events, including liver enzyme abnormalities and myopathy, unacceptable benefit/risk ratio and increased intolerability), and the limited availability of time and resources are perceived to be key barriers for statin titration.[69] On the other hand, there may be a reluctance to change to another statin, especially if it means sacrificing a good all-round lipid profile for lower LDL-c.[68,70]

Although statins are the first-line therapy for treating CVD, a small but significant proportion of patients (1–3%) are unable to tolerate statins due to gastrointestinal or muscular side effects.[71] In addition, more than 30% of patients receiving statins switch from their initial therapy within the first year of treatment[72] and more than 50% of patients discontinue statin therapy within 3 years.[73,74] It is noteworthy that the data for the high discontinuation rates do not seem to be in agreement with the largest published audit on secondary prevention in English general practices, which suggests that the proportion of patients reaching the 5 mmol/l target has progressively increased from 44.7% in 2002 to 67.6% in 2004–5.[59] A more recent figure of 72% has been quoted by Kirby and colleagues,[45] which is based on data from the Quality and Outcomes Framework (QOF) within the General Medical Services Framework (GMF).

Description of technology under assessment

Ezetimibe has been proposed for the treatment of patients with primary hypercholesterolaemia. This section of the report summarises the product characteristics of the intervention (further details are available from the electronic Medicine Compendium website at www.medicines.org.uk).

Summary of interventions

Ezetimibe

Description

Ezetimibe is a unique cholesterol absorption inhibitor that blocks the intestinal absorption of dietary and biliary cholesterol and related plant sterols without affecting the uptake of triglycerides or fat-soluble vitamins. It is orally active and its mechanism of action differs from that of other classes of cholesterol-reducing compounds (including statins, bile acid sequestrants, fibric acid derivatives and plant stenols). Due to its distinct mechanism of action, it can also be combined with a statin (which inhibits the synthesis of cholesterol) to provide complementary cholesterol reduction.

Licensed indications
Ezetimibe monotherapy [Ezetrol®, Merck Sharp and Dohme Limited/Schering-Plough Limited (MSD/SP)] is licensed as an adjunctive therapy to diet for:

- Primary (heterozygous familial and non-familial) hypercholesterolaemia in patients in whom a statin is considered inappropriate or is not tolerated.
- Primary (heterozygous familial and non-familial) hypercholesterolaemia, co-administered with a statin, in patients who are not appropriately controlled with a statin alone.
- Homozygous familial hypercholesterolaemia, co-administered with a statin. Patients may also receive adjunctive treatments such as LDL-c apheresis.
- Homozygous familial sitosterolaemia.

A fixed-dose combination tablet containing ezetimibe and simvastatin (Inegy®, MSD/SP) is also licensed as an adjunctive therapy to diet for use in:

- Primary (heterozygous familial and non-familial) hypercholesterolaemia or mixed hyperlipidaemia where use of a combination product is appropriate: patients not appropriately controlled with a statin alone or patients already treated with a statin and ezetimibe.
- Homozygous familial hypercholesterolaemia. Patients may also receive adjunctive treatments such as LDL-c apheresis.

Dosage and administration
The recommended dose of ezetimibe monotherapy is 10 mg once daily, which may be taken orally at any time of the day with or without food.

A single fixed-dose combination tablet containing ezetimibe/simvastatin is recommended for hypercholesterolaemia at a typical daily dose of 10/20 or 10/40 mg in the evening (administered orally with or without food). The 10/80 mg daily dose is only recommended in patients with severe hypercholesterolaemia at high risk for CV complications.

Contraindications
Ezetimibe monotherapy is contraindicated in patients who:

- have a known hypersensitivity to ezetimibe or to any of the excipients
- are pregnant and lactating (if co-administered with a statin)
- have active liver disease or unexplained persistent elevations in serum transaminases (if co-administered with a statin).

A fixed-dose combination tablet containing ezetimibe/simvastatin is contraindicated in patients who:

- have a known hypersensitivity to ezetimibe, simvastatin or any of the excipients
- are pregnant and lactating
- have active liver disease or unexplained persistent elevations in serum transaminases.

Identification of important subgroups

Current guidelines recommend prescribing lipid-regulating interventions based on patients' CVD status or risk.[39] The current study reviews the role of ezetimibe treatment in individuals with primary hypercholesterolaemia who do not achieve recommended lipid targets on statin treatment. The individuals who have the greatest potential to benefit from additional lipid-lowering strategies include those with the highest baseline risk. It is generally acknowledged that baseline risk is higher in people with diabetes and some ethnic groups. However, the identification of these individuals who are not currently receiving lipid-lowering treatments is outside the remit of this review.

For those individuals on optimal statin treatment, the failure to achieve recommended targets may be due to either non-compliance to treatment, failure to titrate or switch current treatments, high baseline lipid profiles or a combination of these. Identifying subgroups of patients in clinical practice for whom ezetimibe treatment would be particularly appropriate or inappropriate either as combination therapy or as monotherapy should therefore be addressed on an individual basis.

If non-compliance of treatment is the problem, then switching treatments (to a higher dose of current statin, a more potent statin or a combination of ezetimibe plus current statin) is unlikely to increase adherence. Possible reasons for failure to either titrate or switch current treatments are discussed in the section 'Variation in services and/or uncertainty about best practice' (p. 9), and the growth in prescribing rates for ezetimibe (see the section 'Impact on the NHS', p. 69) suggests that clinicians who may be reluctant to titrate or switch to more potent treatment could now be prescribing ezetimibe as an alternative.

It has been suggested that those individuals with a baseline Total-c of 6.5 mmol/l or greater are unlikely to reach targets on simvastatin 40 mg.[45] However, it is likely that individuals who are fully compliant to maximum tolerated treatments who do not achieve target levels would have very high baseline lipids. These patients are likely to include those with HeFH. Although a definitive diagnosis can be made using DNA-based methods, a clinical diagnosis of FH is widely used.[19] In the UK, the Simon Broome Register Group were instrumental in introducing two categories of definite and possible FH and have established a set of clinical diagnostic criteria for FH. These criteria define definite FH by raised cholesterol levels in conjunction with the presence of tendon xanthomas and/or DNA-based evidence of an LDL receptor mutation or familial defective apolipoprotein B-100, whereas possible FH is defined through the presence of raised cholesterol and a family history of either raised cholesterol or early heart disease.[19] A similar diagnostic tool has been developed by the Dutch Lipid Network and is based on pretreatment LDL-c concentrations, other clinical manifestations and a family history, but it also includes a numerical score providing three categories of a FH diagnosis as either definite, probable or possible.[75] Further details of these criteria are presented in Appendix 1 and a comprehensive review of FH diagnostic problems, including a discussion of various classification systems, has been published by Marks and colleagues.[19]

Current usage in the NHS

In 2005, approximately 740,000 prescriptions of ezetimibe were dispensed in England and Wales, costing about £24 million in England[43] and £2 million in Wales.[44]

The growth rate for ezetimibe prescribing is high, as might be expected with a new intervention when the target population is large. It is thought that the growth rate could continue, at least in the immediate future, and based on the current growth rate it is estimated that approximately 1.4 million prescriptions could be dispensed in England and Wales in 2006 and approximately 2 million prescriptions in 2007.

Variation in services is difficult to quantify, but based on data for prescribing of statins, it is likely that prescribing could be influenced by characteristics such as age, possibly type of CHD history and geographical features with individuals in deprived areas being less likely to receive ezetimibe than those in thriving areas.[12]

Due to recently published recommendations, there has been a large increase in the number of statins prescribed in recent years. It is likely that this trend could also be seen in prescribing rates for ezetimibe treatment if long-term evidence demonstrates effectiveness in terms of reductions in CV events.

Primary care trust policies for prescribing rates of lipid-regulating agents have shown a four-fold variation in the past and it is probable that this trend will be reflected in prescribing rates for ezetimibe.[76] With the current and imminent changes in healthcare structures within the UK, it is unlikely that the variation between geographical areas will reduce.

Anticipated costs associated with intervention

Assuming that the growth rate continues, the total gross cost for ezetimibe prescribing in 2006 is expected to be approximately £37 million. A recently published study suggested that a substantial number of patients treated with a statin fail to achieve the recommended cholesterol levels.[68] For those individuals whose treatment strategy is changed, monitoring costs are likely to increase and a recent article suggested that a follow-up and review of patients at 3 months would be required to monitor progress, side-effects and the need for up or down titration of statin treatment.[45] As the safety profile of ezetimibe is unknown, the suggested monitoring would be the minimum that individuals newly prescribed ezetimibe treatment should receive. These costs should be included in the costs associated with treatment.

However, a proportion of the costs associated with ezetimibe treatment are likely to be offset by the costs of alternative lipid-lowering treatments such as statin titration. In addition, if the observed reductions in LDL-c due to ezetimibe treatment translate into additional reductions in CV events, then treatment costs could also be offset by the costs saved through events avoided.

Chapter 2

Definition of the decision problem

Decision problem

Interventions

The following interventions (within their licensed indications) are assessed:

- For patients whose condition is not adequately controlled with a statin alone (defined as failure to achieve target lipid level), the intervention is ezetimibe plus statin combination therapy.
- For patients in whom a statin is considered inappropriate or is not tolerated, the intervention is ezetimibe monotherapy.

Population including subgroups

The population for the assessment will include adults (aged 18 years and over) with primary (heterozygous familial and non-familial) hypercholesterolaemia who are candidates for treatment with statins on the basis of their CVD status or risk and whose condition is not appropriately controlled to UK lipid targets with a statin alone, or in whom a statin is considered inappropriate or is not tolerated. Information will also be sought for people with or without existing IHD or other vascular disease, people with or without diabetes and for different ethnic groups.

Relevant comparators

For patients whose condition is not adequately controlled with a statin alone (defined as failure to achieve a target lipid level), the relevant comparators are:

- optimal statin therapy
- treatment with a statin in combination with other lipid-regulating drugs, such as nicotinic acid, bile acid resins or fibrates.

For patients in whom a statin is considered inappropriate, or is not tolerated, the relevant comparator is:

- other lipid-regulating drugs, such as nicotinic acid, bile acid resins, fibrates or no treatment.

Outcomes

The following outcomes are assessed:

- survival
- fatal and non-fatal CV events
- adverse effects of treatment
- health-related quality of life (HRQoL).

Where information on clinical end-points is unavailable, consideration will be given to surrogate end-points, such as Total-c, LDL-c and HDL-c, together with evidence linking these to clinical endpoints.

Key issues

Linking changes in lipids to clinical outcomes

A large body of epidemiological evidence, including the Framingham Heart Study[77] and the Multiple Risk Factor Intervention Trial (MRFIT),[78] has demonstrated a strong correlation and causal relationship between a broad range of serum cholesterol values (there is no definite threshold below which a lower cholesterol concentration is not associated with a lower risk),[79–81] particularly LDL-c, and the risk of CVD. Although the association between LDL-c concentrations and CHD risk is continuous, it is not thought to be linear. As risk increases more sharply with rising LDL-c levels, this results in a curvilinear or log-linear relationship.[82]

Numerous clinical outcome trials have established that lowering LDL-c is associated with a reduced risk for CV events and mortality in people with or at high risk of CVD. The strongest evidence that reducing LDL-c improves clinical outcomes comes from several systematic reviews and meta-analysis of clinical studies. A study by Law and colleagues,[83] which investigated the relationship between LDL-c reduction and the risk of CHD events in 58 trials (including 148,321 patients) of cholesterol-lowering drugs, showed that a reduction in LDL-c of 1.0 mmol/l reduced the risk of CHD events by up to 36% over 6 or more years of treatment, regardless of initial risk. A more recent meta-analysis by the Cholesterol Treatment Trialists' Collaborators (CTTC),[79] which included data from 90,056 patients in 14 randomised trials

of statins, found 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 Str.

Although the majority of evidence for the benefits of lowering LDL-c is derived from randomised controlled trials (RCTs) investigating statin treatment, treatment to lower LDL-c levels is associated with CV outcome benefits independent of the treatment used. A meta-analysis of data from clinical trials assessing non-statin cholesterol-lowering therapies (including bile acid sequestrants, fibrates, nicotinic acid, surgery and diet) by Gould and colleagues.[84] demonstrated that lowering cholesterol levels was associated with reductions in CHD mortality. Importantly, when statin trials were included in the meta-analysis, the relationship between cholesterol lowering and CHD mortality was found to be similar to that observed in the non-statin trials.

A more recent meta-analysis by Robinson and colleagues,[85] which specifically assessed the relationship between LDL-c and CHD risk using data from 81,859 patients enrolled in nine trials of non-statin treatments (bile acid sequestrants, surgery and diet) and 10 statin trials, found that larger reductions in LDL-c were associated with greater reductions in CHD risk, with no difference between the statin and non-statin trials. These findings are consistent with that of the Gould and colleagues,[84] and the CTTC[79] analysis. It is noteworthy that the study by Robinson and colleagues,[85] specifically assessed treatments that primarily lower LDL-c, and thus excluded trials of fibrates and niacin, which primarily improve triglycerides and HDL-c, respectively. Moreover, they also observed that the pleiotropic effect of statins, either as a class or individually, does not contribute to additional CHD risk reduction beyond that expected from the degree of LDL-c lowering seen in other trials that primarily lowered LDL-c over approximately 5 years.[85]

Modelling the link between changes in lipids and reductions in CV events

As there is no evidence of the effectiveness of ezetimibe in reducing clinical end-points, a literature review was conducted to identify the most robust methodology to link the changes in surrogate measures (the lipid profile) to clinical events (see the section 'Methods', p. 43). The searches identified several possible methods, including the Framingham, United Kingdom Prospective Diabetes Study (UKPDS) or PROCAM equations, evidence based on the WOSCOPS study and the results of a meta-analysis performed by the CTTC.[77,79,86–88]

A combination of soft operational research (OR) (strategic choice approach, cognitive maps) and hard quantitative techniques were used to examine the choice of modelling methods.[89] A selection of predefined criteria[90] was expanded and updated and used to shortlist the possible methods to a final choice between the Framingham risk engines[77,87] and the CTTC evidence.[79,89] A summary of the techniques used is provided in Appendix 13.

The Framingham Heart Study

The Framingham study, based on individuals from the general population of Framingham in Massachusetts, USA, is well known and the CV risk engines generated as a result of this study are used to predict a one-off risk for individuals worldwide[77,87] However, the data were collected several decades ago (from the 1970s) and the incidence of coronary disease has changed in the interim; for example, there has been a 50% drop in male CHD mortality over this period.[91] The sensitivity and specificity of the algorithms have been extensively studied in different populations and the results have shown that the algorithms can substantially underestimate events for individuals at high risk and overestimate events for individuals at low risk.[92–96] The recent literature, which suggests that variables such as geographical and socio-economic factors should be utilised to improve the accuracy of CV risk scores, would presumably apply to the original risk engines.[97,98] However, the Framingham equations have become both national and international standards and are used worldwide to determine thresholds at which treatments should be initiated.

Although Framingham risk engines have been used to predict events before and after treatment in previous economic evaluations,[99–101] the main criticism of using this methodology is that the algorithms were not formulated to predict and continually re-evaluate risks based on chemically induced changes in the parameters used in the regressions. In addition, any errors in the predicted risk will be cumulative when the equations are applied annually over a lifetime.

The Cholesterol Treatment Trialists' Collaborators

The CTTC meta-analysed patient-level data from 14 randomised trials of statins involving over 90,000 individuals.[79] The full cohort included both male and female patients with or without existing CHD or diabetes. Ages ranged from 21 to 79 years[102] and the mean sub-study LDL-c measurements ranged from 3.03[103] to 4.96 mmol/l.[104] The authors concluded that irrespective of the initial lipid profile or other presenting characteristics, statin therapy reduced the 5-year incidence of major coronary events and Str by about one-fifth per mmol/l reduction in LDL-c. Benefits were significant within the first year but were greater in subsequent years.

By examining the incidence rates of first events since the start of the studies, the CTTC analysts established that there was an approximately linear relationship between absolute reductions in LDL-c and the proportional reductions in major vascular events. At 1 year, the mean LDL-c differences in the trials ranged from 0.35 to 1.77 mmol/l. When subgrouped by changes in LDL-c over time, the analysts found that a sustained reduction in LDL-c of 1 mmol/l over 5 years may produce a proportional reduction in major vascular events of about 23% as opposed to 21% when using the weighted analysis.

A core advantage that this particular meta-analysis has over previously published data is the use of individual patient data, which allows detailed subgroup analyses such as exploring the impact of baseline LDL-c levels, age, sex and CV history, which are difficult when using published data. The data demonstrated that the proportional risk reduction increased over the 5-year period (14 versus 29% for CHD events, 4 versus 21% for Str) and it has been suggested that the real reduction could be substantially greater than the cited 23% reduction.[105] It has also been suggested that the results could be underestimated by intention-to-treat (ITT) analyses (a proportion of individuals randomised to placebo switched to statins and a proportion randomised to statins discontinued treatment), the exclusion of studies with larger LDL-c reductions and the inclusion of studies where treatment effectiveness is affected by poor compliance and short duration.[105]

Preferred choice of method to link changes in lipid measurements to CV events

The final decision to use the CTTC data to link changes in lipid measurements to CV events was derived using a combination of problem structuring methods (PSM) and hard OR techniques (Appendix 13). An important criterion in the final decision was that the Framingham evidence was much older than the CTTC data and that the risk equations were not designed to predict changes in risk due to chemically induced changes in cholesterol levels, whereas the results of the CTTC meta-analysis are based on more recent data obtained from patients receiving lipid-lowering therapies. However, it is necessary to assume that the relationship between statin-induced changes in LDL-c and CV events is equivalent for individuals receiving ezetimibe monotherapy or ezetimibe in combination with statin treatment.

Overall aims and objectives of assessment

The main aim of this review is systematically to evaluate and appraise the clinical effectiveness and cost-effectiveness of ezetimibe (in its licensed indication) as combination therapy or monotherapy for the treatment of primary hypercholesterolaemia.

More specifically, the objectives of the review are to:

- Evaluate the clinical effectiveness of ezetimibe as combination therapy or monotherapy in terms of mortality and cardiovascular morbidity. Surrogate end-points (such as total, LDL and HDL cholesterol) will be utilised where information on clinical end-points is unavailable.
- Evaluate the adverse effect profile and toxicity.
- Evaluate the cost-effectiveness of ezetimibe in terms of incremental cost per quality-adjusted life-year (QALY).
- Advise on the patient groups for whom ezetimibe might be particularly appropriate.
- Estimate the possible overall cost in England and Wales.

The review will not consider the use of ezetimibe in people with homozygous familial hypercholesterolaemia or homozygous sitosterolaemia.

Chapter 3

Assessment of clinical effectiveness

A review of the evidence for clinical effectiveness was undertaken systematically following the general principles recommended in the Quality Of Reporting Of Meta-analyses (QUOROM) statement.[106]

Methods for reviewing effectiveness

Identification of studies

Searches were carried out to:

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

The search strategy used to identify studies for the review of clinical effectiveness is reported in this section. All other searches are reported in the sections 'Search strategy' (p. 35) and 'Methods' (p. 43).

Identification of studies for the review of clinical effectiveness

The aim of the search was to provide as comprehensive a retrieval as possible of RCTs of ezetimibe for the treatment of hypercholesterolaemia.

Sources searched

Eleven electronic databases were searched, providing coverage of the biomedical and grey literature and current research. The publications lists and current research registers of seven health services research-related organisations were consulted via the Internet. Keyword searching of the Internet was undertaken using the Google search engine. The submissions of evidence to NICE by sponsors were handsearched, in addition to references of retrieved papers. A list of the sources searched is provided in Appendix 2.

Keyword strategies

Sensitive keyword strategies using free text and, where available, thesaurus terms were developed to search the electronic databases. Synonyms relating to the intervention [e.g. ezetimibe, ezetrol, zetia, vytorin, inegy and Chemical Abstracts Service (CAS) Registry number or Enzyme Commission (EC) number: 163222-33-1] were combined with synonyms relating to the condition (e.g. hypercholesterolaemia, hypercholesterolaemia). Keyword strategies for all electronic databases are provided in Appendix 2.

Search restrictions

A methodological filter aimed at restricting search results to RCTs was used in the searches of MEDLINE and EMBASE. The search of Pre-MEDLINE was restricted to the last 180 days to capture recent and unindexed MEDLINE references. Date limits were not used on any other database. Language restrictions were not used on any database. All searches were undertaken between April and June 2006.

Inclusion and exclusion criteria

Two reviewers independently screened all titles and abstracts. Full texts of any titles/abstracts that were considered relevant by either reviewer were obtained where possible. The relevance of each paper was assessed according to the criteria set out below. A trial flow chart is presented in Appendix 3. Any disagreements were resolved by discussion.

Population

Adult patients (defined as >18 years of age) with primary (heterozygous familial and non-familial) hypercholesterolaemia were included in the review, whereas adults with homozygous familial hypercholesterolaemia or homozygous sitosterolaemia were excluded.

Interventions

This review covered the effectiveness of the following intervention, used within its respective licensed indication:

- For patients whose condition is not adequately controlled with a statin alone, the intervention was ezetimibe (Ezetrol®, MSD/SP) co-administered with a statin or a fixed-dose combination tablet containing ezetimibe and simvastatin (Inegy®, MSD/SP).
- For patients in whom a statin is considered inappropriate, or is not tolerated, the

intervention is ezetimibe monotherapy (Ezetrol®, MSD/SP).

Comparators

The comparator treatment included the following:

- For patients whose condition is not adequately controlled with a statin alone, the relevant comparator was optimal statin monotherapy or treatment with a statin in combination with other lipid-regulating drugs (e.g. nicotinic acid, bile acid resins or fibrates).
- For patients in whom a statin is considered inappropriate, or is not tolerated, the relevant comparator was an alternative lipid-regulating agent (e.g. nicotinic acid, bile acid resins or fibrates) or no treatment.

Outcomes

Data on the following outcomes were included: survival, fatal and non-fatal CV events, adverse effects of treatment and HRQoL. Where information on clinical end-points is unavailable, consideration was given to surrogate end-points, such as LDL-c, Total-c and HDL-c.

Study design

Phase III RCTs of at least 12 weeks' duration were included on the ground that trials of less than 12 weeks' duration are unlikely to inform on survival, CVD events, adverse events or HRQoL due to lipid-lowering treatments. In the absence of clinical end-point data from trials, we identified and included data from RCTs of sufficient duration (i.e. at least 12 weeks) with surrogate end-point data. Studies of less than 12 weeks' duration were excluded to allow for the tachyphaloxis effects. This decision was supported by clinical expert opinion. In addition, current licensing authorities [i.e. European Medicines Agency (EMEA)] require a minimum follow-up of 3 months for surrogate end-points in lipid-lowering drug therapies.[107]

Reviews of primary studies were not included in the analysis, but 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 where insufficient methodological details were reported to allow critical appraisal of the study quality.

Data abstraction strategy

Data relating to study design, quality and results were extracted by one reviewer into a standardised data extraction form and independently checked for accuracy by a second reviewer. Any discrepancies were resolved by consensus. Where multiple publications of the same study were identified, data were extracted and reported as a single study.

Critical appraisal strategy

The quality of the included studies was assessed (unblinded) by one reviewer and independently checked for agreement by a second. Disagreements were resolved by consensus. The quality of the clinical effectiveness studies was assessed according to criteria based on those proposed by the NHS Centre for Reviews and Dissemination.[108] The purpose of this assessment was to give a narrative assessment of the potential for bias in the studies and, in the event that statistical synthesis (meta-analysis) was appropriate, to inform sensitivity analysis.

Methods of data synthesis

Data were tabulated and discussed in a narrative review. Where appropriate, meta-analyses were employed to estimate a summary measure of effect on relevant outcomes. All analyses were by ITT or modified ITT (analysis of subset of patients who received treatment as planned or at least some treatment). Efficacy results were reported as least-squares (LS) mean percentage change from baseline to study end-point for comparison groups. Where appropriate, the standard deviations (SDs) and 95% confidence intervals (CIs) were calculated using the method documented in the Cochrane Handbook to perform meta-analyses of the published literature.[109]

Meta-analyses were carried out using fixed and random effect models, with the Cochrane Collaboration Review Manager 4.2.3 software. Heterogeneity between trial results was explored through consideration of the study populations, methods and interventions, by visualisation of the results and, in statistical terms, by the χ^2 test for homogeneity and the I^2 measure. The χ^2 test measures the amount of variation in a set of trials. Small p-values imply that there is more heterogeneity present than would be expected by chance. The χ^2 test is not particularly sensitive: a cut-off of $p < 0.10$ is often used to indicate significance, but lack of statistical significance does not mean that there is no heterogeneity. The I^2 measure is the proportion of variation that is due to heterogeneity rather than chance. Large values of I^2 suggest heterogeneity. I^2 values of 25, 50, and 75% could be interpreted as representing low, moderate and high heterogeneity, respectively.[110]

Handling of the company submission

Company submissions were screened for data additional to those identified in published studies retrieved from the literature search.

Results

Quantity and quality of research available

Number of studies identified

A total of 397 titles and abstracts were screened for inclusion in the review of clinical effectiveness. Of the titles and abstracts screened, 64 full papers were retrieved and assessed in detail. A flow chart describing the process of identifying relevant literature can be found in Appendix 3.

Number and type of studies included

To date, there have been no published clinical outcome trials (>12 weeks) examining the CV benefit of ezetimibe, either alone or in combination with statins. In the absence of data from hard clinical end-point trials, we identified and included 13 Phase III RCTs with surrogate end-points in the review.

For patients whose condition is not adequately controlled with a statin alone

Fixed dose. Of six identified studies, four compared combination of ezetimibe and simvastatin with simvastatin alone,[111–114] one compared combination of ezetimibe and atorvastatin with atorvastatin alone[115] and one compared combination of ezetimibe and pravastatin with pravastatin alone.[116]

Titration studies. Of the five included studies, two compared combination of ezetimibe and atorvastatin with atorvastatin alone,[117,118] one compared combination of ezetimibe and simvastatin with atorvastatin alone.[119] one compared combination of ezetimibe and simvastatin with simvastatin alone[120] and one compared combination of ezetimibe and statin with combination of niacin and statin.[121]

For patients in whom a statin is considered inappropriate, or is not tolerated

Seven studies compared ezetimibe monotherapy with placebo.[111–113,115,116,122,123]

Number and type of studies excluded

A total of 51 studies were excluded. The majority of the excluded trials either did not meet the Population, Intervention, Comparison and Outcome (PICO) criteria, or were less than 12 weeks' duration, non-RCTs, systematic reviews/meta-analyses or ongoing studies. After a more detailed examination, two studies[124,125] were excluded from the review as one had a mixed hyperlipidaemic[124] population and the other reported results only for the first 5 weeks.[125] A full list of the excluded publications with rationale is presented in Appendix 4.

Ongoing clinical outcome trials

Although there were no RCTs of ezetimibe (used either as monotherapy or in combination with a statin) with clinical outcomes data, there are currently three long-term studies and results should become available between 2008 and 2010 (*Table 9*).

Summary of included trials

Thirteen Phase III multicentre RCTs of 12–48 weeks' duration with sample sizes ranging from 246[117] to 1528[111] were included. All trials involved patients with primary hypercholesterolaemia with mean baseline LDL-c levels ranging from 3.36 to 6.50 mmol/l. A summary of the design and study characteristics of the included studies is given in *Table 10*.

Elevated plasma LDL-c and Total-c concentrations are presented in the main report as they are recognised as major CVD risk factors. More detailed data and data on other lipid profiles (HDL-c and TG) are provided in Appendix 7 (*Tables 54–57*).

Quality and characteristics of identified studies

A table summarising data on quality assessment can be found in Appendix 5. All 13 studies were described as large multicentre RCTs and were published in peer-reviewed journals. McKenney and colleagues.[121] reported in conference abstract form and provided limited data. Most of the studies gave full demographic data.

Inclusion criteria were men and women ⩾18 years of age, with diagnosis of primary hypercholesterolaemia and an LDL-c concentration of 3.38–6.50 mmol/l and a TG level of ⩽3.85 mmol/l. Exclusion criteria for most of the trials were pregnancy and lactation; congestive heart failure; uncontrolled cardiac arrhythmia; MI; coronary bypass surgery, or angioplasty within 6 months of study entry; history of unstable or severe peripheral artery disease within 3 months of study entry; unstable angina pectoris; disorders of the haematological, digestive or central nervous system, uncontrolled or newly diagnosed DM, uncontrolled endocrine or metabolic disease

TABLE 9 *Ongoing clinical outcome trials*

Study	Design	Duration (years)	Population	Intervention	Comparator	Outcomes (primary)
IMPROVE IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial)[126]	Multicentre, double-blind RCT	2.5	Approximately 10,000 high-risk patients (planned recruitment) with CAD presenting with ACS	Fixed-dose combination of ezetimibe (10 mg/d) and simvastatin (40 mg/d)	Simvastatin (40mg/d)	Composite of CV death, MI, non-fatal Str, hospitalisation for ACS or revascularisation
SEAS trial (Simvastatin and Ezetimibe in Aortic Stenosis)[127,128]	Multicentre, double-blind, placebo RCT	4	Patients (n = 1873 subjects aged between 45 and 85 years) with asymptomatic moderate aortic stenosis (defined by Doppler-measured peak flow velocity of 2.5–4.0 m/s)	Ezetimibe (10 mg/d) co-administered with simvastatin (40 mg/d)	Placebo	Composite of CV death, aortic surgery and other CV outcomes (including heart failure, non-fatal MI, coronary revascularisation, hospitalised angina and non-haemorrhagic Str)
SHARP trial (Study of Heart And Renal Protection)[129]	Multicentre, double-blind, placebo RCT	4	Patients aged ⩾40 years with chronic disease [planned recruitment approximately 9000 subjects (around 6000 on predialysis and 3000 on dialysis)]	Ezetimibe (10 mg/d) co-administered with simvastatin (20 mg/d)	Placebo	Composite of major vascular events (non-fatal MI, cardiac death, non-fatal or fatal Str, or revascularisation)

ACS, acute coronary syndromes; mg/d, mg/day.

known to influence serum lipids or lipoproteins; known impairment of renal function; active or chronic hepatic or hepatobiliary disease; positive test for HIV; and coagulopathy. Oral corticosteroids, cyclosporine and orlistat were prohibited. One study[112] did not report the exclusion criteria.

The populations in the studies generally did not fully represent the populations indicated by the scope (i.e. people whose hypercholesterolaemia had not been adequately controlled with a statin alone or those who are intolerant of statins). The majority of the studies required washout or discontinuation of all ongoing lipid-altering drug treatments for up to 12 weeks (6 weeks for statins, bile acid sequestrants and nicotinic acid and 8–12 weeks for fibrates) before randomisation and initiating study treatments. There was no information on pretrial treatment history and previous treatment success (whether the subjects did reach the LDL-c target level) of the participants. Therefore, it was not clear whether the study populations were indeed inadequately controlled with or intolerant of statins.

Where reported, the overall mean age across the studies was 58 years. About 28% (between 19%[118] and 36%)[120] of the overall population were identified as elderly patients aged 65 years and over (Appendix 6).

The patient demographics and baseline characteristics of the included studies are presented in Appendix 6. Where reported, baseline performance status was generally well balanced. The trials were conducted among patients with both primary and secondary CVD.

TABLE 10 *Summary of design and study characteristics of included studies*

Study	Population with primary hypercholesterolaemia	Study design	Active duration treatment (weeks)	Number randomised	Intervention (daily dosage)	Primary outcome (mean % change)	Funding	Comments
Ballantyne *et al.*, 2003[115] USA	*N* = 628 LDL-c 3.77–6.50 mmol/l TG ⩽3.85 mmol/l	Randomised, double-blind, placebo controlled, balanced-parallel group trial	12	T1 = 65 T2 = 255 T3 = 248 T4 = 60	T1: ezetimibe (10 mg/d) T2: ezetimibe (10 mg/d)/ atorvastatin (10–80 mg/d) T3: atorvastatin (10–80 mg/d) T4: placebo	LDL-c	Astra-Zeneca, Merck, Novartis, Pfizer and Schering-Plough Research Institute	
Ballantyne *et al.*, 2004a[117] USA	*N* = 246 LDL-c 3.77–6.50 mmol/l TG ⩽3.85 mmol/l	Multinational, randomised, placebo-controlled, double-blind trial	24	T1 = 201 T2 = 45	T1: ezetimibe (10 mg/d)/ atorvastatin (10-–80 mg/d) T2: atorvastatin (10–80 mg/d)	LDL-c	Schering-Plough Research Institute	Statin doses were titrated
Ballantyne *et al.*, 2004b[119] USA	*N* = 788 LDL-c 3.38–6.50 mmol/l TG ⩽3.85 mmol/l	Multicentre, randomised, active-controlled, double-blind trial	24	T1 = 263 T2 = 263 T3 = 262	T1: ezetimibe (10 mg/d)/ simvastatin (10/80 mg/d) T2: ezetimibe (10 mg/d)/ simvastatin (20–80 mg/d) T3: atorvastatin (10–80 mg/d)	LDL-c from baseline to the end of initial 6 weeks	Merck and Schering-Plough Pharmaceuticals	Statin doses were force-titrated
Bays *et al.*, 2004[111] USA	*N* = 1528 LDL-c 3.77–6.50 mmol/l TG ⩽3.85 mmol/l	Multicentre, randomised, double-blind, placebo-controlled, factorial design study	12	T1 = 149 T2 = 609 T3 = 622 T4 = 148	T1: ezetimibe(10 mg/d) T2: ezetimibe (10 mg/d)/ simvastatin (10–80 mg/d) T3: simvastatin (10–80 mg/d) T4: placebo	LDL-c	Merck and Schering-Plough Pharmaceuticals	
Davidson *et al.*, 2002[112] USA	*N* = 668 LDL-c 3.77–6.50 mmol/l TG ⩽3.85 mmol/l	Randomised, placebo-controlled trial	12	T1 = 61 T2 = 274 T3 = 263 T4 = 70	T1: ezetimibe (10 mg/d) T2: ezetimibe (10 mg/d)/ simvastatin (10-80 mg/d) T3: simvastatin (10–80 mg/d) T4: placebo	LDL-c	Merck and Schering-Plough Pharmaceuticals	

continued

TABLE 10 *Summary of design and study characteristics of included studies (cont'd)*

Study	Population with primary hypercholesterolaemia	Study design	Active duration treatment (weeks)	Number randomised	Intervention (daily dosage)	Primary outcome (mean % change)	Funding	Comments
Dujovne *et al.*, 2002[122] USA	*N* = 892 LDL-c 3.38–6.50 mmol/l TG ⩽ 3.85 mmol/l	Multicentre, double-blind, placebo-controlled trial	12	T1 = 666 T2 = 226	T1: ezetimibe (10 mg/d) T2: placebo	LDL-c	Schering-Plough Research Institute	
Goldberg *et al.*, 2004[113] USA	*N* = 887 LDL-c ⩾3.77 and ⩽6.50 mmol/l TG ⩽3.85 mmol/l	Multicentre randomised, double-blind, placebo-controlled trial	12	T1 = 92 T2 = 353 T3 = 349 T4 = 93	T1: ezetimibe (10 mg/d) T2: ezetimibe (10 mg/d)/ simvastatin (10–10/80 mg/d) T3: simvastatin (10–80 mg/d) T4: placebo	LDL-c	Merck and Schering-Plough Pharmaceuticals	
Knopp *et al.*, 2003[123] USA	*N* = 827 LDL-c 3.36–6.47 mmol/l TG ⩽3.95 mmol/l	Multicentre, randomised, double-blind, placebo-controlled trial	12	T1 = 622 T2 = 205	T1: ezetimibe (10 mg/d) T2 : placebo	LDL-c	Schering-Plough Research Institute	
Masana *et al.*, 2005[120] International	*N* = 433 LDL-c ⩾3.77 and ⩽6.50 mmol/l TG ⩽3.85 mmol/l	Multicentre, randomised, double-blind, placebo-controlled trial	48	T1 = 355 T2 = 78	T1: ezetimibe (10 mg/d)/ simvastatin (10–80 mg/d) T2: simvastatin (10–80 mg/d)/ placebo	LDL-c	Merck and Schering-Plough Pharmaceuticals	Statin doses were titrated
McKenney *et al.*, 2006[121] USA	*N* = 292 LDL-c 5.12 mmol/l, TG 1.86 mmol/l	Multicentre, randomised controlled trial	12	NR	T1: ezetimibe (10 mg/d)/ simvastatin (20, 40 mg/d) T2: niacin (1000 mg/d)/ atorvastatin (20, 40 mg/d) T3: niacin (1000 mg/d)/ rosuvastatin (20, 40 mg/d) T4: rosuvastatin (20, 40 mg/d)	LDL-c	Kos Pharmaceuticals	Conference abstract

continued

TABLE 10 *Summary of design and study characteristics of included studies (cont'd)*

Study	Population with primary hypercholesterolaemia	Study design	Active duration treatment (weeks)	Number randomised	Intervention (daily dosage)	Primary outcome (mean % change)	Funding	Comments
Melani *et al.*, 2003[116] USA	*N* = 538 LDL-c ⩾3.8 and ⩽6.5 mmol/l TG ⩽4.0 mmol/l	Multicentre, double-blind, randomised, placebo-controlled, balanced-parallel-group, 2 × 4 factorial design study	12	T1 = 64 T2 = 204 T3 = 205 T4 = 65	T1: ezetimibe (10 mg/d) T2: ezetimibe (10 mg/d)/ pravastatin (10–40 mg/d) T3: pravastatin (10–40 mg/d) T4: placebo	LDL-c	Merck and Schering-Plough Pharmaceuticals	
Rodney *et al.*, 2006[114] USA	*N* = 247 LDL-c ⩾3.77 and ⩽6.50 mmol/l TG ⩽3.85 mmol/l	Multicentre, double-blind, randomised controlled trial	12	T1 = 124 T2 = 123	T1: ezetimibe (10 mg/d)/ simvastatin (20 mg/d) T2: simvastatin (20 mg)	LDL-c	Schering-Plough Research Institute	
Stein *et al.*, 2004[118] International	*N* = 621 LDL-c ⩾3.8 mmol/l TG ⩾4.0 mmol/l	Randomised, double-blind, multicentre, double-dummy, active controlled comparator study	14	T1 = 305 T2 = 316	T1: ezetimibe (10 mg/d)/ atorvastatin (10–40 mg/d) T2: atorva (10–40 mg/d)/ atorvastatin (10–40 mg/d)	% of patients achieving an LDL-c level ⩽100 mg/dl to study end-point	Merck and Schering-Plough Pharmaceuticals	Statin doses were titrated HeFH *n* (%): genetic diagnosis: T1: 52 (17) T2: 58 (18) clinical diagnosis: T1: 58 (18) T2: 123 (39)

Mg/dl of LDL-C was converted to mmol/l by multiplying by 0.02586; mg/dl of TG was converted to mmol/l by multiplying by 0.01129.

All trials consisted of mixed (primary and secondary) populations. Patients in each study were mainly subdivided into those who had a family history of CHD, risk factors of CHD/CVD, history of hypertension, DM and existing CVD. Where data were available, on average 30–45% of patients reported having a known family history of CHD. History of hypertension was reported by 29–38% and DM by 4–32% of patients. In some studies, the patients' baseline characteristics were also described in terms of Framingham score as having established CHD or its risk equivalent conferring a 10-year risk of >20% for CHD.

Ethnicity was reported explicitly by all trials apart from those of Ballantyne and colleagues[115] and Stein and colleagues[118] which reported data by race (whites and non-whites). The majority of the studies' populations were Caucasians followed by Black, Hispanic, Asian and other ethnicities. The study by Rodney and colleagues.[114] was conducted exclusively on African Americans. Ballantyne and colleagues,[119] Davidson and colleagues[112] and Goldberg and colleagues[113] did not report baseline information on body mass index (BMI), smoking status and the number (percentage) of physically active patients. Most trials described their population as primary hypercholesterolaemic referring to a plasma LDL-c level of ⩾3.36 mmol/l and a TG level of ⩽3.85 mmol/l. Only Stein and colleagues[118] reported separate subgroup analyses for patients with HeFH diagnosed by genetic and clinical diagnoses.

Seven trials reported the method of assignment as being central stratification by baseline LDL-c level,[119] single computer-generated[112–114,116] or computer random schedule.[122,123] However none of the trials reported method of allocation concealment. It was not clear whether the assessors were blinded to the treatment allocation in the trials by Dujovne and colleagues,[122] Knopp and colleagues,[123] Masana and colleagues,[120] Rodney and colleagues[114] and Stein and colleagues.[118] It was not clear whether the individuals who administered the intervention were blinded to the treatment allocation in the trials by Davidson and colleagues[112] and Dujovne and colleagues.[122] Patients were all blinded; however, none of the studies assessed the success of the blinding. All trials used ITT or modified ITT analyses, apart from that by Stein and colleagues.[118] All studies report the number and reasons of withdrawals. In the titration studies, patients who achieved their target LDL-c level continued to receive the same dose until the end of the trial. The power calculation was reported as 80–90% by the majority of the trials.[112,114–116,118,119,123]

Overall, all trials were relatively well designed and conducted and included relatively balanced populations.

Outcomes and synthesis of information

The available evidence from the included RCTs is grouped and presented in the following order.
For patients whose condition is not adequately controlled with a statin alone:

1. Fixed-dose studies:
   (a) Comparison 1: ezetimibe plus statin versus statin alone.
   (b) Comparison 2: ezetimibe plus statin versus statin plus other lipid lowering drugs (nicotinic acid, bile acid resins or fibrates).
2. Titrated studies:
   (a) Comparison 1: ezetimibe plus statin versus statin alone.
   (b) Comparison 2: ezetimibe plus statin versus statin plus other lipid lowering drugs (nicotinic acid, bile acid resins or fibrates).

   For patients in whom a statin is considered inappropriate, or is not tolerated:
   (a) Comparison 1: ezetimibe versus placebo
   (b) Comparison 2: ezetimibe versus other (non-statin) lipid lowering drugs (nicotinic acid, bile acid resins or fibrates).

   Safety and tolerability.
   Quality of life.

Assessment of effectiveness

For patients whose condition is not adequately controlled with a statin alone

Fixed-dose studies

Comparison 1: ezetimibe plus statin versus statin alone.
Lipid profiles for fixed-dose studies assessing combination of ezetimibe and statin with statin alone for the primary hypercholesterolaemic population whose condition is not adequately controlled with a statin alone are summarised in *Figures 1* and *2*. Six studies[111–116] with a total sample size of 3610 were identified as eligible for this comparison.

Meta-analyses of the relevant data indicate that the combination of ezetimibe and statin treatment was associated with statistically significant incremental reduction of 13.94% (95% CI –14.90 to –12.98, $p < 0.00001$) in LDL-c and 10.36% (95% CI –11.09 to –9.63, $p < 0.00001$) in Total-c compared with statin alone and a direction of effect was consistent across all studies. There was low heterogeneity (LDL-c: $\chi^2 = 5.31$, $p = 0.38$,

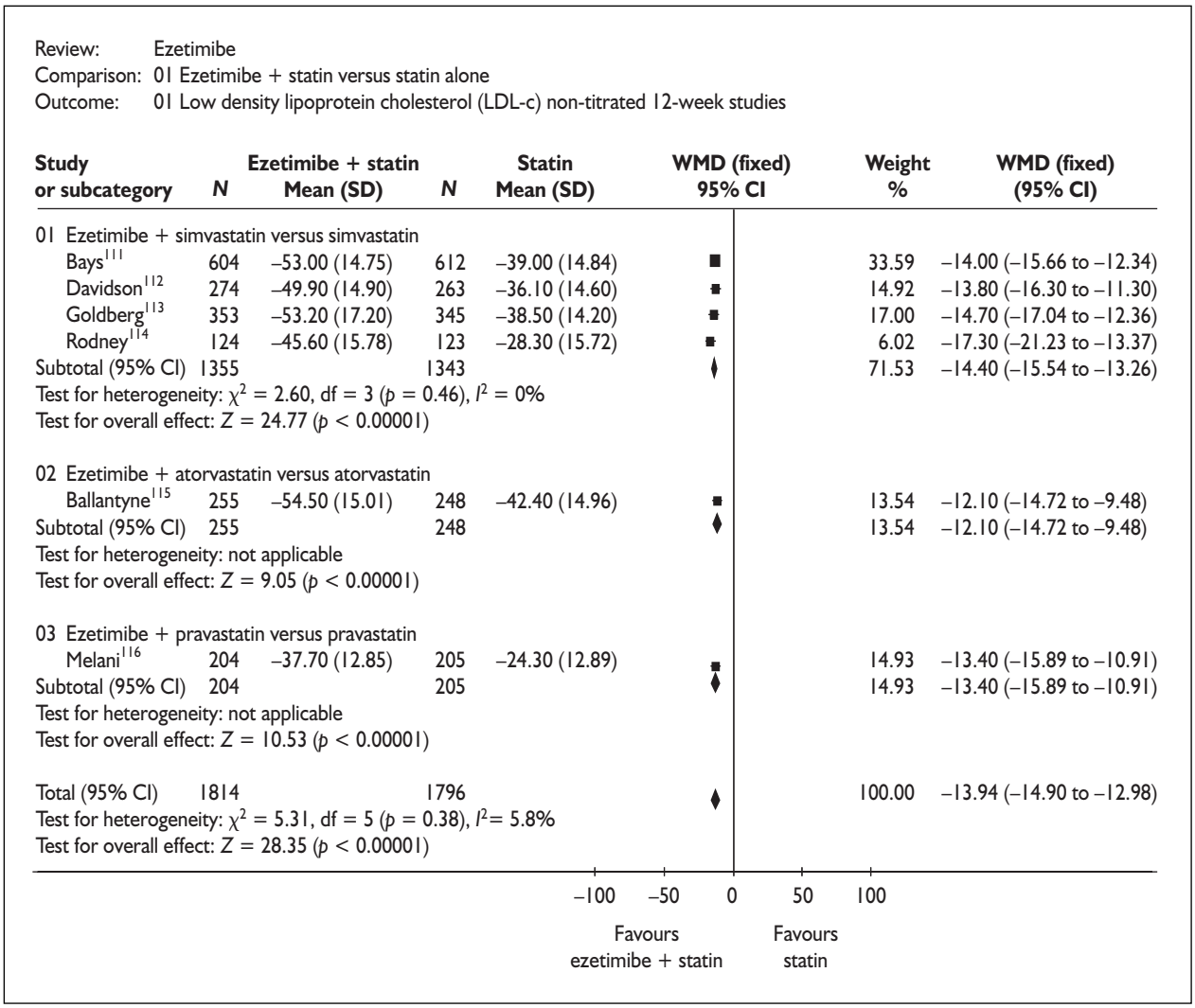


FIGURE 1 *For patients whose condition is not adequately controlled with a statin alone: mean % change in LDL-c (mmol/l)*

I^2 = 5.8%; Total-c: χ^2 = 5.65, p = 0.34, I^2 = 11.4%).

Comparison 2: ezetimibe plus statin versus statin plus other lipid-lowering drugs (nicotinic acid, bile acid resins or fibrates). To our knowledge, no RCTs have been published on this comparison.

Titrated studies

Comparison 1: ezetimibe plus statin versus statin alone. Lipid profiles for titrated dose studies assessing a combination of ezetimibe and statin with statin alone for the patients whose condition is not adequately controlled with a statin alone are summarised in *Table 11*. Sensitivity analyses showed a high degree of heterogeneity across the studies, suggesting that meta-analyses may not be appropriate for this subgroup.

A total of 1800 patients participated in the four studies. In three studies,[117,118,120] subjects who did not reach their target plasma LDL-c concentration were titrated to the next higher dose of statin until they reached their goal or maximum dose of statin. One study[119] used a force titration method where patients were administered the next higher dose of statin every 6 weeks regardless of whether they achieved their target LDL-c level. All four studies used the NCEP ATP II/III target level. Two studies[117,118] compared the LDL-c-lowering effect of co-administered ezetimibe and atorvastatin against atorvastatin monotherapy in patients with primary hypercholesterolaemia. One study[120] compared ezetimibe plus simvastatin with simvastatin and one trial[119] looked at a combination of ezetimibe and simvastatin against atorvastatin. The source of heterogeneity may be due to differences in the type of statin, dose titration and duration of the studies. Therefore, the results were tabulated and discussed accordingly (*Table 11*). For more detailed information, see Appendix 8 (*Table 58*).

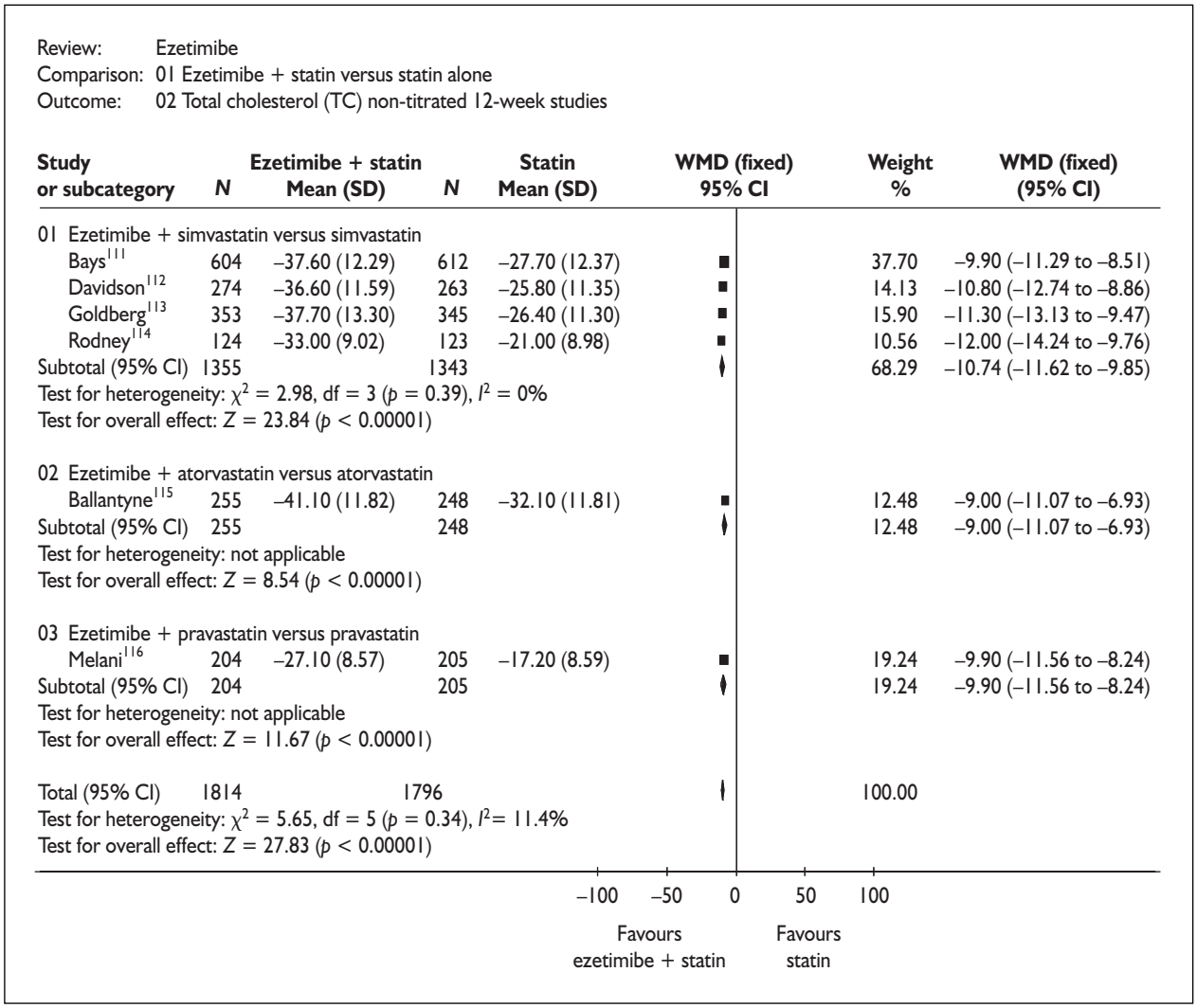


FIGURE 2 *For patients whose condition is not adequately controlled with a statin alone: mean % change in Total-c (mmol/l)*

TABLE 11 *For patients whose condition is not adequately controlled with a statin alone: summary of titrated studies (mmol/l)*

Study	Lipid profile (mmol/l)	Mean % reduction (SD)		Between-treatment mean % difference[a]
		Ezetimibe + atorvastatin	Atorvastatin	
Ballantyne *et al*., 2004a[117]	LDL-c	–48.4 (18.80)	–38.6 (12.4)	–9.8
	Total-c	–35.4 (14)	–27.5 (10.4)	–7.9
Stein *et al*., 2004[118]	LDL-c	–33.2 (11.98)	–20.30 (15.67)	–12.9
	Total-c	–26.1 (11.98)	–16 (12.18)	–10.1
		Ezetimibe + simvastatin	**Atorvastatin**	
Ballantyne *et al*., 2004b[119]	LDL-c	–59.4 (10.62)	–52.5 (15.10)	–6.9
	Total-c	–43.3 (8.11)	–40.2 (11.33)	–3.1
		Ezetimibe + simvastatin	**Simvastatin + placebo**	
Masana *et al*., 2005[120]	LDL-c	–23.7 (33.67)	3.30 (22.96)	–27
	Total-c	–1.9 (22.45)	2.5 (15.90)	–18.4

[a] All comparisons are statistically significant ($p < 0.05$).

Owing to incomplete and missing data, it was not possible to analyse the interaction of each statin dose during the titration process and the results presented in this review are the data pooled across all doses.

Co-administration of ezetimibe and statin was significantly more effective in reducing plasma LDL-c concentration. Two fully published trials[117,118] demonstrated that administration of ezetimibe with atorvastatin has a significantly greater LDL-c-lowering effect than atorvastatin alone (between-treatment mean % difference –9.8%, $p < 0.05$, and –12.9%, $p < 0.05$, respectively). One trial[119] compared ezetimibe co-administered with simvastatin with atorvastatin monotherapy and found that ezetimibe plus simvastatin reduced LDL-c by 59.4 versus 52.5% with atorvastatin (difference of 6.9%, $p < 0.05$). One trial[120] compared the LDL-c-lowering effect of co-administration of ezetimibe and simvastatin against simvastatin monotherapy and found the between-treatment mean % difference to be 27%, $p < 0.05$. A similar pattern of efficacy was observed in plasma Total-c concentration (*Table 11*).

Stein and colleagues[118] reported the only trial that looked at the HeFH patient subgroup. The study reported that the HeFH subgroup achieved the target level of ≤2.6 mmol/l approximately four times more in the co-administration group than in atorvastatin monotherapy group (17 versus 4%, $p < 0.01$). In the non-HeFH subgroup, the number who achieved the LDL-c goal was three times larger in the ezetimibe plus atorvastatin arm than the atorvastatin monotherapy arm (29 versus 11%, $p < 0.01$). Further evidence on HeFH and non-HeFH subgroups is described in the section 'Efficacy and safety of ezetimibe across different patient subgroups' (p. 28).

Comparison 2: Ezetimibe plus statin versus statin plus other lipid-lowering drugs (nicotinic acid, bile acid resins or fibrates). One study conference abstract met the inclusion criteria for this comparison.[121] The treatments of interest in McKenney and colleagues[121] were ezetimibe plus statin versus niacin plus statin.

McKenney and colleagues[121] reported that low–moderate doses of atorvastatin/rosuvastatin plus niacin achieved similar marked LDL-c reductions, with greater HDL-c increases ($p < 0.001$) compared with highest doses of rosuvastatin monotherapy or ezetimibe/simvastatin with no observed myopathy or hepatotoxicity. No further details were reported.

For patients in whom a statin is considered inappropriate, or is not tolerated

Comparison 1: ezetimibe versus placebo. Pooled analyses of the plasma LDL-c and Total-c level of ezetimibe monotherapy for patients with primary hypercholesterolaemia in whom a statin is considered inappropriate or is not tolerated are reported and summarised in *Figures 3* and *4*. Seven studies[111–113,115,116,122,123] with a total of 2577 participants were included in this category.

Comparison: 02 Ezetimibe versus placebo
Outcome: 01 Low density lipoprotein cholesterol (LDL-c) non-titrated 12-week studies

Study or subcategory	N	Ezetimibe Mean (SD)	N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) (95% CI)
Dujovne[122]	666	–16.86 (14.19)	226	0.36 (12.48)		32.89	–17.22 (–19.17 to –15.27)
Ballantyne[115]	65	–18.40 (14.92)	60	5.90 (14.87)		4.59	–24.30 (–29.35 to –19.07)
Knopp[123]	621	–17.69 (14.70)	204	0.79 (12.43)		29.50	–18.49 (–20.55 to –16.43)
Melani[116]	64	–18.70 (12.80)	65	1.30 (12.90)		6.37	–20.00 (–24.43 to –15.57)
Bays[111]	148	–18.90 (14.60)	146	–2.20 (14.50)		11.32	–16.70 (–20.03 to –13.37)
Davidson[112]	61	–18.10 (14.84)	70	–1.30 (14.22)		5.02	–16.80 (–21.80 to –11.80)
Goldberg[113]	89	–19.80 (10.50)	92	2.70 (13.30)		10.31	–22.50 (–25.98 to –19.02)
Subtotal (95% CI)	1717		863			100.00	–18.56 (–19.68 to –17.44)

Test for heterogeneity: $\chi^2 = 13.44$, df = 6 ($p = 0.04$), $I^2 = 55.4\%$
Test for overall effect: $Z = 32.50$ ($p < 0.00001$)

–100 –50 0 50 100
Favours ezetimibe Favours placebo

FIGURE 3 *For patients in whom a statin is considered inappropriate, or is not tolerated: mean % change in LDL-c (mmol/l)*

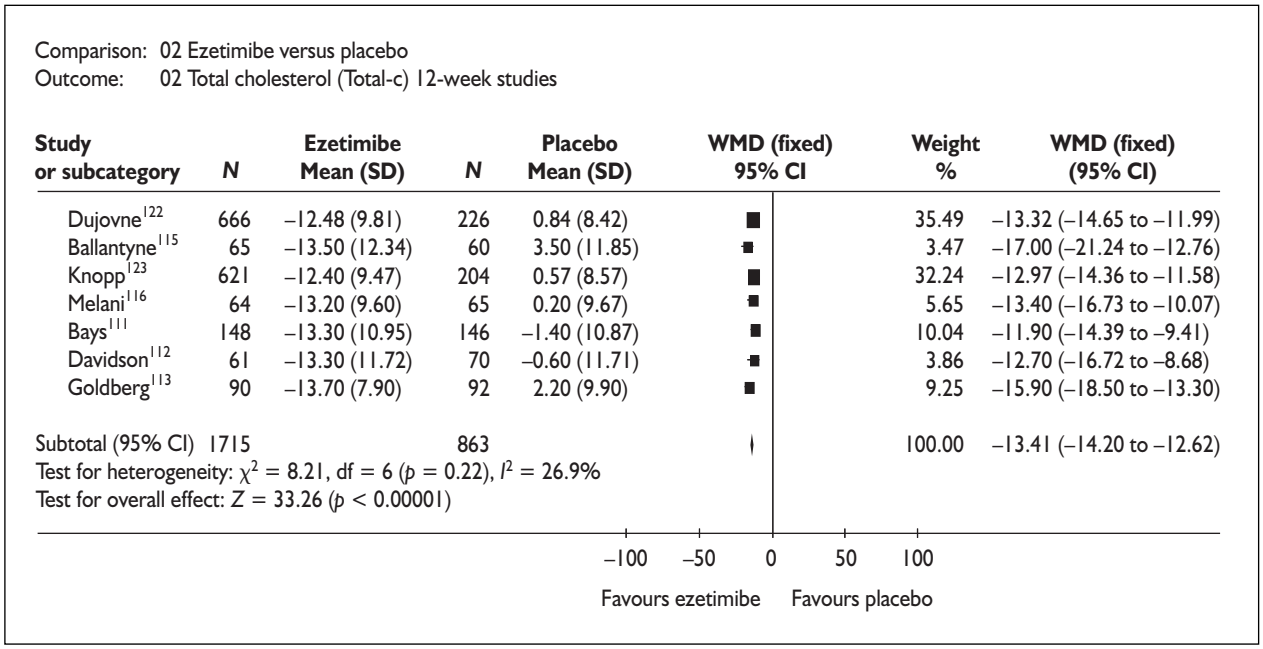


FIGURE 4 *For patients in whom a statin is considered inappropriate, or is not tolerated: mean % change in Total-c (mmol/l)*

Efficacy analyses showed that ezetimibe reduced the plasma concentration of LDL-c from baseline to end-point by a mean 18.56% (95% CI –19.68 to 17.44, $p < 0.00001$) compared with placebo. This effect was generally consistent across all trials. There was a moderate heterogeneity [$\chi^2 = 13.44$, df = 6 ($p = 0.04$), $I^2 = 55.4\%$]. Ezetimibe also significantly decreased Total-c by a mean 13.41% (95% CI –14.20 to –12.62, $p < 0.00001$) compared with placebo.

Comparison 2: ezetimibe versus other lipid-lowering drugs (nicotinic acid, bile acid resins or fibrates). No RCTs were found that directly compared the efficacy and safety of ezetimibe with other lipid-lowering combinations (nicotinic acid, bile acid resins or fibrates).

Overall, the results demonstrated that ezetimibe plus statin was significantly more effective at lowering LDL-c and Total-c concentrations than statin alone. The LDL-c-lowering effect of the statins was consistent with previous meta-analyses[37,130] and was around 25–40%. Co-administration with ezetimibe generally resulted in an additional mean 13 and 10% reduction in LDL-c and Total-c, respectively. When ezetimibe was compared with placebo it resulted in a mean percentage decrease in LDL-c of approximately 18.56% and this reduction was similar to that observed in previous meta-analyses.[131–133]

Efficacy and safety of ezetimibe across different patient subgroups

Four studies have demonstrated[111,113,114,123] (*Table 12*) LDL-c-lowering effects of the treatment across different subgroups such as people with or without existing CHD or other vascular disease, people with or without diabetes, different ethnic groups. Other trials reported (without data) that there were no statistically significant differences in LDL-c-lowering effects across different subgroups. All trials report that the effects of ezetimibe on LDL-c were generally consistent across all subgroups and provide additional LDL-c reductions when added to statin therapy; however, these findings were not discussed any further.

Pooled analyses of three similarly designed 12-week double-blind RCTs showed that superior lipid-altering effects of ezetimibe plus simvastatin versus simvastatin observed in the entire cohort were consistent across all subgroups.[134] However, a recent meta-analysis[135] found that the LDL-c-lowering effect of combination of ezetimibe and statins (simvastatin, atorvastatin, pravastatina and lovastatin) was lower in African-Americans than Caucasians. A study by Rodney and colleagues[114] was undertaken to explore this difference and was conducted exclusively on participants of African-American origin. In this study it was observed (*Figure 1*) that ezetimibe added to simvastatin resulted in a significant incremental reduction of 17.30% in LDL-c concentration compared with

TABLE 12 *Mean % LDL-c reduction and between-treatment mean % LDL-c reduction by patient subgroups*

Mean % LDL-c reduction by patient subgroups

Subgroups[a]	Arms	Study 1: Bays *et al.*, 2004[111]	Study 2: Goldberg *et al.*, 2004[113]
Gender			
Male	Ezetimibe + statin	–53	–51
	Statin	–39	–39
Female	Ezetimibe + statin	–53	–53
	Statin	–39	–39
Age (years)			
<65	Ezetimibe + statin	–52	–52
	Statin	–38	–39
⩾65	Ezetimibe + statin	–45	–55
	Statin	–56	–40
Race			
White	Ezetimibe + statin	–52	–52
	Statin	–39	–39
Non-white	Ezetimibe + statin	–59	–43
	Statin	–38	–35
CVD risk factors			
Hypertension			
Yes	Ezetimibe + statin	–54	–53
	Statin	–42	–39
No	Ezetimibe + statin	–53	–52
	Statin	–37	–39
Established CVD			
Yes	Ezetimibe + statin	NR	NR
	Statin	NR	NR
No	Ezetimibe + statin	NR	NR
	Statin	NR	NR
Diabetes mellitus			
Yes	Ezetimibe + statin	–56	–56
	Statin	–38	–35
No	Ezetimibe + statin	–53	–54
	Statin	–39	–39

[a] All subgroup comparisons were not significant.

Between-treatment mean % LDL-c reduction by patient subgroups

Subgroups[a]	Study 3: Rodney *et al.*, 2006[114] Ezetimibe + statin vs statin	Study 4: Knopp *et al.*, 2003[123] Ezetimibe vs placebo
Gender		
Male	–18	–17.5
Female	–17	–18
Age (years)		
<65	–15	–18
⩾65	–19	–18
Race[b]		
White		–18
Non-white		–19
CVD risk factors		
Yes	–22	–22
No	–14	–16
Established CVD		
Yes	–22	–17.5
No	–16	–19
Diabetes mellitus		
Yes	–18	–26
No	–16	–17.5

[a] All subgroup comparisons were not significant.
[b] The study by Rodney and colleagues[114] was conducted only on African-Americans.

simvastatin alone. This reduction was also consistent with that observed in the Caucasian population (average LDL-c reduction of 14%). However, the reduction in LDL-c level with simvastatin monotherapy appeared to be lower (28.30%) compared with the typical response in Caucasians (38%). The authors note that the reason for the apparent smaller statin response in African-Americans compared with Caucasians has not been clarified and this issue remains unresolved.

Patients with heterozygous familial hypercholesterolaemia (HeFH)

An additional *post hoc* analysis was requested by NICE for patients with and without HeFH. Although a subgroup analyses had been undertaken by Stein and colleagues,[118] it provided limited data. Further unpublished data obtained from the authors allowed a more detailed comparison of changes in lipids between the HeFH and non-HeFH groups. A summary of the baseline demographics and changes in plasma lipid concentrations after treatments are provided in *Tables 13* and *14*.

Baseline characteristics for both HeFH and non-HeFH groups patients were generally similar and balanced, except that the HeFH group were younger, proportionately greater male and lighter (*Table 13*). There were no major differences in terms of the baseline lipid profiles between the two groups. After 14 weeks of treatment, ezetimibe plus atorvastatin treatment (*Table 14*) demonstrated consistent, significant favourable changes in both groups. The LDL-c level reduced by 34.6% in the HeFH group and 31.1% in the non-HeFH group, the Total-c level reduced by 27% in the HeFH group and 24.7% in the non-HeFH group and the TG level reduced by 16.3% in the HeFH group and 23.4% in the non-HeFH group. Changes in HDL-c were not significant in both groups.

The mean differences for LDL-c for each group were calculated from mean percentages (Appendix 9), and were evaluated for statistical significance using a two-sample *t*-test (independent samples *t*-test). Although the HeFH group performed better than the non-HeFH group in lowering LDL-c, the analysis indicated that there was no statistically significant difference between the two estimates of lipid-lowering effect ($p = 0.1$). It is likely that this trial was powered only to detect a difference between the two therapies and not a difference in treatment effect size between the two population subgroups. If data were available from other trials, a meta-analysis might provide evidence that the difference in treatment effect was significantly greater in the HeFH group; at present, there is insufficient evidence.

Safety and tolerability

Safety was evaluated through adverse events, physical examinations and laboratory tests reported in each of the included studies. Adverse event results are summarised in Appendix 11. Meta-analyses were considered inappropriate due to insufficient data and low occurrences of the adverse events.

Ezetimibe alone (compared with placebo) was well tolerated. Overall adverse event profiles were similar between the ezetimibe and placebo groups. Approximately 61% of subjects in the placebo group and 63% in the ezetimibe group reported adverse events. The most commonly reported adverse events, regardless of relationship to study drug, were musculoskeletal disorders (2–5%) and upper respiratory infections (7–11%) (Appendix 11, *Table 59*). Other common adverse events included headache, back pain and gastrointestinal adverse events. There were no significant between-group differences in laboratory or clinical parameters. Creatine phosphokinase (CPK) and liver enzymes [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)] were not influenced by treatments. Treatment-related adverse events ranged from 9 to 20% of all adverse events. Serious adverse events occurred rarely (up to 1.4%) and all trials reported no serious treatment-related adverse events. A death which occurred in the ezetimibe arm was considered by investigators not to be related to study treatment.

Ezetimibe plus statin was also well tolerated, having a similar overall safety profile to that of statin alone (Appendix 11, *Table 59*). Some 63% and 65% of participants reported having adverse effects in combination and statin alone arms, respectively. Of these, 17.5% of patients in the pooled statin arm and 18.5% in the ezetimibe plus statin arm were considered treatment-related adverse events. Serious treatment-related adverse events were not statistically significant between the statin group and the combination group. The numbers of patients discontinuing because of these adverse events were similar across the treatment groups (4.9 and 5.9%, respectively). A total of four deaths were reported. The causes of death were CV incidences ($n = 2$), respiratory failure ($n = 1$) and an accident ($n = 1$). All deaths were considered by investigators not to be related

TABLE 13 *Baseline characteristics of the HeFH and non-HeFH groups*[a]

Characteristic	Parameter	HeFH group		Non-HeFH group	
		Atorvastatin *N* = 181	Ezetimibe + atorvastatin *N* = 181	Atorvastatin *N* = 135	Ezetimibe + atorvastatin *N* = 135
Age (years)	*N*	181	181	135	124
	Mean (SD)	48.1 (12.9)	50 (12.5)	56.4 (12.1)	57.4 (11.4)
Baseline diet rating (RISCC rating)	*n*	54	52	47	44
	Mean (SD)	16.5 (4.6)	17 (5.4)	16.9 (5.9)	17.6 (5.9)
Baseline diet rating (MEDFICTS score)	*n*	116	118	79	69
	Mean (SD)	26.2 (16.1)	25 (16.7)	26.5 (17.5)	25.4 (17.9)
Baseline weight (kg)	*n*	181	181	135	124
	Mean (SD)	74.8 (14.8)	74.3 (13.9)	79.2 (16.3)	79.6 (14.8)
Baseline BMI (kg/m^2)	*n*	181	179	135	124
	Mean (SD)	26.9 (4.5)	26.7 (3.8)	27.4 (4.1)	27.8 (4.2)
Gender	Female	88 (49%)	93 (51%)	57 (42%)	53 (43%)
	Male	93 (51%)	88 (49%)	78 (58%)	71 (57%)
Age class (years)	<65	166 (92%)	157 (87%)	100 (74%)	83 (67%)
	⩾65	15 (8%)	24 (13%)	35 (26%)	41 (33%)
Race	Caucasian	168 (93%)	171 (94%)	121 (90%)	108 (87%)
	Black	2 (1%)	2 (1%)	2 (1%)	4 (3%)
	Asian	2 (1%)	0	4 (3%)	4 (3%)
	Hispanic	9 (5%)	8 (4%)	8 (6%)	7 (6%)
	Other	–	–	0	1 (<1%)
Physical activity	Yes	103 (57%)	94 (52%)	86 (64%)	79 (64%)
	No	78 (43%)	87 (48%)	49 (36%)	45 (36%)
Smoking use	Yes	51 (28%)	45 (25%)	34 (25%)	31 (25%)
	No	130 (72%)	136 (75%)	101 (75%)	93 (75%)
Washout information	Yes[b]	165 (91%)	167 (92%)	120 (89%)	108 (87%)
	Statins	160 (88%)	165 (91%)	119 (88%)	105 (85%)
	Fibrates	8 (4%)	4 (2%)	4 (3%)	8 (6%)
	Bile acid resin	29 (16%)	34 (19%)	6 (4%)	12 (10%)
	Nicotinic acid	6 (3%)	5 (3%)	2 (1%)	7 (6%)
	Others	13 (7%)	15 (8%)	15 (11%)	8 (6%)
	No	16 (9%)	14 (8%)	15 (11%)	16 (13%)

MEDFICTS, Meats, Eggs, Dairy, Fried foods, In baked goods, Convenience foods, Table fats, Snacks; RISCC, ratio of ingested saturated fat and cholesterol to calories.
[a] Obtained by personal communication from Stein and colleagues, 2004.[118]
[b] Subjects may appear in more than one category.

to treatments. The total incidence of musculoskeletal adverse events was similar in both combination and monotherapy groups (9 and 10%, respectively). No cases of rhabdomyolysis were reported. Consecutive and presumed consecutive elevations in ALT and/or AST level more than three times the upper limit of normal (ULN) were uncommon apart from the study by Ballantyne and colleagues,[119] which reported 2.3 versus 2.4% for ALT and 1.2 versus 0.8% for AST in the ezetimibe plus statin versus statin monotherapy arms, respectively. Creatine kinase (CK) values more than 10 times the ULN were reported by ⩽1% of patients across all trials and had a similar incidence in the combination and monotherapy arms.

Overall, the majority of the adverse events were considered to be of mild or moderate intensity. Specific clinical syndromes such as myopathy defined by the presence of myalgia in conjunction with CK elevations more than 10 times the ULN and liver function tests showed no pattern of relationship with respect to ezetimibe,

TABLE 14 *Changes in plasma lipid/lipoprotein concentrations (mmol/l) in HeFH versus non-HeFH groups*[118a,b]

Lipid profiles (mmol/l)	Baseline		End of treatment	
	HeFH: mean (SD)	Non-HeFH: mean (SD)	HeFH: mean % change (SD)	Non-HeFH: mean % change (SD)
LDL-c	5.15 (1.27)	4.40 (0.96)	–34.6 (0.42)	–31.1 (0.41)
Total-c	7.05 (1.33)	6.46 (1.01)	–27.0 (0.31)	–24.7 (0.29)
HDL-c	1.31 (0.33)	1.28 (0.29)	3.5 (0.31)	4.1 (0.35)
TG (median)	1.17	1.58	–16.3	–23.7

[a] Full details of the titration process of this trial are reported in Appendix 10.
[b] Obtained by personal communication from Stein and colleagues, 2004.[118]

administered either alone or with statins. No particular trend was found for any adverse event category in either treatment group. There were no clinically meaningful differences in the combination and monotherapy groups for the incidence of adverse events or in the number of discontinuations because of the adverse events. A recent review summarising muscle safety profile from RCTs also concluded that ezetimibe administered with simvastatin was no more likely to cause muscle-related side-effects than corresponding doses of simvastatin.[136]

It is established that myopathy and rhabdomyolysis are known adverse events with statins, and occur more commonly at higher doses.[39] The low frequency of adverse events observed in the current review may be explained by the relatively short periods of the studies.

Quality of life

No evidence was found which assessed HRQoL directly in individuals receiving ezetimibe monotherapy or coadministered with a statin.

Discussion

Thirteen RCTs (one of which was published as an abstract) assessing the clinical effectiveness of ezetimibe 10 mg/day as combination therapy (with statins) or monotherapy for the treatment of primary hypercholesterolaemia in adults were identified. None of these studies examined clinical outcomes such as CV events or mortality. The main outcome of all trials was the percentage decrease in LDL-c during the study period. Evidence suggests that combination treatment of ezetimibe with statin provides significantly more benefit by reducing the LDL-c level by 13.94% compared with statin monotherapy. In addition, ezetimibe monotherapy is associated with a significant decrease in LDL-c concentration of 18.56% compared with the placebo arm. There is no evidence that the LDL-c-lowering effect of ezetimibe differs across various patient subgroups such as women, the elderly and people with higher CVD risk factors. Although there are concerns regarding the relatively short periods of the studies, ezetimibe was generally considered to be well tolerated and the combination of ezetimibe plus a statin has a safety profile similar to that of a statin alone in the studies reviewed.

All studies were described as multicentre, of randomised design, with treatment lasting for at least 12 weeks. Some important details of randomisation method such as allocation concealment, treatment allocation and assessment of blinding success were omitted. However, power calculations and statistical analyses were considered adequate. The number of withdrawals and reasons were presented. Study groups were comparable at baseline and the overall likelihood of confounding bias was considered as moderate to low.

Only four trials reported the LDL-c-lowering effect by different subgroups in the section 'Efficacy and safety of ezetimibe across different patient subgroups' (p. 28). There was insufficient evidence to establish any differential effects of ezetimibe (with and without other lipid-lowering drugs) on people with no history of CVD compared with those with established CVD. Even if the authors could make such comparisons (as has been discussed in HeFH versus non-HeFH comparison; see the section 'Efficacy and safety of ezetimibe across different patient subgroups' (p. 28), the lack of a statistically significant difference would not imply that a difference did not exist. It could mean that the sample sizes were too small to provide enough power to detect a difference.

It should be recognised that FH is an inborn error of LDL metabolism in which the increased risk of CVD is driven very specifically by increased LDL concentrations. Therefore, a reduction in CV risk is to be expected if there is a reduction in LDL cholesterol. This cause and effect relationship is more direct for FH than for other situations, where there is increased CVD with less direct links to hypercholesterolaemia.

An abstract[121] reporting a statistical significance between two treatment groups (ezetimibe plus statin versus niacin plus statin) provided limited information. Without examination of the detailed study method and outcomes, it was not possible to evaluate and validate the results fully.

It was not possible to differentiate the effectiveness between varying doses of different statins on the basis of the evidence; therefore, the statins were pooled across all doses and all types of statins and evaluated as a class drug. In particular, because of the complex administration, it was not possible to establish in the titrated studies how many patients reached the target LDL-c level at certain doses and how many were titrated to the next higher dose of statin.

No information was given in the primary studies about pretrial medication of the participants. Moreover, the populations in the studies did not fully reflect the populations defined by the scope (i.e. people whose hypercholesterolaemia had not been adequately controlled with a statin alone, or among statin-intolerant people). The patients in the statin groups should ideally be people whose cholesterol levels do not reach the target (i.e. JBS2, NSF; see *Table 6*) after statin treatment or those intolerant to statin treatment. Therefore, it is uncertain if ezetimibe will have the same effect on the clinically relevant population.

No studies reported objective clinical end-points (mortality and morbidity) and the effectiveness obtained from the reviewed studies relates to surrogate outcomes such as LDL-c. It has been widely accepted that surrogate outcomes such as LDL-c level are directly correlated with CVD mortality and morbidity. However, reducing hypercholesterolaemia sufficiently to impact on major adverse events often requires long-term strategies. In clinical practice, single risk factor interventions are rare and are less likely to have a significant impact on outcomes. It is also unclear if the ezetimibe-induced changes in LDL-c will translate to observed reductions in CV events. The recent ILLUMINATE trial,[274] which compared a combination of torcetrapib and atorvastatin with atorvastatin alone in 15,000 patients, was terminated early based on an interim analysis that showed a significantly higher rate of death in the combination therapy treatment group (n = 82) than in the atorvastatin alone group (n = 51). Earlier findings from this study based on 8-week data[137,138] showed significant reductions in LDL-c and significant increases in HDL; therefore, extrapolations from changes in lipids to clinical outcomes with a new drug should be treated with caution.[139] An exploratory meta-analysis (Appendix 12) of short-term studies (6–8 weeks), which analysed the efficacy of ezetimibe added to ongoing statin therapy, showed that ezetimibe decreased LDL-c by 23%. Although significant short-term reductions were observed, they are unlikely to inform on long-term clinical outcomes and adverse events, and were therefore excluded from the review.

The evidence demonstrates the efficacy of ezetimibe in reducing LDL-c when administered as monotherapy and in combination with a statin. When used as monotherapy, ezetimibe's LDL-c-lowering ability is less than that of statins. However, an additional LDL-c-lowering effect has been shown when ezetimibe is added to baseline statin therapy. The long-term efficacy and safety of ezetimibe alone or in combination with a statin are unknown.

High-dose statins are associated with increased adverse effects; hence the incidence of those who cannot tolerate the drugs may also increase.[140] Although ezetimibe co-administered with statins appears well tolerated in the short-term clinical trials, there is no long-term evidence that this strategy is any safer than maximising the dose of a statin. If the long-term data on ezetimibe co-administered with statin show a good or low adverse event profile, this strategy could increase adherence in individuals who potentially have more to gain from lipid-lowering treatments.

To date, there is limited evidence assessing the effectiveness, safety and tolerability of co-administration of ezetimibe with other lipid-lowering drugs. There is also a need for evidence on patients who are on treatment but have not reached the lipid goals and patients with very high levels of plasma cholesterol, including people with HeFH, who may have lipid-lowering treatment initiated at a younger age than the general population. Studies of longer duration and head-to-head comparison with nicotinic acid, resins or fibrates are required to assess fully the efficacy of ezetimibe.

Chapter 4

Assessment of cost-effectiveness

Systematic review of existing cost-effectiveness evidence

The main objective of this review is systematically to identify literature that explores the cost-effectiveness of ezetimibe for individuals with primary hypercholesterolaemia.

Search strategy

Studies were identified through searches of the following databases: MEDLINE, EMBASE, Cochrane Library, NHS EED, NHS CRD DARE, NHS CRD HTA, CINAHL, OHE HEED and Web of Science. Publications lists and current research registers of HTA organisations were consulted via the Internet. Handsearching and citation searches of included studies and of the company submission were undertaken. All searches were undertaken between April and June 2006. A list of the sources consulted and the keyword strategies used are given in Appendix 22.

Inclusion and exclusion strategy

The inclusion of papers identified through searches mentioned above was assessed using the following inclusion and exclusion criteria.

Inclusion criteria

- cost effectiveness/cost–utility analyses
- ezetimibe monotherapy
- ezetimibe co-administered with statins
- the benefits in terms of life-years gained (LYGs) or QALYs
- adult population (aged 18 years and over).

Exclusion criteria

- studies that do not report results in terms of incremental cost-effectiveness ratios (ICERs).

Quality assessment strategy

The Eddy checklist on mathematical models for technology assessments[141] in combination with the *BMJ* checklist for economic evaluations[142] was used to assess the quality of studies.

Results of review

Quantity and quality of research available

The total number of potentially relevant publications identified through electronic literature searches was 1553. Based on titles and abstracts, 1547 studies that did not meet the inclusion criteria were excluded. Six studies were retained at this stage.[143–148] After more detailed evaluations of the full papers, it was found that one of the studies[145] was not a cost-effectiveness analysis and two did not meet all the inclusion criteria because they were discussions about the use of ezetimibe and clinical practice.[143,148] Two studies were excluded as the results were presented as the drug cost versus percentage of LDL-c reduction.[146,147] One paper satisfied all inclusion and exclusion criteria.[144] One additional potentially relevant study[149] and three abstracts were identified by random handsearching. One of the identified abstracts had not yet been published.[150] Two full papers and one abstract have been included in this review.[144,149,151] The abstract provides insufficient detail for review but is retained for information as it is the only UK (Scotland)-based evidence.

Published cost-effectiveness analyses

The two papers[144,149] and the abstract[151] included in the review describe country-specific evaluations using a core economic model developed by Cook as colleagues.[144] Only one study[151] was UK based (Scotland) and this was published in abstract form only. The core model used is also used to inform the economic evaluation for the industry submission. As the model is reviewed in detail in the section 'Review of the MSD/SP economic evaluation' (p. 38), a very brief synopsis (*Table 15*) of the differences in the assumptions, parameter values and the reported results for the three studies identified in the literature searches is provided in this section.

Adaptations to the core model include country-specific epidemiological and cost data, subgroup analyses, treatment regimens and lipid targets. To compare the results, the currencies are converted to UK pounds using the Gross Domestic Product Purchasing Power Parities,[153] and results are adjusted to 2006 using the Pay and Prices annual percentage increase (1.9%).[154]

Cook and colleagues.[144] Cost-effectiveness of ezetimibe co-administration in statin-treated patients not at cholesterol goal: application to

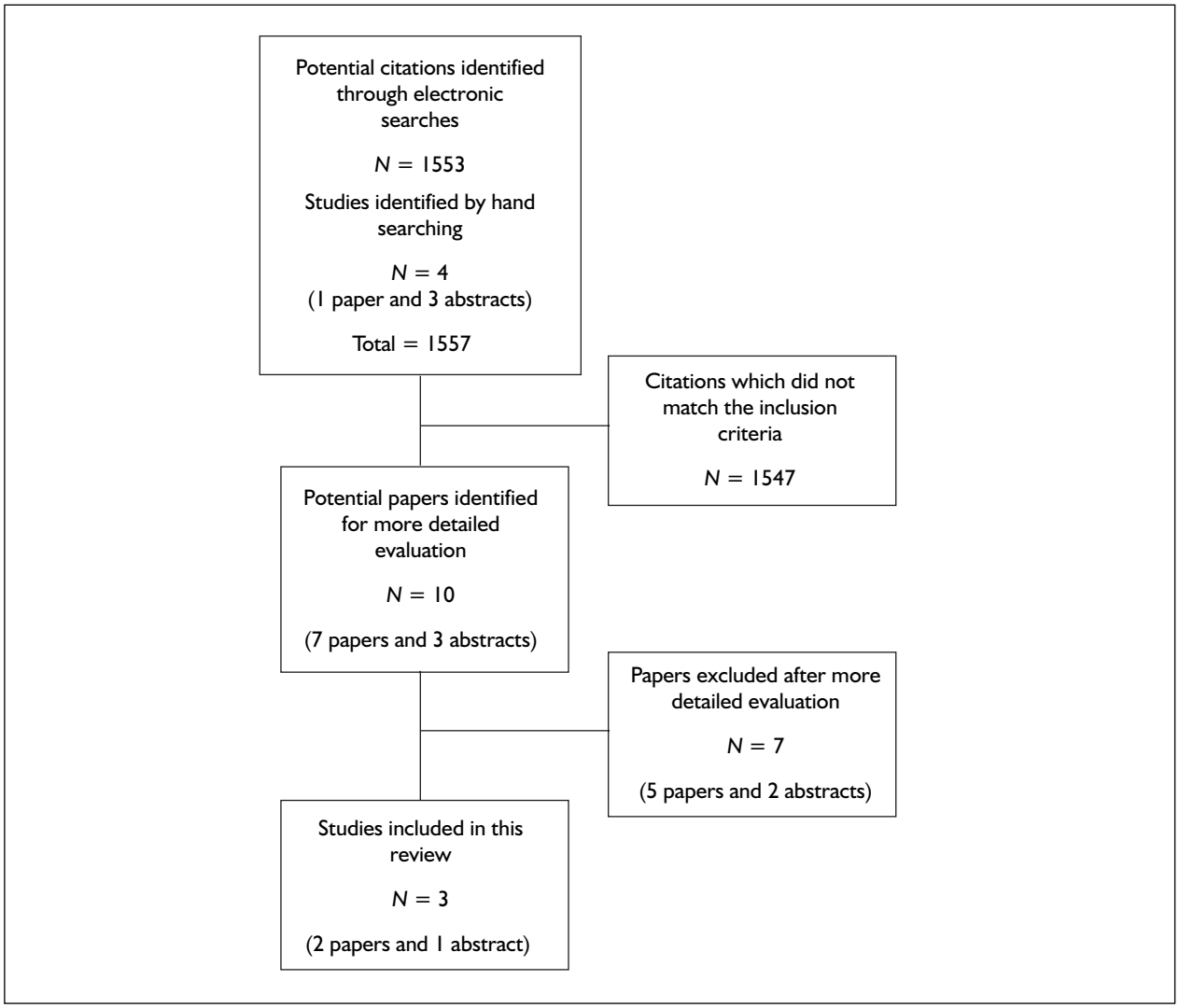


FIGURE 5 *Studies eliminated/selected for the review after applying the inclusion/exclusion criteria*

Germany, Spain and Norway. *Pharmacoeconomics* 2004;22 Suppl 3:49–61
This study[144] evaluates the cost-effectiveness of ezetimibe in Germany, Spain and Norway. A health insurance perspective was used for the Germany evaluation whereas a government payor perspective was used for Spain and Norway. Costs and benefits were discounted at an annual rate of 3% for the three countries.

The model compared ezetimibe co-administration with three statin-only strategies using simvastatin and atorvastatin. The first strategy compared ezetimibe co-administration versus continuing the same statin and dose. In the second strategy, the statin dose was titrated for patients who failed to achieve lipid goals up to the maximum dose recommended per country. The third strategy compared ezetimibe co-administration against a 'titrate to goal', where all patients were titrated up to the highest daily dose approved. Results were presented in terms of gains in life-years and incremental cost per life-year gained (LYGs).

The ICERs for patients with CHD were under £18,900 LYG for ezetimibe plus statin versus statin monotherapy and under £27,300 per LYG for ezetimibe plus statin versus 'titrate to goal'. The ICERs for diabetic patients with no history of CHD were under £27,300 per LYG for ezetimibe plus statin versus statin monotherapy and under £50,400 per LYG for ezetimibe plus statin versus 'titrate to goal'.

Kohli and colleagues.[149] Cost-effectiveness of adding ezetimibe to atorvastatin therapy in patients not at cholesterol treatment goal in Canada. *Pharmacoeconomics* 2006;24:815–30
Kohli *et al.*[149] evaluated the cost-effectiveness of ezetimibe treatment in a Canadian population.

TABLE 15 *Summary of the cost-effectiveness studies identified*[a]

Study	Setting	Population	Treatment goal	Treatment strategies	Cost-effectiveness range (£)
Cook *et al.*, 2004[144]	Germany Spain Norway	Adult patients with a history of CHD or diabetic patients with no history of CHD	Germany and Spain: LDL-c = 100 mg/dl (2.59 mmol/l) Norway: Total-c = 5 mmol/l	Ezetimibe plus statin vs statin (no titration) Ezetimibe plus statin vs observed titration rate Ezetimibe plus statin vs 'titrate to goal'	7,565–49,867 (cost per LYG)
Cook *et al.*, 2004[151] (abstract only)	Scotland	Patients aged 65 years with a history of CVD not attaining Total-c goal	Total-c ⩽5 mmol/l	Ezetimibe plus statin vs statin (no titration) Ezetimibe plus statin vs statin titration	8,090–8,511 8,735–9,118 (cost per QALY)
Kohli *et al.*, 2006[149]	Canada	Patients aged 65 years with no history of CAD with baseline LDL-c levels of 3.1 or 3.6 mmol/l	LDL-c <2.5 mmol/l	Ezetimibe plus statin vs statin monotherapy Ezetimibe plus statin vs statin titration	26,221–45,867 (cost per QALY)

[a] Further details of the core model (originally published by Cook and colleagues[144]) are provided in the section 'Review of the MSD/SP economic evaluation' (p. 38).

A Ministry of Health perspective was used and all costs were adjusted to 2002 price levels. Cost and benefits were discounted at an annual rate of 5%. The evaluation compared a number of different treatment strategies: atorvastatin monotherapy versus atorvastatin titration, ezetimibe combined therapy versus atorvastatin titration and cholestyramine combined therapy versus ezetimibe combined therapy. The basecase analysis focused on 65-year-old patients classified as very high risk of CAD with baseline LDL-c levels of 3.1 or 3.6 mmol/l. QALYs were calculated assuming utilities of 0.91 up to 2 years after an MI, 0.93 up to 2 years after an angina attack and 1.00 for subsequent years. The ICERs for ezetimibe plus statin compared with atorvastatin monotherapy or atorvastatin titration ranged from £26,200 to £45,900 per QALY. The cholestyramine plus statin treatment was dominated by the ezetimibe plus statin treatment.

Cook and colleagues.[151] The cost-effectiveness in CHD and CHD equivalent patients not at total cholesterol goal on statin monotherapy in Scotland. ***Abstract, European Society of Cardiology Annual Meeting (ESC), 28 August–1 September, 2004, Munich, Germany***

This abstract[151] presented a cost-effectiveness analysis of ezetimibe plus statin treatment for patients with CHD not reaching their Total-c goal of <5 mmol/l in Scotland. The patients considered in this study had an average age of 65 years, and a Total-c level of 6.1 mmol/l. The discounted cost per QALY for ezetimibe plus statin versus statin titration was £8900 and for ezetimibe plus statin versus statin monotherapy the cost per QALY was £8300.

Based on the information provided within the papers, the model structure used appears to be reasonable and flexible, although the methodology used to link changes in lipids to CV risk has now been superseded by the new evidence published by the CTTC. The economic model described in the studies has also been used in the industry submission. Several major errors have been identified in the model (described in the next section); consequently, it is uncertain if results generated by the model are robust. The results for Canada were reported to be £45,800 per QALY for patients with an average age of 65 years with no history of CHD when comparing ezetimibe plus atorvastatin 10 mg with atorvastatin titrated. When comparing ezetimibe co-administered with current statin with current statin treatment with no titration in Germany, the results for adults with a history of CHD were £7700 per life-year whereas the results for adults with diabetes but no history of CHD in Spain were estimated to be £50,700 per life-year when comparing ezetimibe

co-administered with current statin treatment with current statin treatment titrated by one dose. The results for Scotland were estimated to be approximately £8000 per QALY for patients with an average age of 65 years with a history of CVD when comparing ezetimibe plus current statin therapy with titration of current statin.

Review of the MSD/SP economic evaluation

Two models were submitted by the MSD/SP analysts. In keeping with the MSD/SP report, the main health economic model is referred to as the 'Cook' model in this report and the second model is referred to as the 'Basic' model. The Cook model is an adaptation of the existing model (built in Excel using Visual Basic programming) used in all the publications described in the section 'Systematic review of existing cost-effectiveness evidence' (p. 35). This model was designed to explore the cost-effectiveness of ezetimibe in patients with raised cholesterol levels and examines the potential benefits of treatment using changes in Total-c and HDL-c. The primary objective of the second model submitted was to determine "if a very simple model, developed from key clinical results, can be used to predict approximately the results of the more sophisticated modelling exercise". The Basic model examines the potential benefits of treatment using changes in LDL-c.

The following section describes the methods, the inputs and the results generated by each model. This is followed by a critique of the models and the implications of the findings.

Overview of the Cook model submitted by MSD/SP

The Cook model uses a Markov process with nine discrete health states: event free, primary MI, primary angina, primary Str, secondary MI, secondary angina, no event in previous 12 months, CHD death and non-CHD death (Appendix 15). The probability of non-fatal Str is also predicted and used as an additional risk factor for secondary events. The costs and benefits associated with these events are not included in the evaluation. The analyses for primary diabetic patients include only fatal CHD and non-fatal MI events.

Probabilities of events are calculated using the D'Agostino risk equations for non-diabetic patients with or without a history of CVD and for diabetic patients with a history of CVD.[87] The predicted primary event risk is distributed across fatal CHD, non-fatal MI and non-fatal angina by using a combination of the Anderson equations.[77] For the secondary analyses, the predicted ratios across the event types are also weighted according to the distribution of secondary events observed in the Framingham cohort.[87] The UKPDS algorithms are used to calculate probabilities of events for diabetic patients with no history of CHD.[155] The predicted risk for primary CHD diabetic patients is distributed across fatal CHD and non-fatal MI using a combination of UKPDS equations.[86,156,157] The UKPDS 60 is used to predict the probability of Str.[158]

A 1-year cycle is used and probabilities are recalculated each year based on changes in age, primary CVD history and lipids. No limit is placed on the number of events that an individual can have. Costs and benefits accrue over a maximum of 50 years with analyses terminating when patients reach the age of 99 years. Annual age- and gender-specific risks for non-CVD death are calculated using national all-cause mortality rates adjusted for CV deaths. A UK NHS perspective is used, hence direct costs only are evaluated. Costs and benefits are discounted at 3.5%.

Populations considered in the Cook model

For people who tolerate statin therapy, ezetimibe co-administration with statins is evaluated in people currently on statins whose lipid levels are not adequately controlled with statin monotherapy. For people who do not tolerate statin therapy and those in whom statins are contraindicated, ezetimibe monotherapy is also evaluated.

The following four population groups are used:

- people with clinical evidence of CVD (with or without diabetes)
- people with diabetes but no evidence of CVD
- people with no clinical evidence of CVD but with a 20% or greater 10-year risk of developing CVD
- people of South Asian origin at high risk of developing CVD.

The fourth group assumes that people of South Asian origin have a 50% higher age-standardised CHD mortality rate than that for the general population of England and Wales.[159] Probabilities of events for this population are calculated by inflating the baseline CHD risk by 50%.

Scenarios used in the Cook model

Several scenarios, which are summarised in *Table 16*, are used to evaluate different treatment strategies.

The baseline risk profiles and the methodology used to predict risks are provided in *Table 17*.

Effectiveness of treatment regimens used in the Cook model

The benefits of the different treatment regimens are modelled by applying the percentage changes in Total-c and HDL-c levels derived from either previously published meta-analyses (*Table 18*).

Costs of health states and monitoring in the Cook model

The costs of CHD events (*Table 19*) and monitoring costs are based on values used in the 2004 statin Health Technology Assessment report.[39] The costs of the CHD events (but not the monitoring costs) are inflated to 2006 costs using a 3.8% annual inflation rate.

TABLE 16 *Treatment scenarios evaluated in the MSD/SP economic evaluation*

Population[a]	Treatment 1	Treatment 2
Base case a: ezetimibe plus current statin vs double the dose of current statin **Base case b: ezetimibe plus current statin vs current statin** Current statin therapy: the distribution across types and doses for current statin therapy is based on current prescribing rates derived from sales data in the UK		
(i) Adults with clinical evidence of CVD (ii) Adults with diabetes and no evidence of CVD (iii) Adults with a 10-year CHD risk ⩾20% (iv) Adults of South Asian origin at high risk of developing CVD	Ezetimibe plus current statin therapy	(a) Double the dose of current statin therapy (b) Continue current statin therapy without modification
Alternative Scenario 1: ezetimibe plus low-cost statin vs switch to more potent high-cost statin Assumes current statin therapy: 50% simvastatin 20 mg and 50% simvastatin 40 mg		
(i) Adults with clinical evidence of CVD (ii) Adults with diabetes and no evidence of CVD (iii) Adults with a 10-year CHD risk ⩾20%	Ezetimibe plus 50% on simvastatin 20 mg and 50% on simvastatin 40 mg	50% on atorvastatin 20 mg and 50% on atorvastatin 40 mg
Alternative Scenario 2: titration of high-cost statin vs switch to low-cost statin plus ezetimibe Assumes current statin therapy: 50% atorvastatin 10 mg and 50% atorvastatin 20 mg		
(i) Adults with clinical evidence of CVD (ii) Adults with diabetes and no evidence of CVD (iii) Adults with a 10-year CHD risk ⩾20%	50% on atorvastatin 20 mg and 50% on atorvastatin 40 mg	Ezetimibe plus 50% on simvastatin 20 mg and 50% on simvastatin 40 mg
Ezetimibe monotherapy: ezetimibe monotherapy vs no treatment For individuals in whom a statin is considered inappropriate or is not tolerated		
(i) Adults with clinical evidence of CVD (ii) Adults with diabetes and no evidence of CVD (iii) Adults with a 10-year CHD risk ⩾20%	Ezetimibe monotherapy	No pharmacological treatment

[a] Results are presented separately for males (females) aged 50, 60, 70 or 80 years.

TABLE 17 *Baseline lipid levels and additional risk factors modelled in the MSD/SP economic evaluation*

	HDL-c (mmol/l)	SBP (mmHg)	DM (%)	Smoke (%)	HbA1c	Risk engine
People with clinical evidence of CVD	1.35	134.9	17	19		D'Agostino
People at high risk of a primary CVD event	1.0	150	0	100		Anderson
People with diabetes	1.35	143.1	100	20	7.41	UKPDS

HbAlc, glycosylated haemoglobin; SBP, systolic blood pressure.

TABLE 18 *Mean (SD) changes in Total-c and HDL-c used in the MSD/SP economic evaluation*

Scenario	Total-c mean (SD, SE)	HDL-c mean (%)
Ezetimibe co-administered with current statin therapy Source: MSD/SP meta-analysis (Appendix 18)	–15.93 (18.37, 0.38)	1.69
Ezetimibe monotherapy Source: MSD/SP meta-analysis (Appendix 18)	–13.30 (9.91, 0.38)	2.90
Double statin dose Source: Knopp,[67] McKenney[160]	–5.98 (12.45, 0.28)	0.15

TABLE 19 *Health state and monitoring costs used in the MSD/SP economic evaluation*

CHD event	1st year cost (£)	Subsequent year cost (£)
Angina	184	184
MI	4792	184
Fatal CHD	1256	NA
Monitoring costs	124	33.42

NA, not applicable.

Costs of treatments used in the Cook model

All treatment costs (Appendix 16, *Table 69*) are based on drugs tariffs (July 2006) with the exception of ZOCOR, LIPOSTAT and SIMVADOR, which are based on eMIMS prices. Sales figures representing the type and dose of statin used in practice (Appendix 16, *Table 70*) are used to derive a weighted average (*Table 20*) cost of statin for the basecase analyses.

Utilities used in the Cook model

The health state QoL utilities (Appendix 17) and the utility by age are based on the data used in the NICE statin appraisal.[39] It is assumed that disutilities associated with treatments are small and these are not modelled.

Validation of the Cook model

The model is validated by comparing the number of events predicted by the model with the number of events observed in the 4S and AFCAPS/TexCAPS RCTs and in a UK-based observational/cross-sectional study.[161–164] Both the AFCAPS/TexCAPS and Whickham data are used to validate the model's accuracy in predicting events in patients with no history of CVD. Using the AFCAPS/TexCAPS data, the model underestimates both the percentage of patients who experience a non-fatal CHD event and the benefit of lipid lowering. The model over-predicts the rate of CHD events slightly for the 10-year Whickham data. The model predicts the 20-year Whickham data accurately, although the ratio between fatal and non-fatal CHD events is not equal to the observed ratio. The 4S data are used to validate the model's accuracy in predicting events in patients with a history of CVD. The model under-predicts both the percentage of patients who experience a non-fatal CHD event and the benefit of lipid lowering.

Overview of the Basic model submitted by MSD/SP

The alternative Basic model examines the effectiveness of treatment regimens by utilising the relationship between LDL-c reductions and CHD

TABLE 20 *Weighted daily cost of statin treatment and statin titration used in the Cook model*

	Weighted daily cost of current statin dose (£)	Weighted daily cost of next statin dose (£)
People who have not reached maximum dose of statin	0.4162	0.6733
People who have reached the maximum dose of statin	0.5416	0.5416
	Daily cost	
Simvastatin 10 mg (20 mg)	0.1001	
Atorvastatin 10 mg (20 mg)	0.945[a]	
Ezetimibe 10 mg	0.94	

[a] Scenario 1 uses a daily cost of £0.94, Scenario 2 £0.9438 and the Basic model £0.9450.

risk.[79] The objective of this model was to test if the ICERs generated were comparable to the more sophisticated modelling approach. The methods and assumptions used in the simple model are summarised below:

- Simple decision tree structure.
- Health state and utility data as in the Cook model.
- The model predicts a first CHD event only.
- The annual CHD risk (2.5, 3, 3.5 or 4%) remains constant over time.
- The distribution across CHD events (fatal CHD event, 15%; non-fatal MI, 62%; non-fatal angina, 23%) is constant for all analyses based on a ratio derived from the Anderson equations.[77]
- 1 mmol/l reduction in LDL-c = 23% reduction in risk.[33]
- Rule of 6, doubling statin dose = 6% reduction in LDL-c.[67,160]
- Ezetimibe co-administered with statin treatment gives an additional 23% reduction in LDL-c compared with statin monotherapy (meta-analysis of ezetimibe clinical trial data, data on file).

Using baseline LDL-c levels of 3, 3.5, 4 or 4.5 mmol/l, two treatment comparisons are evaluated:

1. Ezetimibe (£0.94 per day) plus a weighted average dose of generic and branded simvastatin (10, 20, 40, 80 mg), atorvastatin (10, 20, 40, 80 mg), generic and branded pravastatin (10, 20, 40, 80 mg) and rosuvastatin (5, 10, 20, 40 mg (£0.4162 per day) versus a weighted average dose of generic and branded simvastatin (20, 40, 80 mg), atorvastatin (20, 40, 80 mg), generic and branded pravastatin (20, 40 mg) and rosuvastatin (10, 20, 40 mg) (£0.6733 per day).
2. Ezetimibe (£0.94 per day) plus 50% of individuals on simvastatin 20 mg and 50% of individuals on simvastatin 40 mg (£0.1001 per day) versus 50% of individuals on atorvastatin 20 mg and 50% of individuals on atorvastatin 40 mg (£0.945 per day).

Cost-effectiveness results estimated by the MSD/SP models

Results from the Cook MSD/SP model

The results are presented in terms of ICERs and are summarised in *Table 21*. The base case (a) evaluates ezetimibe plus current statin therapy compared with titration of current statin therapy. The results range from £8800 per QALY (for South Asian males at high risk of a CHD event aged 60 years with a baseline Total-c of 6.5 mmol/l) to £122,000 per QALY (for females with no history of CVD aged 80 years with a baseline Total-c of 4.5 mmol/l).

Results from the Basic MSD/SP model

The authors conclude the simplified model "gives results of a similar order to those calculated using

TABLE 21 *Summary of results from the Cook model*[a]

Population	Patient profile[b]	Discounted ICER (£000)
Base case (a): ezetimibe plus current statin vs current statin titration		
Minimum: South Asian males at high risk of CVD	M, 60, 6.5	8.8
Maximum: females with no history of CVD	F, 80, 4.5	121.9
Base case (b): ezetimibe plus current statin vs current statin without titration		
Minimum: South Asian males at high risk of CVD	M, 60, 6.5	7.9
Maximum: females with no history of CVD	F, 80, 4.5	110.0
Ezetimibe monotherapy versus no treatment		
Minimum: South Asians males at high risk of CVD	M, 60, 6.5	9.9
Maximum: females with no history of CVD	F, 80, 4.5	131.1
Alternative scenario 1: ezetimibe plus low-cost statin vs switch to more potent high-cost statin		
Minimum: males with no history of CVD	M, 80, 6.5	1.0
Maximum: females with no history of CVD	F, 80, 4.5	15.6
Alternative scenario 2: titrate high-cost statin vs switch to low-cost statin plus ezetimibe		
Minimum: males with no history of CVD	M, 80, 6.5	1.0
Maximum: females with no history of CVD	F, 80, 4.5	14.9

[a] Additional results are provided in Appendix 19.
[b] Patient profile = gender (M = male, F = female), age (years), baseline Total-c (mmol/l).

the more sophisticated model". The examples provided are for a male aged 50 years with an annual risk of a primary cardiac event of 3.5% and a baseline LDL-c of 4.0 mmol/l. The ICER is estimated to be £21,100 per QALY when comparing a titration strategy using the weighted cost of all statins. Using the same baseline profile, the ICER is estimated to be £2000 per QALY when comparing ezetimibe plus simvastatin 20/40 mg with atorvastatin 20/40 mg.

Probabilistic results from the Cook model

Using a threshold of £20,000 per QALY, the results of the probabilistic analyses suggest that, with the exception of those aged 80 years with a Total-c of 4.5 or 5.5 mmol/l, ezetimibe co-administered with weighted statin therapy compared with titrated statin therapy is cost-effective for all men who have a history of CVD. Conversely, the cost-effectiveness acceptability curves (CEACs) generated for females suggest that, with the exception of diabetic patients, when using a threshold of £20,000 per QALY none of the treatment regimens are cost-effective (Appendix 19).

Critique of the MSD/SP economic models

When the Cook model was originally constructed, the algorithms from the Framingham study were potentially the most appropriate methodology for predicting future CV events in economic models when only surrogate outcome measures are available. However, this methodology has been superseded by the evidence published by the CTTC, which enables chemically induced changes in lipids to be linked to reductions in cardiovascular risk based on evidence from lipid lowering RCTs (see the section 'Introduction', p. 1).[79]

The evidence which links treatment-induced changes in LDL-c and CV risk was used by the MSD/SP analysts in the Basic model. Although this is the preferred methodology, as stated by the authors of the MSD/SP report, the Basic model was constructed to predict approximate results only (p. 242, Appendix 28, of the industry submission report) for individuals with no history of CVD.

A number of potential issues were identified with the model and the three main areas of concern are summarised below. A more detailed discussion of the critique is provided in Appendix 21 together with a description of minor inconsistencies and responses to initial enquiries (Appendices 20 and 21).

1. The algorithm used to calculate risk for females with no history of CVD has been incorrectly coded. A term in the algorithm has been misinterpreted, with the consequence that the predicted risk for females decreases as age increases. As the risks for these cohorts are substantially underestimated, the number of events avoided is also underestimated. The errors have a large impact on the results.
2. The Framingham algorithms are used to predict annual risks in all the analyses up to the age of 99 years. These functions are valid within the range 35–74 years only.[77,87] The modelled D'Agostino risks for cohorts aged over 70 years are considerably higher than the corresponding Anderson rates (Appendix 21). The impact on the ICERs is unknown.
3. The total CHD risk for individuals receiving no treatment can be allocated to non-fatal MI and CHD death only. This distribution does not reflect the definition of events included in the total CHD risk or the distribution across events in the data used to derive the risks: total CHD risk is defined as non-fatal MI plus CHD death plus angina pectoris plus coronary insufficiency;[87] fatal MI plus CHD death account for only 58% (38%) of male (female) initial events in the study.[87] Individuals receiving statin monotherapy may have more angina events than those receiving no treatment and individuals receiving ezetimibe plus statin treatment may have more angina events than those receiving either statin monotherapy or no treatment. This does not reflect published evidence from lipid-lowering RCTs. The results from a recent meta-analysis of statin data show that the relative risks (RRs) for stable angina and unstable angina versus placebo are 0.59 (95% CI 0.38 to 0.90) and 0.82 (95% CI 0.74 to 0.90), respectively.[39]

As the total predicted CHD risk is distributed unevenly in the treatment arms, the number of more serious events prevented and therefore the benefits of treatment are overestimated. The magnitude of error in the ICERs is unknown.

In summary, it is not possible to estimate the full magnitude or direction of errors in the reported ICERs for each of the individual analyses and subgroups. The risk for females with no history of CVD is substantially underestimated, hence the corresponding ICERs are considerably higher than they should be. The validity of the predicted risk for older ages (over the age of 74 years), which affects all analyses, is questionable. The magnitude and direction of any errors are

uncertain. The number of serious events prevented is overestimated and therefore the ICERs are lower than they should be. The magnitude of this error is not known. The reviewers have not attempted either to correct the errors or to modify the methods used. The results generated using the MSD/SP models are therefore not considered to be robust.

Independent economic assessment by ScHARR

Objective

The primary objective of this evaluation is to appraise the cost-effectiveness of the use of ezetimibe treatment in patients with raised cholesterol levels who have not achieved the UK target levels (*Table 6*, p. 7) on current statin therapy. A secondary objective is to appraise the cost-effectiveness of ezetimibe in patients in whom statin therapy is contraindicated or in whom statins are not tolerated.

Methods

A Markov model was developed to explore the costs and health outcomes associated with a lifetime of treatment using a UK NHS perspective. Effectiveness of treatments is modelled using a reported link between chemically induced LDL-c reductions and CV events. Distribution across event types is based on UK-specific incidence and prevalence rates. Meta-analyses of published RCT data are used to inform efficacy of treatments in lowering LDL-c levels. Results are presented in terms of cost per QALY.

Sources of evidence

The evidence used to develop and populate the model was identified and selected from a number of key sources as listed in *Table 22*. Individual sources are referenced, as appropriate, in the report. An overview of the methods used to identify the evidence base supporting the model is presented in Appendix 23.

Populations considered in the ScHARR economic evaluation

The model evaluates the cost effectiveness of treatments in the following populations:

1. individuals who tolerate statin treatment
2. individuals in whom statin treatment is contraindicated and those in whom statins are not tolerated.

Each of the above is subdivided as follows:

- gender
- age groups (45, 55, 65, 75 years)
- primary or secondary CVD
- individuals with mild (2.5 mmol/l), moderate (3.0 mmol/l) and high (3.5 mmol/l) baseline LDL-c measurements.

Treatment/comparator

NICE guidance recommends statin treatment for individuals with existing CVD and those with a 10-year CVD risk $\geqslant 20\%$[39] with therapy initiated with a drug with a low acquisition cost (taking into account required daily dose and product price per dose). However, a proportion of individuals who receive the recommended therapy will fail to achieve national target lipid goals (*Table 6*) on initial doses and a proportion will not tolerate statins. Failure to achieve goals may be due to insufficient doses of statins being used, a reluctance to titrate doses when response is inadequate or poor patient compliance.[165] However, it is likely that more aggressive lipid-lowering strategies will prevail due to the anticipated changes to both the General Medical Services (GMS) contract and the QOF, and a shift towards payment by result.[45] Consequently the proportion of individuals who would have remained on current statin therapy without modification is expected to decrease.

If ezetimibe is co-administered with the current statin therapy compared with the alternative of titrating current statin therapy by one dose, there are numerous regimens that could be compared.

TABLE 22 *Key sources of evidence used to inform the model*

Review of clinical effectiveness
ScHARR economic analysis of statin therapy
Searches undertaken to inform model development
Searches undertaken to inform the review of cost-effectiveness
Searches undertaken to inform the review of clinical effectiveness
Ad hoc searches
Expert opinion
Reference sources [e.g. British National Formulary (BNF)]

Clinical advice was sought and the most useful comparison doses were suggested to be atorvastatin 40 mg and atorvastatin 80 mg. It was also suggested that simvastatin 40 mg and simvastatin 80 mg may be useful comparators, although if a patient fails to achieve a satisfactory reduction on simvastatin 40 mg a switch to atorvastatin and then titration through the doses was thought to be a more likely alternative to adding ezetimibe to simvastatin. Simvastatin 80 mg is not used widely due to the flat response and increase in adverse events. However, if the guideline development group on lipids recommend simvastatin 80 mg for both secondary and primary prevention and pravastatin 40 mg for primary prevention, these would also be relevant regimens.[166] It was suggested that for patients who fail to achieve adequate reductions on atorvastatin, the most likely alternative would be a switch to rosuvastatin. The treatment strategies modelled are described below.

Comparator literature search

A systematic literature search (reported in Appendix 23) was undertaken to identify possible comparators. Published systematic reviews and meta-analyses of lipid-lowering therapies identified in the systematic review described in Chapter 3 were used to identify studies on the possible comparators. New evidence and studies excluded from the existing reviews were identified through a berrypicking technique[167] whereby the existing list of studies identified was expanded until it was thought that any additional data would not alter the results. Clinical opinion was sought to clarify areas of uncertainty.

Results

Based on the results of the searches, the most likely alternatives for individuals who tolerate statins but do not achieve goals are:

- Titrate current statin by one dose.
- Switch to a more potent statin.
- Add other lipid-regulating treatments such as nicotinic acid, bile acid resin or a fibrate to current statin treatment.

The most likely alternatives for individuals who do not tolerate statins are:

- nicotinic acid, bile acid resin, a fibrate or a combination of these
- no treatment.

Comparators for patients who tolerate statins

In the absence of robust evidence on effectiveness rates for combination and alternative therapies, the comparator used in the evaluation for patients who tolerate statin treatment is statin monotherapy. The comparators modelled are current statin treatment titrated by one dose or a switch to a more potent statin. Details of the treatment regimens compared are described in the next section.

Comparators for patients who do not tolerate statins

For individuals in whom statins are contraindicated and those in whom statins are not tolerated, the results of the literature searches suggest that the most appropriate comparator to ezetimibe monotherapy would be either nicotinic acid, bile acid resin, a fibrate or a combination of these. Prescribing rates for fibrates, resins and nicotinic acid are low, representing only 2.37, 0.21 and 0.07%[44] of patient-days of lipid-lowering therapy in the UK, respectively, possibly due to poor tolerability and palatability, moderate effects on LDL-c levels and a high prevalence of intolerable side-effects (see the section 'Current service provision', p. 6). These treatments are generally reserved for individuals with hypertriglyceridaemia, mixed hyperlipidaemia HeFH or diabetes.

Based on expert opinion (Yeo WW, Royal Hallamshire Hospital, Sheffield: personal communication, May 2006), small prescribing rates and the conflicting evidence on the effectiveness of fibrates (Robins S, Boston University School of Medicine, Boston: personal communication, May 2005), fibrates are not considered to be an appropriate comparator to ezetimibe treatment for the majority of individuals not achieving cholesterol goals.

The most appropriate study identified which provided sufficient detail for resins was a placebo controlled study of cholestyramine (24 g/day) involving over 3800 individuals.[168] However, this treatment is very rarely prescribed in the UK to lower LDL-c due to limited effectiveness and the adverse event rate associated with higher doses (see *Table 8*).

Niacin is very rarely prescribed in the UK and is not generally used to achieve an LDL-c target (see *Table 8*). This treatment can also cause unpleasant adverse events,[42] particularly when taken in the larger doses that would be required to achieve targets. The minimum dose that would be applicable is 1 g/day (Durrington P, Department of Medicine, University of Manchester: personal communication, October 2006). A placebo-controlled trial by Knopp.[67] using niacin 1.5 g/day provided detail on the effectiveness of treatments

in reducing LDL-c. At this dose, niacin is only slightly less costly than ezetimibe, the evidence suggests that niacin is also less effective in reducing LDL-c than ezetimibe and, as individuals are more likely to incur disutilities due to the adverse events, this treatment is not considered as a comparator to ezetimibe.

Consequently, the most appropriate comparator for ezetimibe monotherapy in patients who are contraindicated for statin treatment and those in whom statins are not tolerated is considered to be no treatment.

Treatment regimens modelled in the ScHARR economic evaluation

- **Scenario 1**: compares ezetimibe co-administered with current weighted statin versus current weighted statin titrated by one dose.
  Current statin therapy and the corresponding weighted cost are based on published data on prescribing rates in England and Wales.[43,44]
- **Scenario 2**: compares the costs and benefits of ezetimibe therapy in individuals who are either contraindicated for statin treatment or in whom statin therapy is not tolerated. The treatment regimen is ezetimibe (10 mg/day) monotherapy compared with no treatment.
- **Scenario 3**: compares ezetimibe co-administered with generic simvastatin with a more potent dose of atorvastatin (50% on 20 mg and 50% on 40 mg for each statin).
  The UK guidelines for statin treatment recommend initial therapy is a drug with a low acquisition cost (taking into account required daily dose and product price per dose).[39] Prescribing data suggest that this recommendation is adhered to in general, with almost 50% of patient days of treatment in England being generic simvastatin.[43] The majority of the balance is accounted for by atorvastatin therapy.[43]
- **Scenario 4**: compares ezetimibe co-administered with current weighted statin versus current weighted statin.
- **Scenario 5**: compares ezetimibe co-administered with rosuvastatin 40 mg versus rosuvastatin 40 mg.
  If ezetimibe is added to statin *x* (any dose or cost) and compared with the same statin *x* (of equal dose and cost), the cost of statin treatment in each arm will cancel. Due to the lack of detailed data on any differences in effectiveness of ezetimibe in combination with different statins compared with the same statin, the clinical impact of adding ezetimibe to the statin will be the same for each regimen.
  Scenarios 4 and 5 are used to demonstrate the cost-effectiveness of the alternative regimens. Any differences in the ICERs generated will be due to rounding errors and will be minimal.
- **Scenario 6**: compares ezetimibe co-administered with current statin treatment with switching to the same dose of a more potent statin.

When switching to the same dose of a more potent statin, there are 10 alternative treatment regimens (*Table 23*). The only difference in the 10 analyses is the incremental annual cost of the regimens being compared.

Treatments for cohorts of patients with diabetes

Based on clinical advice (Durrington P, Department of Medicine, University of Manchester: personal communication, October 2006), if simvastatin 40 mg does not lower LDL-c sufficiently in patients with diabetes, they are likely to be switched to atorvastatin as opposed to titrated to simvastatin 80 mg due to the plateau effect and increased risk of adverse effects observed with the latter dose. They will also be titrated through the doses for atorvastatin. The most likely treatment comparisons for patients with diabetes when comparing the cost-effectiveness of adding ezetimibe to ongoing statin treatment versus switching to a more potent statin are:

- **Scenario 6, treatment regimen 4**: ezetimibe 10 mg plus atorvastatin 40 mg versus rosuvastatin 40 mg.
- **Scenario 6, treatment regimen 6**: ezetimibe 10 mg plus atorvastatin 20 mg versus rosuvastatin 20 mg.
- **Scenario 6, treatment regimen 10**: ezetimibe 10 mg plus simvastatin 40 mg versus atorvastatin 40 mg.

Scenario 2, ezetimibe monotherapy versus no treatment, would also be applicable for patients with diabetes who do not tolerate statins.

Treatments for HeFH cohorts

It is assumed that patients with HeFH will require more potent statin treatment than patients without HeFH and the analyses for the HeFH subgroups use:

- **Scenario 6, treatment regimen 4**: ezetimibe 10 mg plus atorvastatin 40 mg versus rosuvastatin 40 mg.
- **Scenario 2**, ezetimibe monotherapy versus no treatment, would also be applicable for individuals with HeFH who do not tolerate statins.

TABLE 23 *Possible treatment regimens and annual costs when switching to the same dose of a more potent statin*

	Treatment regimen[a]		Annual cost (£)		Incremental annual cost (£)
No.	Combination therapy	Monotherapy	Combination therapy	Monotherapy	
1	E10 + P10	S10	368.00[b]	23.59[b]	344.40
2	E10 + A10	R10	578.00	235.03	342.97
3	E10 + P20	S20	366.56[b]	30.50[b]	336.06
4	E10 + A40	R40	710.71	387.03	323.68
5	E10 + P40	S40	375.17[b]	55.14[b]	320.03
6	E10 + A20	R20	664.17	387.03	277.14
7	E10 + S10	A10	366.56[b]	235.03	131.53
8	E10 + S80	A80	453.25[b,c]	367.74	85.51
9	E10 + S20	A20	373.47[b]	321.20	52.27
10	E10 + S40	A40	398.11[b]	367.74	30.37

[a] A = atorvastatin, E = ezetimibe, P = pravastatin, R = rosuvastatin, S = simvastatin; combination therapy: E10 + P10 = ezetimibe 10 mg plus pravastatin 10 mg; E10 + A10 = ezetimibe 10 mg plus atorvastatin 10 mg, etc.; monotherapy: S10 = simvastatin 10 mg; R10 = rosuvastatin 10 mg, etc.
[b] Costs are for generic pravastatin and generic simvastatin.
[c] Cost is for 2 × 40 mg generic simvastatin.

Structure of the Markov model

A Markov model is used to explore the clinical pathway of individuals at risk of a CVD event. The pathway is divided into a finite number of mutually exclusive health states. At any point in time, all patients within the model exist in one of these states. This methodology is useful for diseases involving risks that continue or increase over time and where events can occur more than once.[169–171] The methodology increases flexibility for tracking costs and utilities over numerous health states. The proportion of patients in each of the health states is governed by age-dependent time-variant transition matrices which describe the annual probability of moving to an alternative health state. CVD risk is updated annually.

Time horizon

When assessing the impact of treatments on reducing major events such as MI, Str and CV deaths, a lifetime horizon is appropriate to explore the full costs and benefits accrued through events avoided. However, in the current evaluation, this requires two large assumptions: (1) that the surrogate outcomes (changes in lipids) will translate to reductions in cardiovascular events and (2) that the extremely short-term surrogate outcomes will be sustained over long time horizons. The results are presented using both 20-year and lifetime horizons.

Markov health states modelled

For the purposes of this evaluation, a CVD event is defined as onset of stable angina, unstable angina, a non-fatal MI, death from CHD-related causes, a TIA, a non-fatal Str or death from Str/TIA-related causes. This definition is based on the evidence that is available for incidence and prevalence in the UK.

For the primary prevention CVD analyses, all individuals commence in the event-free health state (*Table 24*). During each annual cycle of the model, a proportion enter one of the qualifying event health states: MI, stable angina, unstable angina, CHD death, TIA, Str, CVD death or death through other causes, while the remainder remain in the event-free state.

For the secondary prevention analyses, all patients commence in post-health states. In each cycle, patients have a non-fatal event, a fatal event, die through other causes or move to a post-health state. The secondary analyses allow a maximum of two subsequent events, while primary analyses also allow one primary event. A full list of secondary transitions is provided in *Table 28*.

Perspective

A UK NHS perspective is used, hence direct costs only are applied and productivity lost through illness or costs incurred directly by patients are not included.[172] As per current NICE guidance, discount rates of 3.5% are applied to both costs and health benefits.[39,172] Costs are at 2006 prices. Half cycle correction is used for both costs and benefits.

Baseline LDL-c measurements

The baseline LDL-c values modelled are based on data from individuals on ongoing lipid-lowering

TABLE 24 *Markov health states used in the ScHARR economic evaluation*

Primary events		Secondary events	
From	**To**	**From**	**To**
Event free	Stable angina	Stable angina	Post-stable angina
	Unstable angina		Unstable angina
	Non-fatal MI		Non-fatal MI
	TIA		Fatal CHD event
	Non-fatal Str		Death from other causes
	Fatal CHD event	Unstable angina	Post-unstable angina
	Fatal CVD event		Non-fatal MI
	Death from other causes		Fatal CHD event
			Non-fatal Str
			Fatal CVD event
			Death from other causes
		Non-fatal MI	Post-non-fatal MI
			Non-fatal MI
			Non-fatal Str
			Fatal CHD event
			Fatal CVD event
			Death from other causes
		TIA	Post-TIA
			Non-fatal MI
			Non-fatal Str
			Fatal CHD event
			Fatal CVD event
			Death from other causes
		Non-fatal Str	Post-non-fatal Str
			Non-fatal MI
			Non-fatal Str
			Non-fatal MI/Str
			Fatal CHD event
			Fatal CVD event
			Death other causes
		Non-fatal MI/Str	Non-fatal MI/Str
			Non-fatal Str
			Fatal CHD event
			Fatal CVD event
			Death from other causes

treatment: range 3.1 mmol/l (SD = 0.38)[124] to 3.6 mmol/l (SD = 0.10).[173] For the main analyses, three different baseline LDL-c measurements are modelled: mild, moderate and high (2.5, 3.0 and 3.5 mmol/l).

Baseline primary CVD risks

Baseline 10-year primary CVD risks modelled are assumed to be greater than 20% at the age of 45 years (*Table 25*). The initial risk is assumed to increase up to the age of 75 years, based on trends observed in the HSE 2003 data.[174] Due to the limited amounts of data, particularly at younger and older ages, subgroup analyses for individuals receiving CVD medications were not performed.

The baseline risks are updated annually using gender-specific regressions derived from analyses of the HSE 2003 data (Appendix 26).[174] The natural increase by age is less rapid for females than males, reflecting the trends observed in the HSE data.

Primary incidence rates/distribution of risk across health states

As per recommendations,[172] UK-specific data are utilised where possible and UK epidemiological data (*Table 26*) are used to apportion the total primary risk to event type. As used in the recent HTA statin economic evaluation, incidence rates for primary CHD events are taken from the Bromley Coronary Heart Disease Register[175] and TIA and Str are taken from the Oxfordshire Community Stroke Project.[176,177]

In the absence of reported UK data for primary CHD events for older age groups, it is assumed that the rates for angina and non-fatal MI for the

TABLE 25 *Baseline primary 10-year CVD risk (%) and corresponding annual rate (%)*

Age (years)	Males		Females	
	10-year CVD risk	Annual CVD rate[a]	10-year CVD risk	Annual CVD rate[a]
45	20	2.2	20	2.2
55	23	2.6	24	2.7
65	28	3.3	28	3.2
75	34	4.1	34	4.0

[a] The annual rate corresponding to the 10-year risk is calculated using the equation annual rate = 1 – (1 – 10-year probability) × (1/10).

TABLE 26 *Distribution (%) across primary events in the ScHARR economic evaluation*

Age (years)	Stable angina	Unstable angina	MI	Fatal CHD	TIA	Str	Fatal CVD	Total event rate per 1000 per annum[a]
Male								
45	30.7	10.7	29.5	7.1	6.0	12.9	3.0	4.2
55	32.8	7.1	17.2	8.6	8.9	20.6	4.8	13.7
65	21.4	8.3	17.3	9.7	10.0	27.0	6.3	24.3
75	19.1	8.1	16.1	6.3	8.0	34.3	8.0	37.5
85	21.4	9.6	18.6	5.5	1.6	35.1	8.2	42.6
Female								
45	32.5	11.7	8.0	3.7	16.0	22.9	5.4	1.6
55	34.6	7.3	9.2	3.9	9.5	28.8	6.7	6.6
65	20.2	5.2	12.1	8.1	7.3	38.2	9.0	12.4
75	14.9	3.4	10.2	4.3	9.8	46.4	10.9	23.4
85	13.6	2.9	10.0	3.0	8.7	50.1	11.7	32.9

[a] The total event rates are for all CVD events per 1000 population per annum.

age groups 75–84 and 85+ years increase. The rate of increase is based on the ratio of increases reported for the age groups 55–64 and 65–74 years. The rates for fatal CHD events for patients aged over 74 years are held constant at the reported rate for age 65–74 years. The published rates for first-ever Str by age are assumed to be distributed 81:19 for non-fatal:fatal events, based on the overall published figures from the Oxfordshire study.[176]

Prevalence for secondary evaluations

Published UK prevalence data are used to distribute patients to initial health states for the secondary prevention evaluations (*Table 27*). For angina, MI and Str these are taken from the British Heart Foundation Statistics Database[178] whereas evidence from Bots and Kastelein[179] is used to inform prevalence for TIA. It is assumed that the published angina figures include both stable and unstable angina patients and prevalence for these health states are derived using the ratios for stable and unstable angina reported in the incidence data. As TIA prevalence is unavailable for the age group 45–54 years, this is scaled using the prevalence rates for Str.

Secondary event rates

UK-specific data were used wherever possible to ensure that event rates match the likely distribution in the UK. Two main sources were used: with the exception of stable angina, for patients with a primary CHD event, the occurrence of further MI, Str and vascular deaths is derived from patients on the Nottingham Heart Attack Register (NHAR),[180] whereas the probabilities of subsequent Str and vascular deaths for patients with a history of a Str are derived from patients on the South London Stroke Register (SLSR).[181]

Logistic and multivariate regression analyses were used to estimate the probability of experiencing secondary events within 1 year of a qualifying primary event (Appendix 24). First, logistic regression was used to estimate the probability of experiencing a secondary event of any type, that is, the combined rate of non-fatal MI, non-fatal Str

TABLE 27 *Distribution (%) of patients in initial health states for secondary analyses by age and gender*

Age (years)	Unstable angina	MI	Fatal CHD	Str	Fatal CVD	Total per annum
Male						
45	28.7	10.0	37.4	7.2	16.6	7.2
55	37.2	8.0	36.2	4.3	14.2	23.2
65	31.2	12.0	32.1	7.5	17.2	36.1
75	29.0	12.4	30.5	4.8	23.3	44.2
Female						
45	34.1	11.9	26.3	4.6	23.0	3.04
55	41.1	8.9	21.8	8.2	20.0	11.0
65	33.4	12.9	25.7	4.7	23.4	21.4
75	34.3	14.6	18.7	6.9	25.4	34.7

and vascular death. Multivariate regression analysis was then used to determine the distribution of secondary events between each type, should an event occur. The results confirm the importance of accounting for age in the model. For patients experiencing an MI, the probability of a secondary event within 1 year is strongly correlated with age (mean probability of 14.7% at age 45 years and 29.5% at age 85 years). Similarly for patients experiencing a Str, their probability of a secondary event within 1 year increases by age (mean probability of 5.4% at age 45 years and 29.8% at age 85 years), whereas patients with unstable angina have a mean probability of an event of 8.7% at age 45 years compared to 31.3% at age 85 years.

Similar analyses were performed to estimate the probabilities of subsequent events in subsequent years. In the absence of data, these results are used to inform all subsequent events. This is a conservative approach as the application of these data implies that there is no additive effect on fatal or non-fatal event rates from previous events.

TIA transitions are taken from a study by Rothwell and colleagues.[182] As this evidence provides a constant rate across all ages (TIA to non-fatal Str = 0.042, non-fatal MI = 0.006, fatal CVD = 0.02 and fatal CHD = 0.019 at age 67 years), the data are adjusted using the corresponding changes in incidence rates to derive probabilities by age.

The transitions from stable angina to unstable angina, non-fatal MI and fatal CHD are based on RCT data.[183] The trial enrolled 2035 patients from a primary care setting in Sweden between 1985 and 1989. The primary end-point was the first occurrence of non-fatal or fatal MI or sudden death. Median follow-up time was 50 months. The number of events and hence probability of events at 1 year are estimated from the number of patients at risk at 1 year and the ratio of the number of events at trial end. As the results are reported as a constant rate across all ages (stable angina to unstable angina = 0.006, non-fatal MI = 0.011 and fatal CHD = 0.007 at age 67 years), the data are combined with the corresponding changes in incidence rates to derive probabilities by age. It is assumed that the probabilities of a non-fatal Str and fatal CVD events are based on the corresponding transitions for post-MI and unstable angina rates, respectively.

The data used in the secondary transitions are from patients with a history of CVD. The event rates for transitions in the first year, after an event are higher than the event rates in subsequent years reflecting the initial increase in risk after an event. It is possible that the overall risk for post-health states (i.e. when the patient has not had an event in the previous 12 months) for younger cohorts is lower than the primary risk modelled. Based on clinical advice, we have adjusted the post-event rates to ensure that the total risk for a secondary event is always greater than the risk for an individual of the same age in a primary health state. The transitions differ by age and gender and an example is provided in *Table 28*.

Evidence used to translate changes in LDL-c to reductions in CVD events

By examining the incidence rates of first events since the start of the studies, the CTTC analysts established that there was an approximate linear relationship between absolute reductions in LDL-c and the proportional reductions in major vascular events (see the section 'Description of health problems', p. 1). When subgrouped by changes in LDL-c over time, their findings suggest that a sustained reduction in LDL-c of 1 mmol/l over 5 years may produce a proportional reduction in

TABLE 28 *Annual transitions for secondary events (%)*[a]

	Unstable angina	Non-fatal MI	Non-fatal Str	CHD death	CVD death
Age 45 years					
Stable angina	0.48	1.16	0.15	0.32	0.13
Unstable angina (1st year)		5.0	0.1	3.62	0.16
Unstable angina (subsequent year)		1.86	0.04	0.81	0.04
MI (1st year)		12.8	0.1	1.67	0.07
MI (subsequent year)		1.6	0.04	0.52	0.02
TIA		0.4	0.9	0.60	0.34
Str (1st year)		0.41	4.3	0.46	0.46
Str (subsequent year)		0.41	1.44	0.21	0.21
Age 55 years					
Stable angina	0.60	1.45	0.4	0.40	0.19
Unstable angina (1st year)		5.0	0.3	5.85	0.26
Unstable angina (subsequent year)		3.27	0.09	0.98	0.04
MI (1st year)		11.7	0.3	3.00	0.13
MI (subsequent year)		1.95	0.10	0.95	0.04
TIA		0.6	1.2	0.81	0.46
Str (1st year)		0.6	4.6	1.02	1.02
Str (subsequent year)		0.56	1.82	0.45	0.45
Age 65 years					
Stable angina	0.81	1.71	0.6	0.97	0.14
Unstable angina (1st year)		4.9	0.6	9.80	0.44
Unstable angina (subsequent year)		5.96	0.20	1.17	0.05
MI (1st year)		10.3	0.6	5.63	0.25
MI (subsequent year)		2.18	0.24	1.71	0.08
TIA		0.3	2.0	1.03	0.78
Str (1st year)		0.3	4.8	2.39	2.39
Str (subsequent year)		0.35	2.20	0.97	0.97
Age 75 years					
Stable angina	1.19	2.18	0.9	1.39	0.12
Unstable angina (1st year)		4.7	1.3	15.95	0.71
Unstable angina (subsequent year)		10.6	0.43	1.37	0.06
MI (1st year)		8.9	1.3	4.07	0.18
MI (subsequent year)		2.2	0.54	10.27	0.46
TIA		0.6	4.2	1.85	1.63
Str (1st year)		0.6	4.8	1.93	1.93
Str (subsequent year)		0.55	2.45	5.42	5.42

[a] Transitions to MI, Str or fatal events following a Str are assumed to be the highest of the transitions from individuals with a history of Str or MI.

major vascular events of about 23% as opposed 21% when using the weighted analysis. The proportional reduction varies according to event type and the RRs corresponding to a reduction of 1 mmol/l LDL-c are provided in *Table 29*.

A number of assumptions were used to model the relationship:

- The RR for angina is equal to the RR for non-fatal MI.
- The RR for non-TIA is equal to the RR non-fatal Str.
- The RR for fatal Str is equal to one, as the CIs cross one and evidence from a recent meta-analysis of RCT event rates was also inconclusive.[39,184]
- 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 in LDL-c is independent of presenting level of lipids (Figure 5, CTTC[79]).
- The proportional reduction in event rate per mmol/l in LDL-c is independent of baseline prognostic factors (Figure 5, CTTC[79]) such as age, sex, diabetes status or CVD history.

TABLE 29 *Proportional effects on major vascular events per mmol/l LDL-c reduction*

Event	RR	95% CI	Source
Non-fatal MI	0.74	0.70 to 0.79	Table 2, CTTC[79]
Angina	0.74	0.70 to 0.79	See text, p. 50
CHD death	0.81	0.75 to 0.87	Table 1, CTTC[79]
Any Str	0.83	0.78 to 0.88	Table 2, CTTC[79]
TIA	0.83	0.78 to 0.88	See text, p. 50
Fatal Str[a]	0.91	0.74 to 1.11	Table 1, CTTC[79]
Any major vascular event	0.79	0.77 to 0.81	Table 2, CTTC[79]

[a] Assumed RR = 1; see text, p. 50.

The CTTC findings suggest a highly significant 10% proportional reduction in major vascular events per mmol/l reduction in LDL-c during the first year and larger reductions (approximately 20–30% per mmol/l) during every successive year of treatment. However, in keeping with the conflicting evidence on the observed delay in benefits after commencing statin treatment,[185–187] no benefits are modelled in the first year of treatment. This is possibly a conservative assumption and the effect of varying the time delay in treatment effects is explored in sensitivity analyses.

It has been assumed that treatments have no impact on the RR of fatal Str. This assumption is based on both the results reported by the CTTC and the results of the recent meta-analysis of event rates in statin RCTs.[39] There have been conflicting reports on the differential effects of lipid-lowering therapies on Str and whereas the reported RR from the CTTC is used in the base case, the impact of modelling no benefits on Str or TIA is explored in sensitivity analyses.

It has also been assumed that the proportional reduction in event rate per mmol/l in LDL-c is generalisable to ezetimibe monotherapy and ezetimibe combination treatment with a statin. To our knowledge, there is no published evidence to support this assumption. As demonstrated in the literature on the benefits of fibrates, the relationship between changes in any lipids and CV events may be treatment specific. However, until the results from the long-term studies of ezetimibe emerge, the association between ezetimibe-induced changes in lipids and CV events remains unknown.

Benefits of treatments

The benefits of treatment regimens modelled are derived from published data on reductions in LDL-c (*Table 30*). The effectiveness of ezetimibe monotherapy and ezetimibe in combination with statin therapy is based on the meta-analyses in the section 'Results' (p. 19). It is assumed that statin titration of one dose provides an additional reduction of 6% based on published data.[67]

The evidence used in the meta-analysis for ezetimibe plus statin therapy is taken from studies which involved a washout period prior to commencing study treatments (*Figure 1*). As we are modelling ezetimibe as an 'add-on' treatment for patients who have not achieved an adequate response to statin monotherapy, an adjustment has been made to the effectiveness rates.

Looking at the example in *Figure 6* for first-line treatment:

- x = baseline LDL-c value after washout
- y = LDL-c value for statin arm at end of RCT
- z = LDL-c value for statin plus ezetimibe arm at end of RCT
- $\%S$ = percentage reduction in the statin monotherapy arm
- $\%ES$ = percentage reduction in the statin plus ezetimibe arm
- $\%E_i$ = additional percentage reduction due to ezetimibe treatment
- $\%E_a$ = additional percentage reduction due to ezetimibe treatment, adjusted for second-line.

Using the above example:

$\%S = (6 - 3.6)/6 = 40\%$; $\%ES = (6 - 2.7)/6 = 55\%$; incremental $E_i = 55 - 40\% = 15\%$

When assuming that y is achieved through statin monotherapy, then the incremental percentage reduction through ezetimibe 'add-on' treatment is

$\%E_a = (3.6 - 2.7)/3.6 = 25\%$

TABLE 30 *Treatment scenarios; mean change in LDL-c and annual costs*

Treatment regimen	Annual cost (£)	Adjusted mean % LDL-c change[a]	Source
Scenario 1			
(a) Ezetimibe 10 mg plus current weighted statin	493	–22.4	Meta-analysis
(b) Current weighted statin titrated by one dose	226	–9.5	Knopp[67]
Scenario 2			
(a) Ezetimibe 10 mg monotherapy	343	–18.56	Meta-analysis *Figure 1*
(b) No treatment	0	–	
Scenario 3			
(a) Ezetimibe 10 mg plus generic simvastatin 50% simvastatin 20 mg + 50% simvastatin 40 mg	386	–22.4	Meta-analysis
(b) More potent dose of atorvastatin 50% atorvastatin 20 mg + 50% atorvastatin 40 mg	344	–9.5	Knopp[67]
Scenario 4			
(a) Ezetimibe 10 mg plus current weighted statin	493	–22.4	Meta-analysis
(b) Current weighted statin	150	–	
Scenario 5			
(a) Ezetimibe 10 mg plus rosuvastatin 40 mg	730	–22.4	Meta-analysis
(b) Rosuvastatin 40 mg	387	–	
Scenario 6			
(a) Ezetimibe 10 mg plus current statin	Various (*Table 23*)	–22.4	Meta-analysis
(b) Same dose of a more potent statin		–9.5	Knopp[67]

[a] Mean percentage reduction in LDL-c. Weighted cost for current statin therapy is based on published prescribing rates for 2005.[43] The cost of titrated weighted statin is calculated by assuming that all individuals on 10 mg (20, 40 mg) will receive 20 mg (40, 80 mg). Those on the maximum doses remain constant. Individual treatment costs are provided in *Table 32*.

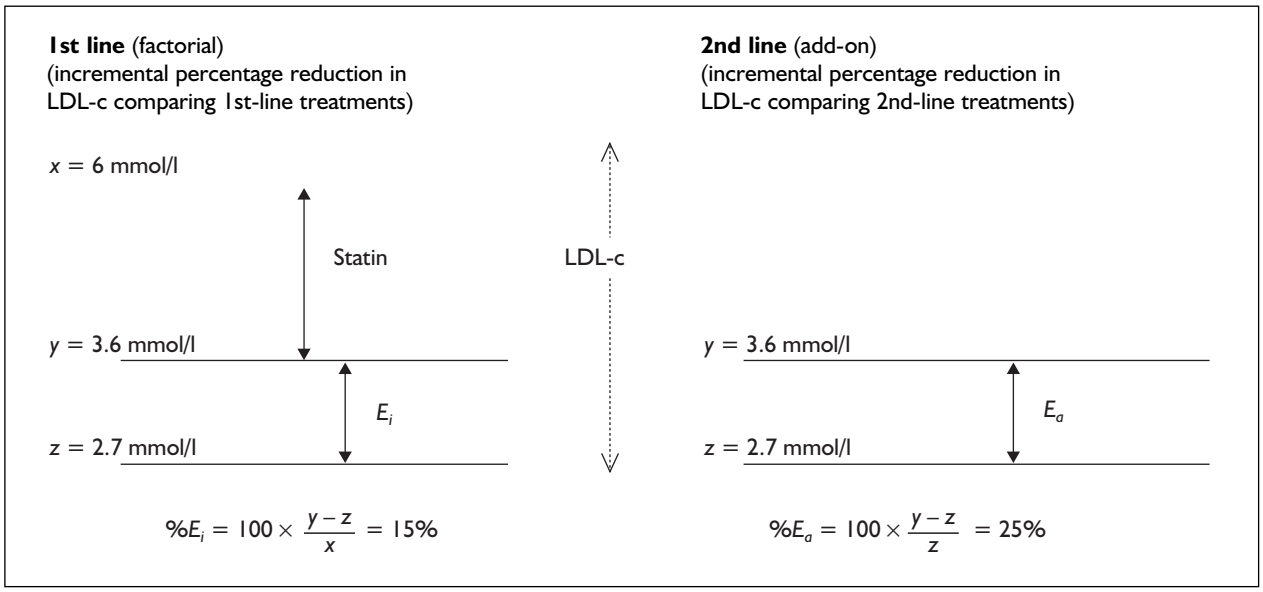


FIGURE 6 *Percentage decrease in LDL-c due to first- or second-line treatment*

Based on the ezetimibe RCT evidence, the baseline LDL-c is 4.65 mmol/l. Using the evidence from the statin arms in the ezetimibe trials, the mean LDL-c after statin monotherapy is 2.92 mmol/l. Using the evidence from the ezetimibe plus statin combination arms, the mean LDL-c after combination therapy is 2.27 mmol/l. Adjusting for the second-line treatment as in the above example, the percentage reduction due to 'adding on' ezetimibe is 22.4% [22.4% = (2.92 – 2.27)/2.92].

Assuming that titrating to the next highest dose of statin provides an additional 6% reduction in LDL-c, the additional benefit due to second-line statin treatment would be 9.5%. This is calculated using the evidence from the statin arms in the ezetimibe trials: baseline LDL-c is 4.65 mmol/l, the mean LDL-c after statin monotherapy (S_1) is 2.92 mmol/l, which equates to a percentage reduction of 36.5%. Assuming an additional 6% reduction for the follow-on statin the mean LDL-c after titration would be 2.65 mmol/l. Hence the percentage reduction for the second-line statin treatment would be 9.5% [9.5% = (2.92 – 2.65)/2.92].

Applying the benefits of treatments

The RR of an event is calculated by multiplying the baseline LDL-c by the percentage reduction in LDL-c to obtain an absolute reduction in LDL-c. The RR of an event is then calculated by multiplying the absolute reduction in LDL-c by the RR of the event.

Health states costs

A detailed review was undertaken to obtain the most recent and appropriate published evidence on costs for the different health states modelled (see Appendix 23) (*Table 31*). Published literature is sparse and, in general, the evidence used in the recent statin appraisal has been retained. Medication costs are taken from the August 2006 BNF,[188] costs for GP contact are taken from Curtis and Netten[189] and other costs are adjusted to 2006 using the Pay and Prices annual percentage increase (1.9%).[154] First year and subsequent year costs are assigned for each of the health states modelled.

Stable angina. The annual cost of stable angina is calculated considering only primary care support (patients are usually not hospitalised). It is assumed that each patient will visit the GP three times per annum for monitoring and prescribing of medication.[39] Additionally, it is assumed that 90% of these patients receive glyceryl trinitrate (GTN) spray, isosorbide mononitrate, one of verapamil, atenolol or diltiazem and aspirin. The estimated total cost per patient per annum of GP contact plus medication described above is £201.

Unstable angina. To calculate the first year annual cost of unstable angina, three assumptions are made: the medication costs are the same as stable angina, 60% of patients also receive clopidogrel and 50% of patients will be hospitalised. The total cost for the first year is estimated to be £477. It is assumed that the annual cost for subsequent years is the same as for stable angina.

Non-fatal MI. The non-fatal MI cost of year 1 is taken from Palmer and colleagues[190] (£4070) and inflated to 2006. This cost is derived from data in the Nottingham Heart Attack Register and provides an annual average cost estimated by aggregating the resources consumed by each patient in the cohort. It is assumed that only primary care is required in subsequent years, hence cost is the same as for stable angina.

Fatal MI. The cost of fatal MI is taken from Clarke and colleagues[155] (£1152) and inflated to 2006.

TIA. Although a TIA has no costs associated with the actual episode, after the event patients will have tests and continue on medication for the long term. It is assumed that the patient attends an outpatient visit and undergoes appropriate tests (including an ultrasound, computed tomography scan and an angiography); a small number of patients will also require an

TABLE 31 *Cost of health states in ScHARR cost-effectiveness model*

Health state	Cost (2006 £)	Assumption/source
Stable angina (year 1)	201	3 times 15 minutes GP contact plus medication costs
Stable angina (subsequent year)	201	3 times 15 minutes GP contact plus medication costs
Unstable angina (year 1)	477	As stable angina costs plus 60% of patients on clopidogrel
Unstable angina (subsequent year)	201	3 times 15 minutes GP contact plus medication costs
MI (year 1)	4934	Palmer *et al*., 2002[190] inflated to 2006 (£4457) + primary care and medication costs as unstable angina (£477)
MI (post-year 1)	201	3 times 15 minutes GP contact plus medication costs
MI (fatal event)	1261	Clarke *et al*., 2003[155] inflated to 2006
TIA (year 1)	1104	£1064 inflated to August 2006
TIA (subsequent year)	274	£264 inflated to August 2006
Str (year 1)	8070	Youman *et al*., 2003[191] weighted by severity and inflated to 2006
Str (subsequent year)	2169	Youman *et al*., 2003[191] weighted by severity and inflated to 2006
Str (fatal event)	7425	Youman *et al*., 2003[191] inflated to 2006

endartectomy. On average, the cost per patient in 2004 was calculated to be £800.[39] After a TIA, patients are assumed to undergo long-term medication which is a combination of aspirin, dipyridamole, an acetylcholinesterase inhibitor and a diuretic at an evaluated cost of £264.[39] First year costs are estimated to be £1104 (inflated to 2006), with the costs of each following year assumed to be £274 (inflated to 2006).

Non-fatal stroke. The costs of non-fatal Str for the first year are based on the costs of acute events taken from Youman and colleagues[191] weighted by the distribution of severity of Str. The costs of acute events are £5009 for mild Str, £4816 for moderate Str and £10,555 for severe Str. The cost of non-fatal Str for subsequent years is based on the costs of ongoing care at home (£326) or in an institution (£3872)[191] weighted by the distribution of severity of Str and discharge locations.

Fatal stroke. The cost of fatal Str is also taken from Youman and colleagues[191] (£6781) and inflated to 2006.

Treatment costs. Annual treatment costs (*Table 32*) are taken from the BNF. The proprietary tablet, ezetimibe 10 mg plus simvastatin 20 mg (40 mg), is not considered as the cost is higher than for ezetimibe plus a generic statin (e.g. ezetimibe plus generic simvastatin 40 mg = £30.54 whereas Inegy = £33.42 per 28-tablet pack). However, it should be noted that there would be a cost saving if the proprietary combination of ezetimibe plus simvastatin 80 mg (£41.21 per 28-tablet pack) was prescribed as opposed to ezetimibe plus a generic simvastatin 80 mg (£50.38 per 28-tablet pack).

Costs of monitoring. It is assumed that all patients receiving treatments have the following tests: a liver function test (£2.17) at baseline 3, 6 and 12 months, then annually thereafter, a cholesterol test (£2.17) at baseline 6 and 12 months, then annually thereafter. In addition, it is assumed that these patients receive a baseline creatinine kinase test (£1.66) with 10% of patients having additional annual tests. It is also assumed that tests are conducted by the practice nurse (£13 per visit). Based on the above, monitoring costs are £68.85 for the first year [(7 × £2.17) + (4 × £13) + £1.66] and £17.51 for subsequent years [(2 × £2.17) + £13 + (0.1 × £1.66)]. The costs for the practice nurse are taken from Curtis and Netten[189] and the costs for tests are taken from the NHS reference costs.[192]

HRQoL utility by health state

A literature review was undertaken to obtain the most recent and appropriate published evidence on preference-based utility measures for the different health states modelled (Appendix 22).

The studies identified were evaluated based on the following criteria:

- The population setting – UK studies were preferred to non-UK studies.
- Use of a preference based utility instrument – the EK-5D instrument is the recommended instrument.[172]

The utility values used are provided in *Table 33* and the sources are summarised below.

Stable angina. There is a dearth of preference-based utility evidence for individuals with stable angina. A recent study by Lenzen and colleagues exploring the HRQoL of patients diagnosed with CAD reported median (inter-quartile range) EQ-5D values of 0.85 (0.69 to 1.00) for individuals eligible for revascularisation (n = 3109) and 0.76 (0.62 to 1.00) for individuals ineligible for revascularisation (n = 504).[193] A US study collected QoL data in 387 patients with multivessel CAD and angina or documented ischaemia using the time trade-off method.[194] They found that patients with angina had a mean time trade-off score of 7.03 compared with a mean score of 8.7 in patients without angina. By adjusting the baseline score for individuals without angina to 1, the mean HRQoL for stable angina is estimated to be 0.808. It has been assumed that

TABLE 32 *Annual costs (£) of individual treatments*

Dose (mg)	Pravastatin generic	Simvastatin generic	Atorvastatin	Rosuvastatin	Ezetimibe
10	25.03	23.59	235.03	235.03	342.97
20	23.59	30.50	321.20	387.03	–
40	32.20	55.14	367.74	387.03	–
80	–	110.28	367.74	–	–

Source: BNF.org, accessed 15 February 2007.

patients with angina have a mean utility score of 0.808 during the first year after diagnosis and 0.90 in subsequent years.

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 General Hospital in Sheffield: suggest that the mean utility score measured using the EQ-5D at 6 months post-diagnosis of unstable angina was 0.77 (Goodacre S, Medical Care Research Unit, School of Health and Related Research, University of Sheffield: personal communication, November 2004).[195] Kim and colleagues report changes in HRQoL at 4 and 12 months in individuals (n = 1810) with unstable angina or non-ST-segment elevation MI who were randomised to either interventional or a conservative treatment strategy.[196] The mean EQ-5D in both cohorts increased from 0.748 and 0.714 at 4 months to 0.752 and 0.736 at 12 months. Again these results suggest that there may be a small increase in HRQoL over time. It has been assumed that 0.80 represents the long-term HRQoL associated with unstable angina and this has been decreased to 0.731 during the first year after diagnosis.

MI. The study by Goodacre and colleagues also collected EQ-5D data on individuals who had an MI and found the mean value to be 0.76.[195] A study (n = 222) by Lacey and Walters reported a change in mean EQ-5D from 0.683 at 6 weeks post-MI to 0.718 at 1 year post-MI.[197] It has been assumed that the mean utility in the first year after an MI is 0.700 based on Lacey and Walters' evidence whereas the mean utility in subsequent years after an MI is increased to 0.80 based on Goodacre and colleagues' data and clinical advice.

TIA. A German study by Haacke and colleagues, who explored the QoL in individuals 4 years post-diagnosis, reported an EQ-5D value of 0.90 for individuals (n = 18) with TIA.[198] However, the minimum age of the cohort was 50 years and it is assumed that the reduction from perfect health is more likely to be due to age than TIA. The HRQoL for individuals with TIA is assumed to be the same as the population norm[199] (Stevenson M, University of Sheffield: personal communication, 2007; Durrington P, Department of Medicine, University of Manchester: personal communication, October 2006).

Stroke. A meta-analysis of QoL estimates for Str combining 53 QoL estimates from 20 studies reported utility values of 0.87, 0.68 and 0.52 for mild, moderate and severe Str, respectively.[200] These results give a mean utility of 0.629 when weighted by the proportion (0.19 mild, 0.27 moderate, 0.54 severe) of newly diagnosed patients (n = 290,000) experiencing Str in a UK trial.[191] A Dutch study (n = 355) by Exel (2004) reported changes in QoL between 2 and 6 months after a Str using the EQ-5D.[201] The changes in QoL are different depending on the severity of the Str. For individuals (n = 138) who are independent (Barthel Index 20), utility increases from a mean of 0.76 to 0.81; for individuals (n = 155) with a mild or moderate Str (10 < Barthel Index < 20), utility decreases from a mean of 0.557 to 0.499; for individuals (n = 61) with severe or very severe Str (Barthel Index < 10), utility increases from a mean of –0.023 to 0.007. The weighted mean value remains unchanged at 0.536 and 0.535 at 2 and 6 months, respectively. A study by Leeds and colleagues compared long-term changes in HRQoL for individuals discharged to a care home (n = 43) as opposed to their own home (n = 50) using the EQ-5D.[202] They found that at 1 year after discharge, HRQoL had increased from mean 0.33 (SD = 0.26) to 0.35 (SD = 0.2) for those discharged to a care home and had increased from mean 0.46 (SD = 0.32) to 0.60 (SD = 0.30) for those discharged to their own home. A study (n = 98) by Pickard and colleagues reported an increase in mean EQ-5D from 0.31 (SD = 0.38) at baseline to 0.62 (SD = 0.33) at 6 months post-Str.[203] These figures suggest that there is an initial large reduction in HRQoL and that the long-term HRQoL, while substantially lower than before the Str, increases in the majority of individuals. It has been assumed that HRQoL in subsequent years is 0.629 whereas the utility in the first year after a Str is 0.50.

Subsequent major events. No evidence was found which could be used to model the impact on HRQoL for patients who have more than one CV event. It has been assumed that for second and third events an additional decrement of 10 and 15% will be applied, respectively, based on clinical advice (Durrington P, Department of Medicine, University of Manchester: personal communication, October 2006).

HRQoL utility by age

A study by Kind and colleagues[199] valued the utility by age in the UK general population (n = 3395) using the EQ-5D questionnaire and significant differences in HRQoL were found between age groups. Examples of the utility values modelled are provided in *Table 34*. It is acknowledged that by including a baseline utility

TABLE 33 *Health state HRQoL utilities*

Health state	1st year	Subsequent years	Reference (source)
Stable angina	0.808	0.90	193, 194 and clinical input from P Durrington
Unstable angina	0.731	0.80	195, 196 and clinical input from P Durrington
MI	0.700	0.80	195, 197 and clinical input from P Durrington
TIA	1.00	1.00	198 and clinical input from P Durrington
Str	0.50	0.629	200–203 and clinical input from P Durrington
2nd event	10% additional reduction	10% additional reduction	Clinical input from P Durrington
3rd event	15% additional reduction	15% additional reduction	Clinical input from P Durrington

TABLE 34 *Utility values by age*[199]

Age (years)	Utility[a]
45	0.869
50	0.848
55	0.826
60	0.805
65	0.784
70	0.763
75	0.741

[a] Utility = 1.060 – 0.004 × age.

adjusted for age there will be a small element of double counting as a proportion of individuals in the sample used in the Kind study will have a history of CVD. However, using the alternative of a constant utility of one across all ages would bias the results in favour of ezetimibe treatment. The overestimation of benefits would come from two sources: if a constant utility of one was used all patients remaining in the event free health state would accrue a larger health benefit than was appropriate. This would have a larger impact on the results for cohorts with no history of CVD where individuals commence in the event-free health state. In addition, few older patients will have a utility of one irrespective of CVD history. Consequently, any benefits achieved by events avoided in these patients should reflect their probable baseline utility. Using a baseline utility which varies by age is considered to be the more conservative alternative. A sensitivity analysis is conducted where baseline utility is set to one for all ages.

HRQoL disutility due to treatments

The short-term evidence available suggests that adverse events associated with ezetimibe are no more severe than those observed from other lipid-lowering treatments. It is possible that patients who are prescribed multi-drug therapies and those who are prescribed treatments for life will have a disutility associated with the treatment regimens. It is assumed that this disutility is small in comparison with the potential benefits received and no disutility due to the treatment regimens is modelled. However, there remains a degree of uncertainty associated with this assumption. Data from long-term studies are required to confirm the initial findings on both the rate and type of adverse events associated with ezetimibe monotherapy and combination therapy and the potential disutilities associated with multi-drug regimens.

Compliance

Compliance with treatment is required if target cholesterols are to be achieved. Although the literature has shown that the discontinuance rates during the first 5 years of lipid-lowering treatment can be as high as 50%,[204] the authors of a recent study on the issues and implications of switching statins state that 72% of patients nationally are to target and suggest that this may be due in part to tighter follow-up.[45] The impact on compliance rates of switching treatments, titrating doses and multi-drug therapies remains uncertain. There is no robust evidence to suggest that compliance with ezetimibe in combination with a statin would be any different to compliance with statin monotherapy. As the individuals are already receiving treatment at the start of the model, the impact of differing compliance rates for the treatment regimens compared is not modelled.

Mortality

To account for the proportion of patients dying from non-vascular causes, interim life tables published by the Government Actuary Department, available from: http//www.gad.gov.uk/ were used.[205]

Key modelling assumptions

The key modelling assumptions are discussed throughout the text and a summary is provided in Appendix 28.

Cost-effectiveness ratios

ICERs demonstrate the additional cost per QALY gained of treatment A versus treatment B:

$$\text{ICER} = \frac{\text{cost treatment A} - \text{cost treatment B}}{\text{utility treatment A} - \text{utility treatment B}}$$

Results

This section presents the results for cohorts of 1000 individuals. All analyses use a baseline LDL-c of 3.0 mmol/l, and are presented in terms of discounted incremental values unless stated otherwise. This is followed by a more detailed explanation and summary of the full set of results for each treatment scenario by age, gender and baseline LDL-c. The discounted costs and QALYs are provided in Appendix 29.

Results for Scenario 1: ezetimibe 10 mg plus current weighted statin versus current weighted statin titrated by one dose

The lifetime results for treatment Scenario 1 (*Table 35*) range from £24,000 per QALY to £42,000 per QALY for the secondary cohorts and from £24,000 per QALY for males aged 45 years with a baseline LDL-c of 3.5 mmol/l and no history of CVD to £62,000 per QALY for females aged 75 years with a baseline LDL-c of 2.5 mmol/l and no history of CVD.

Results for Scenario 2: ezetimibe monotherapy versus with no treatment

The ICERs for Scenario 2 (*Table 36*) decrease as the time horizon increases, as would be expected. Looking at the results for the 20-year horizon, the ICERs for the primary cohorts range from £34,000 per QALY for males aged 65 years to £60,000 per QALY for females aged 45 years. For the secondary prevention analyses, the results when using a 20-year time horizon are of a similar magnitude (32,000–38,000), with the exception of the younger age cohorts (aged 45 years), which are approximately £53,000 per QALY.

On using the lifetime horizon, the results for the primary cohorts are of a similar magnitude for cohorts under the age of 75 years (range 24,000–30,000 per QALY), while the ICERs for cohorts aged 75 years are higher at approximately £41,000 per QALY. The majority of lifetime ICERs for cohorts with a history of CVD are below £30,000 (range 26,000–34,000) per QALY.

TABLE 35 *Scenario 1, discounted ICERs (£000) on varying the baseline LDL-c value*

Age (years)	Primary			Secondary		
	Baseline LDL-c (mmol/l)					
	2.5	3.0	3.5	2.5	3.0	3.5
20-year horizon						
Male						
45	71.5	59.2	50.5	69.2	57.4	49.0
55	59.7	49.4	42.1	49.1	40.7	34.7
65	49.6	41.0	34.9	41.2	34.2	29.3
75	59.2	49.0	41.8	42.6	35.5	30.4
Female						
45	88.4	73.2	62.3	75.3	62.5	53.4
55	64.8	53.5	45.5	50.2	41.7	35.6
65	53.2	43.9	37.3	42.0	34.9	29.9
75	63.5	52.5	44.7	41.4	34.5	29.5
Lifetime horizon						
Male						
45	34.7	28.7	24.4	36.6	30.4	25.9
55	37.4	31.0	26.4	34.1	28.3	24.2
65	41.3	34.1	29.0	36.5	30.4	26.0
75	57.4	47.6	40.5	42.0	35.0	30.0
Female						
45	39.8	32.9	27.9	38.0	31.6	27.0
55	40.0	33.1	28.1	34.5	28.7	24.6
65	44.4	36.7	31.2	37.1	30.9	26.4
75	61.6	51.0	43.4	40.8	34.0	29.1

TABLE 36 *Scenario 2, discounted ICERs (£000) using different time horizons and a baseline LDL-c of 3.5 mmol/l*

Age (years)	Primary			Secondary		
	5 years[a]	20 years[a]	Life	5 years	20 years	Life
Male						
45	277.7	48.3	24.1	275.2	51.0	28.5
55	251.9	40.5	25.8	203.2	36.8	26.2
65	186.9	33.8	28.3	136.1	31.8	28.4
75	164.4	40.6	39.4	105.6	34.5	34.0
Female						
45	356.1	59.8	27.7	301.7	56.6	30.2
55	282.6	44.1	27.8	220.5	38.4	27.1
65	196.8	36.3	30.5	142.7	32.9	29.3
75	178.4	43.7	42.5	102.3	33.8	33.3

[a] Truncating the costs and benefits associated with events avoided at 5 and 20 years.

The incremental discounted costs (*Table 37*) increase as the time horizon increases, as would be expected as the cost offsets due to events avoided accrue over a longer period. The costs offsets for the lifetime horizons decrease as age increases, as events avoided in the older cohorts have less time to accrue benefits than those avoided in the younger cohorts. The incremental costs are of a similar magnitude when comparing primary and secondary cohorts of the same age.

The incremental QALYs (*Table 38*) increase as the time horizon increases, as would be expected. Looking at the QALYs accrued over a lifetime, the total incremental QALYs decrease steeply as age increases. This is because the younger cohorts have a longer opportunity to save additional events and an event saved at the age of 45 years accrues benefits over a longer period than one saved at the age of 75 years. The incremental QALYs for the 5-year horizons increase by age for the secondary analyses, reflecting the increased risk for older cohorts, whereas those for the primary cohorts do not increase as sharply, reflecting the similar starting risks of the cohorts modelled.

On comparing the lifetime primary and secondary QALY gain for cohorts of the same age group, the QALY gain in the primary analyses is larger than in the secondary analyses for the younger cohorts. The difference decreases as the starting age increases, reflecting both the time horizon over which the cohorts can accrue benefits and the difference in QALY gain from saving either a primary or a secondary event.

On varying the baseline LDL-c (*Table 39*), looking at the 20-year ICERs the results range from £28,000 per QALY for males aged 65 years with a history of CVD and a baseline LDL-c of 4.0 mmol/l to £70,000 per QALY for females aged

TABLE 37 *Scenario 2, discounted costs (£000) using different time horizons and a baseline LDL-c of 3.5 mmol/l*

Age (years)	Primary			Secondary		
	5 years	20 years	Life	5 years	20 years	Life
Male						
45	1553	4501	5948	1613	4654	6053
55	1538	4169	4946	1582	4184	4874
65	1491	3550	3810	1517	3492	3700
75	1410	2713	2742	1413	2590	2609
Female						
45	1562	4542	6088	1622	4732	6286
55	1541	4251	5084	1594	4356	5138
65	1497	3619	3888	1536	3635	3858
75	1401	2679	2707	1409	2611	2631

TABLE 38 *Scenario 2, discounted QALYs using different time horizons and a baseline LDL-c of 3.5 mmol/l*

Age (years)	Primary			Secondary		
	5 years	20 years	Life	5 years	20 years	Life
Male						
45	5.6	93.1	246.9	5.9	91.2	212.4
55	6.1	102.8	191.6	7.8	113.8	185.8
65	8.0	105.1	134.7	11.1	109.9	130.4
75	8.6	66.9	69.6	13.4	75.1	76.8
Female						
45	4.4	75.9	219.4	5.4	83.6	208.3
55	5.5	96.3	182.9	7.2	113.3	189.7
65	7.6	99.6	127.3	10.8	110.3	131.7
75	7.8	61.3	63.7	13.8	77.3	79.1

TABLE 39 *Scenario 2, discounted ICERs (£000) on varying the baseline LDL-c value*

Age (years)	Primary			Secondary		
	Baseline LDL-c (mmol/l)					
	3	3.5	4	3	3.5	4
20-year horizon						
Male						
45	56.9	48.3	42.0	59.9	51.0	44.4
55	47.7	40.5	35.1	43.1	36.8	32.0
65	39.8	33.8	29.2	37.3	31.8	27.6
75	47.8	40.6	35.2	40.4	34.5	30.0
Female						
45	70.4	59.8	51.9	66.4	56.6	49.2
55	52.0	44.1	38.2	45.1	38.4	33.4
65	42.9	36.3	31.4	38.6	32.9	28.7
75	51.6	43.7	37.8	39.6	33.8	29.4
Lifetime horizon						
Male						
45	28.4	24.1	20.9	33.5	28.5	24.8
55	30.4	25.8	22.4	30.8	26.2	22.8
65	33.4	28.3	24.5	33.3	28.4	24.7
75	46.4	39.4	34.2	39.8	34.0	29.6
Female						
45	32.7	27.7	24.0	35.4	30.2	26.3
55	32.8	27.8	24.0	31.8	27.1	23.6
65	36.1	30.5	26.4	34.3	29.3	25.5
75	50.1	42.5	36.8	39.0	33.3	29.0

45 years with no history of CVD (primary analyses) with a baseline LDL-c of 3.0 mmol/l.

Looking at the results when accruing costs and benefits over a lifetime, all ICERs for the secondary prevention analyses are below £40,000 (range 22,800–39,800) per QALY. The results for the cohorts with no history of CVD range from £21,000 per QALY for males aged 45 years with a baseline LDL-c of 4.0 mmol/l to £50,000 per QALY for females aged 75 years with a baseline LDL-c of 3.0 mmol/l.

This scenario is particularly informative for individuals who cannot tolerate statins. It is possible that their baseline LDL-c could be well above the 4.0 mmol/l value modelled. Further results were generated using higher baseline LDL-c levels. Plotting the lifetime ICERs against the baseline LDL-c (*Figures 7* and *8*), it is clear that

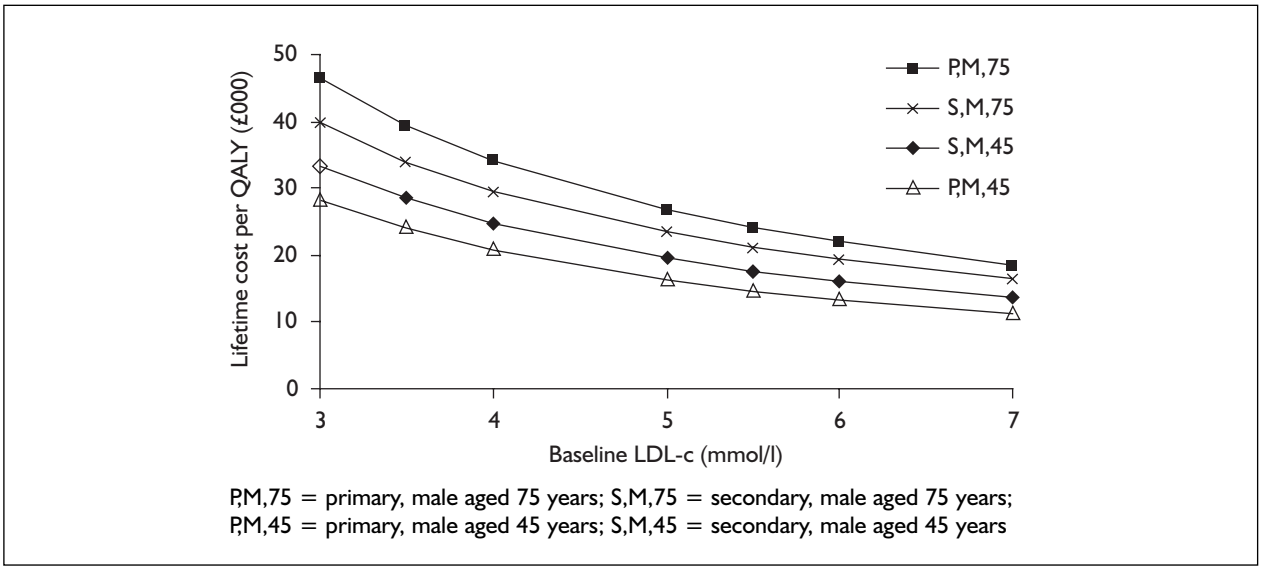


FIGURE 7 *Plotting the lifetime discounted ICERs for males against baseline LDL-c for Scenario 2 (ezetimibe versus no treatment)*

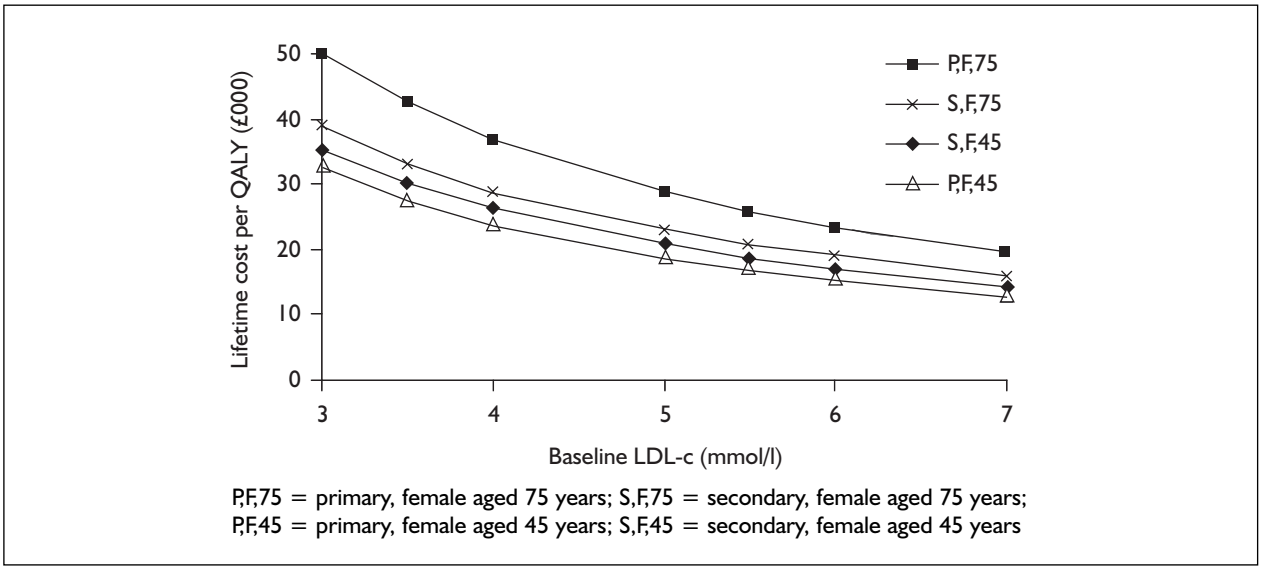


FIGURE 8 *Plotting the lifetime discounted ICERs for females against baseline LDL-c for Scenario 2 (ezetimibe versus no treatment)*

for individuals with baseline LDL-c greater than 5.0 (5.5) mmol/l, all results are below a threshold of £30,000 (£25,000) per QALY.

Univariate sensitivity analyses for Scenario 2

A series of sensitivity analyses (*Tables 40* and *41*) were performed to explore the impact on the results of changing values used to represent the key parameters. When looking at the ICERs for CHD events only (i.e. no RR applied to the non-fatal Str or TIA event rates), the ICERs increase, as would be expected as the potential to save benefits and costs is reduced. This sensitivity analysis has a larger impact on the results for the primary cohorts than the secondary cohorts. The 20-year horizon primary ICERs increase by 23% at the age of 45 years and increase by 67% at the age of 75 years. The impact on the secondary cohorts is smaller with results increasing by approximately 10–15%. Increases of a similar magnitude are seen in the lifetime ICERs. The large difference in the impact on the secondary and primary results is due to the difference in QoL gains from saving a primary Str compared with saving a secondary Str event due to the baseline HRQoL modelled for the different cohorts.

The results are sensitive to the changes in values used for the HRQoL. On increasing the QoL measures used for the health states by 10%, the

TABLE 40 *Scenario 2, discounted univariate ICERs (£000) for males with baseline LDL-c of 3.5 mmol/l using a lifetime horizon*

Value	Primary prevention				Secondary prevention			
Age (years)	45	55	65	75	45	55	65	75
Scenario 2	24.1	25.8	28.3	39.4	28.5	26.2	28.4	34.0
Discount rates for costs and utilities								
0%	16.9	19.3	22.8	33.5	20.7	20.4	23.6	29.7
Time lag for effectiveness of treatment								
0	22.9	24.2	25.6	33.5	27.1	24.5	25.4	28.6
2 years	25.4	27.7	31.4	47.0	30.1	28.2	32.0	41.2
Health state costs								
Plus 20%	23.8	25.4	27.8	38.8	28.3	26.1	28.2	33.7
Minus 20%	24.4	26.2	28.8	40.0	28.7	26.4	28.6	34.2
HRQoL utilities								
Plus 10%	26.6	28.1	30.4	42.3	26.2	24.0	26.1	31.1
Minus 10%	22.0	23.9	26.4	36.9	31.3	29.0	31.1	37.4
Constant utility by age	18.5	19.2	20.4	27.5	22.0	19.7	20.7	23.9
Constant utility by age plus 10% on health state utilities	20.3	20.8	21.9	29.5	20.3	18.0	19.0	21.8
Constant utility by age minus 10% on health state utilities	17.0	17.8	19.1	25.7	24.2	21.7	22.7	26.3
RR on events corresponding to reduction in LDL-c								
LCI	19.4	20.6	22.5	31.3	22.8	21.1	22.8	27.4
UCI	31.4	34.0	37.5	52.4	36.6	33.6	36.4	43.6
Effectiveness of ezetimibe treatment								
LCI	22.6	24.2	26.6	37.0	26.8	24.7	26.7	32.0
UCI	25.7	27.6	30.2	42.1	30.4	28.0	30.3	36.2
No RR on Str or TIA								
	31.6	37.1	43.7	65.7	31.6	29.0	32.5	39.2
Baseline LDL-c (mmol/l)								
3.0	28.4	30.4	33.4	46.4	33.5	30.8	33.3	39.8
4.0	20.9	22.4	24.5	34.2	24.8	22.8	24.7	29.6

LCI, lower CI; UCI, upper CI.

lifetime ICERs increase (decrease) by approximately 10% for the primary (secondary) analyses. Conversely, on decreasing the QoL measures used for the health states, the lifetime ICERs decrease (increase) by approximately 10% for the primary (secondary) analyses. When using a baseline utility of one as opposed to the utility adjusted by age, the ICERs decrease by approximately 30%. The difference is to be expected as by increasing the baseline utility to one, events saved gain more in terms of QoL than when using the utility adjusted by age. On increasing the QoL measures used for the health states and using a constant utility of one across all ages the results for the primary (secondary) analyses decrease by approximately 15–25% (30–35%). On decreasing the QoL measures used for the health states and using a constant utility of one across all ages, the results for the primary (secondary) analyses decrease by approximately 30–35% (15–30%).

The results are not sensitive to changes in health state costs. Using the CIs for the effectiveness rates for ezetimibe has little impact on the ICERs. However, when using the upper (lower) CIs for the RR of events corresponding to reductions in LDL-c, the ICERs increase (decrease) by 30% (20%). The ICERs decrease by approximately 20% when using no time lag for applying the RR of treatment effects.

Results for Scenario 3: ezetimibe plus generic simvastatin versus a more potent dose of atorvastatin (50% on 20 mg and 50% on 40 mg for each statin)

On varying the baseline LDL-c (*Table 42*), the ICERs for Scenario 3 are below £10,000 per QALY irrespective of time horizon (20 years or lifetime), age, gender or history of CVD.

Results for Scenario 4: ezetimibe plus average weighted statin versus average weighted statin

On comparing the treatment regimen ezetimibe 10 mg plus the weighted average statin versus the weighted average statin of the same dose (*Table 43*), the results for the lifetime horizon range from £18,700 per QALY for males aged 45 years with no history of CVD and a baseline LDL-c of 3.5 mmol/l to £47,300 per QALY for

TABLE 41 *Scenario 2, univariate discounted ICERs (£000) for males with a baseline LDL-c of 3.5 mmol/l using a 20-year horizon*

Value	Primary prevention				Secondary prevention			
Age (years)	45	55	65	75	45	55	65	75
Scenario 2	48.3	40.5	33.8	40.6	51.0	36.8	31.8	34.5
Discount rates for costs and utilities								
0%	41.5	34.3	28.7	34.9	44.0	31.3	27.5	30.4
Time lag for effectiveness of treatment								
0	43.9	36.7	30.1	34.4	46.6	33.4	28.0	28.9
2 years	53.7	45.0	38.3	48.6	56.6	40.8	36.4	42.0
Health state costs								
Plus 20%	47.7	39.9	33.2	39.9	50.6	36.4	31.5	34.2
Minus 20%	49.0	41.1	34.4	41.2	51.5	37.1	32.1	34.7
HRQoL utilities								
Plus 10%	59.0	46.5	37.0	43.7	47.1	33.7	29.3	31.6
Minus 10%	41.0	35.9	31.1	37.9	55.7	40.5	34.8	38.0
Constant utility by age	39.4	31.3	24.8	28.4	41.6	28.5	23.4	24.3
Constant utility by age plus 10% on health state utilities	48.0	35.9	27.1	30.5	38.4	26.1	21.6	22.2
Constant utility by age minus 10% on health state utilities	33.4	27.8	22.9	26.5	45.5	31.4	25.7	26.7
RR on events corresponding to reduction in LDL-c								
LCI	39.4	32.5	26.9	32.3	41.1	29.5	25.5	27.8
UCI	62.4	53.1	44.7	54.0	65.4	47.1	40.9	44.2
Effectiveness of ezetimibe treatment								
LCI	45.4	38.1	31.7	38.1	48.0	34.6	29.9	32.4
UCI	51.6	43.3	36.1	43.3	54.4	39.2	33.9	36.8
No RR on Str or TIA								
	59.6	56.3	51.6	67.7	56.5	40.3	36.3	39.8
Baseline LDL-c (mmol/l)								
3.0	56.9	47.7	39.8	47.8	59.9	43.1	37.3	40.4
4.0	42.0	35.1	29.2	35.2	44.4	32.0	27.6	30.0

females aged 75 years with no history of CVD and a baseline LDL-c of 2.5 mmol/l.

Results for Scenario 5: ezetimibe plus rosuvastatin 40 mg versus rosuvastatin 40 mg

As expected, the results for Scenario 5 (*Table 44*) are the same as those for Scenario 4 and the lifetime ICERs for the secondary cohorts range from £21,000 to £38,000 per QALY. The lifetime ICERs for the primary cohorts range from £19,000 per QALY for males aged 45 years with a baseline LDL-c of 3.5 mmol/l to £48,000 per QALY for females aged 75 years with a baseline LDL-c of 2.5 mmol/l. The results presented in *Table 44* can be used to illustrate the cost-effectiveness of ezetimibe plus a statin compared with the same statin.

Results for Scenario 6: ezetimibe co-administered with a statin compared with titrating to the same dose of a more potent statin

Looking at the possible treatment regimens in *Table 23* (p. 46), Scenario 6 can be split into two groups:

- Group A: higher incremental annual treatment costs include regimens 1–6
- Group B: lower incremental annual treatment costs include regimens 8–10.

Results for Scenario 6, regimen 1: ezetimibe co-administered with pravastatin 10 mg versus simvastatin 10 mg is used to represent the results for Group A (higher incremental annual treatment costs). The lifetime ICERs for regimen 1 (*Table 45*) range from £31,000 to £54,000 per QALY for cohorts with a history of CVD. The ICERs for the cohorts who have no history of CVD range from £32,000 per QALY for males aged 45 years with a baseline LDL-c of 3.5 mmol/l to £81,000 per QALY for females aged 75 years with a baseline LDL-c of 2.5 mmol/l.

Results for Scenario 6, regimen 10 (*Table 46*): ezetimibe co-administered with simvastatin 40 mg versus atorvastatin 40 mg are used to represent the results for Group B (lower incremental annual treatment costs). The ICERs for regimen 10 are all below £10,000 per QALY irrespective of horizon (20 years or lifetime) age, gender or CVD history.

Diabetic and HeFH cohorts

The analyses comparing ezetimibe monotherapy with no treatment for non-HeFH individuals

TABLE 42 *Scenario 3: discounted ICERs (£000) on varying the baseline LDL-c value*

Age (years)	Primary			Secondary		
	Baseline LDL-c (mmol/l)					
	2.5	3.0	3.5	2.5	3.0	3.5
20-year horizon						
Male						
45	5.0	3.7	2.8	9.3	7.5	6.1
55	4.0	2.9	2.1	6.8	5.5	4.6
65	3.2	2.3	1.6	6.0	4.9	4.1
75	4.1	3.0	2.2	6.6	5.5	4.6
Female						
45	6.0	4.3	3.2	10.3	8.3	6.9
55	4.0	2.8	1.9	7.0	5.6	4.7
65	3.2	2.2	1.4	6.3	5.2	4.4
75	4.2	2.9	2.1	6.3	5.3	4.5
Lifetime horizon						
Male						
45	2.8	2.1	1.6	5.6	4.6	3.9
55	2.9	2.1	1.6	5.3	4.4	3.7
65	2.9	2.1	1.5	5.6	4.6	4.0
75	4.1	3.0	2.2	6.5	5.4	4.6
Female						
45	3.0	2.2	1.6	5.9	4.9	4.2
55	2.9	2.1	1.5	5.4	4.5	3.9
65	3.0	2.1	1.5	5.9	4.9	4.2
75	4.1	2.9	2.1	6.3	5.2	4.5

TABLE 43 *Scenario 4: discounted ICERs (£000) on varying the baseline LDL-c value*

Age (years)	Primary			Secondary		
	Baseline LDL-c (mmol/l)					
	2.5	3.0	3.5	2.5	3.0	3.5
20-year horizon						
Male						
45	53.6	44.2	37.5	56.7	46.9	39.9
55	45.0	37.1	31.4	40.9	33.9	28.8
65	37.6	30.9	26.2	35.4	29.3	25.0
75	45.1	37.2	31.5	38.4	31.9	27.2
Female						
45	66.3	54.7	46.4	62.8	52.0	44.3
55	49.0	40.3	34.1	42.8	35.4	30.1
65	40.5	33.2	28.1	36.7	30.4	25.9
75	48.6	40.0	33.8	37.6	31.2	26.6
Lifetime horizon						
Male						
45	26.9	22.1	18.7	31.8	26.3	22.4
55	28.8	23.7	20.1	29.3	24.3	20.7
65	31.5	26.0	22.0	31.7	26.3	22.4
75	43.8	36.1	30.6	37.8	31.4	26.8
Female						
45	30.9	25.4	21.5	33.6	27.9	23.8
55	31.0	25.5	21.5	30.2	25.1	21.4
65	34.1	28.0	23.6	32.7	27.1	23.2
75	47.3	38.9	32.9	37.1	30.8	26.2

TABLE 44 *Scenario 5: discounted ICERs (£000) on varying the baseline LDL-c value*

Age (years)	Primary			Secondary		
	Baseline LDL-c (mmol/l)					
	2.5	3.0	3.5	2.5	3.0	3.5
20-year horizon						
Male						
45	53.7	44.4	37.7	56.9	47.1	40.1
55	45.2	37.3	31.6	41.2	34.1	29.1
65	37.8	31.2	26.4	35.7	29.6	25.3
75	45.4	37.4	31.8	38.8	32.2	27.5
Female						
45	66.4	54.8	46.5	63.0	52.2	44.5
55	49.2	40.5	34.3	43.0	35.6	30.4
65	40.7	33.4	28.3	37.0	30.7	26.2
75	48.9	40.3	34.1	38.0	31.6	27.0
Lifetime horizon						
Male						
45	27.1	22.3	19.0	32.1	26.6	22.7
55	29.0	23.9	20.3	29.6	24.6	21.0
65	31.8	26.2	22.2	32.0	26.6	22.7
75	44.1	36.4	30.9	38.2	31.8	27.2
Female						
45	31.1	25.6	21.7	33.9	28.2	24.1
55	31.2	25.7	21.8	30.5	25.4	21.7
65	34.3	28.2	23.9	33.0	27.5	23.5
75	47.5	39.2	33.2	37.4	31.1	26.6

TABLE 45 *Scenario 6, regimen 1 (ezetimibe 10 mg + pravastatin 10 mg vs simvastatin 10 mg): discounted ICERs (£000) on varying the baseline LDL-c value*

Age (years)	Primary			Secondary		
	Baseline LDL-c (mmol/l)					
	2.5	3.0	3.5	2.5	3.0	3.5
20-year horizon						
Male						
45	94.1	78.1	66.6	89.4	74.2	63.4
55	78.6	65.2	55.6	63.3	52.5	44.8
65	65.3	54.1	46.1	53.0	44.0	37.6
75	77.7	64.5	55.1	54.7	45.5	39.0
Female						
45	116.4	96.5	82.3	97.3	80.8	69.1
55	85.4	70.7	60.3	64.7	53.7	45.9
65	70.0	58.0	49.4	53.9	44.8	38.3
75	83.5	69.2	59.0	53.1	44.2	37.8
Lifetime horizon						
Male						
45	45.4	37.6	32.0	47.0	38.9	33.2
55	49.0	40.6	34.6	43.7	36.3	31.0
65	54.1	44.9	38.2	46.8	38.9	33.2
75	75.4	62.6	53.4	53.8	44.8	38.4
Female						
45	52.2	43.2	36.7	48.7	40.4	34.5
55	52.5	43.5	37.0	44.2	36.7	31.4
65	58.3	48.3	41.1	47.4	39.5	33.8
75	81.0	67.1	57.3	52.2	43.5	37.2

TABLE 46 *Scenario 6, regimen 10: (ezetimibe 10 mg + simvastatin 40 mg vs atorvastatin 40 mg): discounted ICERs (£000) on varying the baseline LDL-c value*

Age (years)	Primary			Secondary		
	Baseline LDL-c (mmol/l)					
	2.5	3.0	3.5	2.5	3.0	3.5
20-year horizon						
Male						
45	1.8	1.0	0.5	6.4	5.1	4.1
55	1.3	0.7	0.2	4.8	3.8	3.1
65	1.0	0.4	0.0	4.3	3.5	2.9
75	1.5	0.8	0.3	4.8	4.0	3.4
Female						
45	2.0	1.0	0.3	7.1	5.7	4.6
55	1.1	0.3	CS	4.9	3.9	3.2
65	0.8	0.2	CS	4.6	3.8	3.2
75	1.3	0.6	0.0	4.7	3.9	3.3
Lifetime horizon						
Male						
45	1.2	0.8	0.5	4.1	3.4	2.9
55	1.2	0.7	0.4	3.9	3.2	2.8
65	1.1	0.6	0.2	4.1	3.4	2.9
75	1.5	0.8	0.3	4.8	4.0	3.4
Female						
45	1.2	0.7	0.3	4.4	3.7	3.1
55	1.1	0.6	0.2	4.0	3.4	2.9
65	1.0	0.4	0.0	4.4	3.7	3.2
75	1.3	0.6	0.1	4.7	3.9	3.3

CS, cost saving.

demonstrate that for baseline LDL-c values >5.5 mmol/l, all ICERs are below £25,000 per QALY. Individuals with HeFH who do not tolerate statins will have very high baseline LDL-c levels (>5.5 mmol/l) and higher risks of events than the general population. If it is assumed that the observed percentage reduction in LDL-c due to ezetimibe monotherapy in non-HeFH individuals is also applicable for individuals with HeFH, then ezetimibe monotherapy is likely to be a cost-effective treatment for this cohort. Similarly, the baseline risk for diabetic patients will be higher than the baseline risk for non-diabetic individuals, hence the results suggest ezetimibe monotherapy is likely to be cost-effective in diabetic patients who have a very high baseline LDL-c level.

Discussion of results

Summary of key results

A summary of the key results is shown in *Table 47*. Although there is a wide range in the estimated ICERs, depending on the treatment strategies compared, the results suggest that ezetimibe could be a cost-effective treatment for some individuals.

On comparing ezetimibe monotherapy with no treatment (Scenario 2) in individuals with baseline LDL-c values of 3.0–4.0 mmol/l, the lifetime ICERs range from £21,000 to £50,000 per QALY. On looking at the costs and benefits accrued over a 20-year horizon, the results range from £28,000 to £79,000 per QALY. However, for individuals with baseline LDL-c values >5.0 mmol/l when using a threshold of £30,000 per QALY, all lifetime ICERs are cost-effective.

On comparing the costs and benefits of adding ezetimibe to ongoing statin treatment compared with maintaining statin treatment at the current dose (Scenarios 4 and 5), the lifetime ICERs range from £25,000 to £66,000 per QALY for the primary cohorts and from £19,000 to £48,000 per QALY for the secondary cohorts. Based on the evidence available, these results are representative of the cost-effectiveness of any statin co-administered with ezetimibe when compared with the same statin at the same dose and the majority of the ICERs are above values that are generally considered to be cost-effective.

TABLE 47 *Summary of key results (£000)*

Gender	20-year horizon		Lifetime horizon	
	Primary	**Secondary**	**Primary**	**Secondary**
Scenario 1, ezetimibe plus current weighted statin versus current weighted statin titrated by 1 dose				
Males	34.9–71.5	29.3–69.2	24.4–57.4	24.2–42.0
Females	37.3–88.4	29.5–75.3	27.9–61.6	24.6–40.8
Scenario 2, monotherapy versus no treatment				
Males	29.2–56.9	27.6–59.9	20.9–46.4	22.8–39.8
Females	31.4–70.4	28.7–66.4	24.0–50.1	23.6–39.0
Scenario 3, ezetimibe plus generic simvastatin versus a more potent dose of atorvastatin				
Males	1.6–5.0	4.1–9.3	1.5–4.1	3.7–6.5
Females	1.4–6.0	4.4–10.3	1.5–4.1	3.9–6.3
Scenarios 4 and 5, ezetimibe plus a statin versus the same statin with no titration				
Males	25.2–53.7	25.0–56.9	18.7–44.1	20.7–38.2
Females	28.1–66.4	25.9–63.0	21.5–47.5	21.4–37.4
Scenario 6, regimen 1, ezetimibe plus pravastatin 10 mg versus simvastatin 10 mg				
Males	46.1–94.1	37.6–89.4	32.0–75.4	31.0–53.8
Females	49.4–116	37.8–97.3	36.7–81.0	31.4–52.2
Scenario 6, regimen 10, ezetimibe plus a statin versus a more potent statin				
Males	<10		<5	
Females				

On comparing ezetimibe co-administered with current statin treatment with the alternative of switching to a more potent statin (Scenario 1, 3 or 6), the lifetime ICERs range from £14,000 to £116,000 per QALY. However, on comparing ezetimibe co-administered with generic simvastatin with a switch to a more potent statin (Scenario 3), the results are all cost-effective when using a threshold of £20,000 per QALY. Based on the evidence available, on comparing the costs and benefits associated with adding ezetimibe to ongoing statin with a switch to a more potent statin, the ICERs will be governed by the difference in the cost of the treatment regimens compared.

The analyses comparing ezetimibe monotherapy with no treatment for non-HeFH individuals demonstrate that for baseline LDL-c values of >5.5 mmol/l, all ICERs are below £25,000 per QALY. Individuals with HeFH who do not tolerate statins will have very high baseline LDL-c levels (>5.5 mmol/l) and a higher risk of events than the general population. If it is assumed that the observed percentage reduction in LDL-c due to ezetimibe monotherapy in non-HeFH individuals is also applicable for individuals with HeFH, then ezetimibe monotherapy is likely to be a cost-effective treatment for this cohort. Similarly, the baseline risk for diabetic patients will be higher than the baseline risk for non-diabetic individuals, hence the results suggest ezetimibe monotherapy is likely to be cost-effective in diabetic patients who have a very high baseline LDL-c level. Although the results give an approximation of the cost-effectiveness of ezetimibe in these cohorts, the model should be updated and new results generated when more accurate data become available.

The univariate sensitivity analyses suggest that the results are sensitive to changes in the parameters used to represent HRQoL. When using a baseline utility value of 1 as opposed to utility adjusted by age, the ICERs are reduced by approximately 30%. The results are robust to changes in health state costs. When using the upper (lower) CIs for the RR of events corresponding to reductions in LDL-c, the ICERs increase (decrease) by 30% (20%). The ICERs decrease when using no time lag for applying the RR of treatment effects.

Validity of results

Although it is reasonable to assume that individuals with high baseline LDL-c values could potentially gain more from lipid-lowering treatments, the analyses extrapolate beyond the evidence base used to derive the relationship between LDL-c and reductions in CVD events. Research to explore the validity of the relationship in subgroups with high LDL-c values is required to support the assumption used.

The majority of ICERs for the secondary cohorts are smaller than the corresponding ICERs for the primary cohorts of similar ages. However, there are some results where the ICERs suggest that it is more cost-effective to treat patients with no history of CVD. These results occur when using a starting age of 45 years (majority of treatment scenarios), and when comparing treatment regimens which have a relatively low incremental annual treatment costs (Scenario 3 and Group B of Scenario 6).

The life-years and QALYs for Scenario 2 are used to illustrate why the primary results can be lower than the secondary results for cohorts aged 45 years (Appendix 30). When using a 5-year horizon, the secondary cohorts aged 75 years accrue a larger number of incremental life-years (20.1) than the primary cohorts (6.7) of the same age, illustrating the difference in risk and distribution across event types. When accruing benefits over a lifetime, while the secondary cohorts still accrue a larger number of incremental life-years, the difference in gain has reduced (secondary cohorts gain 170.9 life-years whereas primary cohorts gain 112.8 life-years). Similar trends are seen in the results for cohorts aged 45 years, with secondary (primary) cohorts gaining 5.4 (2.2) and 657.9 (598.5) life-years over 5 years and a lifetime, respectively.

All individuals in the secondary analyses commence the model in a CVD health state with a disutility associated with the health state, while all individuals in the primary analyses commence the model in an event-free health state. Consequently, saving a primary event accrues more in terms of QALYs than saving a secondary event (Appendix 30). For an individual aged 45 years, the cumulative QALY gain from a primary fatal event is equivalent to the QALY gain from approximately 1.2 secondary fatal events. Likewise, the cumulative QALY gain from a primary non-fatal Str is equivalent to the QALY gain of up to 5.9 secondary non-fatal Str depending on CVD history (Appendix 30).

At younger ages (i.e. 45 years), the ratio of fatal to non-fatal events means that the majority of risk is attributed to the non-fatal events and therefore the majority of benefits are accrued through non-fatal events. The difference in the risk of primary and secondary fatal events increases as age increases, hence the cumulative impact of saving more fatal events in the secondary cohorts outweighs the differential gain of saving non-fatal events in the primary cohorts for the older age groups.

The difference in the annual treatment costs of the regimens being compared has a large impact on both the ICER and the differences in the primary and secondary prevention results. Treatment regimen 10 (ezetimibe plus generic simvastatin 40 mg versus atorvastatin 40 mg), which has a relatively small difference (£30.37) in the incremental annual treatment cost, and treatment regimen 1 (ezetimibe 10 mg plus pravastatin 10 mg versus simvastatin 10 mg), which has a relatively large difference (£344.40) in the incremental annual treatment cost, are used to illustrate why the primary cohorts have smaller ICERs than the secondary cohorts of the same age (Appendix 30).

Whereas the health state costs are much larger for the secondary cohort than the primary cohort, the cost offsets due to events avoided are larger for the primary cohorts. This is not unexpected as all individuals commence the secondary analyses with an ongoing cost associated with the disease. Saving a subsequent event in a secondary population is worth less than saving the same event in a primary population. Preventing a primary non-fatal Str at the age of 45 years accrues a maximum total cost saving of £103,506. In comparison, saving a secondary non-fatal Str at the age of 45 years accrues a maximum total cost saving of £94,461 reducing to £5091 for individuals with a previous Str.

When the incremental therapy costs are large, the difference in the cost offsets are absorbed resulting in ICERs that are larger for the secondary cohorts than the primary cohorts. However, when the incremental therapy costs are small, the total incremental costs for the primary cohorts are smaller than those for the secondary cohorts, resulting in ICERs which are smaller for the primary cohorts than for the secondary cohorts.

The results presented should be treated with caution as there are several key areas of uncertainty. Conservative decisions have been used throughout due to the number of assumptions used, the translation of changes in surrogate end-points into CV events and the length of extrapolation used.

Limitations of analysis

There are several major limitations associated with the economic evaluation. First, there is a lack of robust long-term data on clinical effectiveness evidence derived from patients who fail to achieve lipid goals on statin treatment or patients who are intolerant of statins. Second, the need to translate

changes in surrogate outcomes to reductions in CV events, and the need to extrapolate well beyond the RCT evidence underpin all analyses and increase the uncertainty in the results generated. Third, it is uncertain if the proportional reduction in event rates per mmol/l in LDL-c derived from patients receiving statin treatment is generalisable to patients receiving either ezetimibe monotherapy or ezetimibe in combination with a statin. Fourth, the lack of direct evidence of ezetimibe plus a low-dose statin versus a more potent dose statin increases the uncertainty associated with the effectiveness of the treatments. Fifth, whereas the short-term safety profile appears to be good, long-term adverse event data associated with ezetimibe monotherapy or ezetimibe combination treatment are not available. It is worth noting that if indirect costs such as productivity and informal care were included, the results would be substantially lower.

The data used for secondary event rates are derived from studies of cohorts with a history of CVD and there are very few data for individuals aged 45 years. Due to the predefined high risks (greater than 20% 10-year CVD risk) modelled for the primary cohorts, the transitions for the secondary event rates are adjusted to ensure that the risk of a secondary event is at least as large as the primary risk for each age. Published data for older age cohorts are also scarce and epidemiological and RCT evidence on these subgroups would reduce the uncertainty.

Published HRQoL data representing disutilities associated with the health states commonly used in CV evaluations are limited and the current evaluation uses several key assumptions to model the changes associated with events. In particular, evidence is required on differences in short- and long-term changes in HRQoL associated with individual events and any potential difference in HRQoL associated with primary or subsequent events. This research is required urgently to enable health economists to provide robust cost-effectiveness estimates for cardiovascular interventions.

Chapter 5

Assessment of factors relevant to the NHS and other parties

Impact on the NHS

The impact on the NHS budget is based on the cost of ezetimibe and the potential reduction in the number of CVD events in patients currently eligible for ezetimibe treatment, that is, those with clinical evidence of CHD, those with diabetes and those with a 10-year CVD risk ≥20%.

Number of patients currently treated with ezetimibe

Based on published prescribing data[206] in 2003, 3854 patients were prescribed with ezetimibe when it was made available in England and Wales (*Table 48*). In 2004, the number of patients prescribed with ezetimibe was 24,651, representing an increase of 20,797. An additional 32,309 patients received ezetimibe in 2005, which represents a growth rate of 55%. This rate is used to calculate the potential number of patients who would receive ezetimibe in 2006 (50,193). A similar increment is assumed for 2007, bringing the total number of patients to 157,346.

Budget impact

To determine the budget impact, three strategies are considered: ezetimibe co-administration with current statin, statin titration and ezetimibe monotherapy. It is assumed that approximately 20% (range 10–30%) of ezetimibe prescriptions are for monotherapy and 80% of prescriptions are for co-administration with a statin (Durrington P, Department of Medicine, University of Manchester: personal communication, October 2006).

The total gross cost of ezetimibe to the NHS in 2007 is estimated to be approximately £54.3 million. This represents an increment of £17.3 million compared with the estimated ezetimibe prescription cost of 2006 (£37.0 million). As mentioned above, it is assumed that an additional 50,193 patients (this is a conservative estimate) will receive ezetimibe by 2007; 20% of these patients will be prescribed ezetimibe monotherapy (10,039) and 80% will be on ezetimibe co-administration (40,154). *Table 49* shows the costs associated with each of the treatment strategies, ezetimibe co-administration, ezetimibe monotherapy and statin titration.

The current annual cost of ezetimibe is estimated to be £343 per patient, the weighted annual cost of statins is calculated as £150 and the total

TABLE 48 *Use and total annual cost of ezetimibe in England and Wales*[43,44]

	2003	2004	2005	2006
Number of patients	3,854	24,651	56,960	107,153
Net ingredient costs (£million)	1.72	11.25	26.33	37.00

TABLE 49 *Cost associated with ezetimibe prescriptions for the additional 50,193 patients*

	No. of patients	Treatment annual cost per patient (£)	Total annual cost (£million)	Total gross budget cost for ezetimibe (£million)	Total net budget cost for ezetimibe (£million)
Additional patients for 2007	50,193	343	17.2	17.2	
20% have ezetimibe monotherapy	10,039	343	3.4		
80% have ezetimibe co-administration	40,154	493	19.8	23.2	
80% have statin titration	40,154	226	9.0		14.2
Total patients for 2007	157,346	343		54.31	

current weighted annual cost of statin titration by one dose is estimated to be £226. The annual cost of managing an additional 40,154 patients with ezetimibe co-administration treatment is approximately £19.8 million whereas managing the same number of patients with statin titration is approximately £9.0 million. Therefore, the incremental cost for the ezetimibe co-administration strategy would be £10.7 million. Including the cost of ezetimibe monotherapy (£3.4 million), the total net budget cost for ezetimibe is estimated to be £14.2 million.

Reduction in the number of CVD events

The Health Survey for England 2003 data contain records with sufficient information to calculate a CVD risk level.[174] *Table 50* shows the mean LDL-c values obtained from the HSE in individuals with a ⩾20% 10-year CVD risk. These values are derived from very small samples and the results may not reflect an accurate measurement when broken down by age and gender, hence the estimates should be interpreted with caution. The CVD data from the survey were used to calculate the reduction in number of CVD events when the three treatment strategies mentioned above are applied.

The assumptions used to predict the reduction in the number of CVD events were as follows:

- The reduction in LDL-c for ezetimibe co-administered with statin is 13.94%.
- The reduction in LDL-c for ezetimibe monotherapy is 18.56%.
- The reduction in LDL-c for statin titration is 6%.[67]
- A reduction of 1 mmol/l in LDL-c is equivalent to a reduction of 21% in the number of CVD events.[79]

Table 51 shows the estimated percentage reduction in CVD events by age and gender for the different treatment strategies: ezetimibe co-administration, ezetimibe monotherapy and statin titration. The highest percentage reduction in CVD events for the three therapy strategies was estimated to be when managing male patients aged 45–54 years and female patients aged 65–74 years. This is due to the fact that in these cases the mean LDL-c levels are higher and therefore the absolute percentage LDL-c reduction will also be greater.

The difference in cost between managing ezetimibe co-administration and statin titration is approximately £14.2 million. This represents a large budget impact to the NHS. However, if the observed reductions in lipids translate to reductions in CV events, there is a large potential for these costs to be offset by the number of events avoided (*Table 51*).

TABLE 50 *LDL-c mean values by age and gender*[207]

Age (years)	LDL-c mean	
	Male	Female
45–54	4.41	3.29
55–64	3.71	3.79
65–74	3.34	4.33
75+	3.69	4.27

Other major issues impacting on the NHS

Uptake of ezetimibe prescribing rates

The current growth rate of prescribing rates for ezetimibe treatment is high. Whether prescribing rates will continue to grow at the current rate is unknown. It is likely that prescribing rates will be influenced by observed effectiveness in clinical practice, tolerability of multi-drug treatment regimens and evidence of effectiveness in reducing CV events. Prescribing rates are also likely to be influenced by Primary Care Trust (PCT) policies. Due to current and imminent restructuring of the health service, it is likely that budget constraints may influence PCT policies, but the effect that this may have on specific treatment regimens is unknown and may vary by region.

TABLE 51 *Estimated percentage reduction in CVD events by treatment strategy*

	Ezetimibe co-administration		Ezetimibe monotherapy		Statin titration	
Age (years)	Male	Female	Male	Female	Male	Female
45–54	12.91	9.64	17.19	12.83	5.56	4.15
55–64	10.86	11.10	14.45	14.78	4.67	4.78
65–74	9.77	12.69	13.01	16.89	4.20	5.46
75+	10.81	12.49	14.39	16.63	4.65	5.37

It has been estimated that 2.8 million individuals were prescribed statins in England and Wales in 2005.[43] Kirby and colleagues reported (based on data from QOF) that 72% of individuals who receive statin treatment achieve targets.[45] Hence it can be assumed that 784,000 patients (28%) may be eligible for ezetimibe treatment. Any changes in lipid goals could impact on the proportion of individuals not at target and hence the number of patients eligible for ezetimibe. Although the future uptake is unknown, if all eligible patients are prescribed ezetimibe the impact on the projected budget could be substantial.

Current and future lipid target levels

With increasing evidence from clinical trials suggesting that aggressive treatment of high cholesterol levels is preferable, there is a general move to lowering lipid targets with each subsequent recommendation and guideline. GPs are currently required to achieve a minimum rate of 60% of patients to target (QOF) and it is likely that this requirement could increase. A recently published report has suggested:

- Lower cholesterol targets could be recommended by 2007–8.
- GPs may be put under pressure to deliver more in terms of target achievements.
- Primary prevention may be introduced in a future GMS contract.

Although the majority of individuals achieve targets on current statin treatment, if targets are reduced further the number of patients eligible for ezetimibe will increase as more powerful statins or combination treatments will be required to achieve the lower targets.

Cost of other lipid-lowering treatments

Whereas the costs of the two generic statins simvastatin and pravastatin are still decreasing, the patent for atorvastatin does not expire until 2011, hence it is unlikely that the costs of the more potent statins will decrease substantially in the near future. However, when atorvastatin comes off patent and generic alternatives become available, this is likely to have a substantial impact on the prescribing rates for more potent statins. When this occurs, the cost of lipid treatments to the NHS is likely to reduce and the ICERs for lipid-lowering regimens involving ezetimibe will change.

Benefit of ezetimibe to individual patients

If the observed reductions in cholesterol do produce corresponding reductions in CV events, then the benefits to individual patients, particularly those who are intolerant of statins and those in whom statins are contraindicated, are potentially large. However, this must be weighed against the unknown long-term safety profile of ezetimibe both as a monotherapy and as a multi-drug lipid-lowering regimen. However, given the increase in adverse event rates and poorer tolerability of the more potent statins, the combination of ezetimibe with a lower dose statin could be a more favourable alternative.

Compliance rates with ezetimibe treatment are unknown and may be influenced by adverse events and tolerability. If target lipids are not achieved because of non-adherence to any treatment, ezetimibe therapy is unlikely to produce a large benefit in terms of lipid changes or reduction in CV events. If, however, targets are not met because of non-adherence to lipid treatment due to the adverse events associated with potent doses of statins, ezetimibe monotherapy or combination therapy with a less potent statin could produce substantial reductions in lipids and corresponding reductions in CV events.

Adding an additional treatment increases the monthly costs of medication to the individual patient. A large proportion of individuals eligible for ezetimibe treatment are asymptomatic younger (<60 years old) patients who will contribute to costs of medication through prescription charges. The cost of an additional medication prescribed for life may be a detriment to some and may increase non-compliance rates. The additional cost may produce a divide in the type of patients likely to be prescribed or to continue to take ezetimibe, with more affluent classes being more likely to adhere to treatments.

Chapter 6
Discussion

Statement of principal findings

Clinical effectiveness

Evidence from 13 short-term RCTs suggests that combination treatment of ezetimibe with statin provides significantly more benefit by reducing LDL-c level by 13.94% compared with statin monotherapy. In addition, ezetimibe monotherapy is associated with a significant decrease in LDL-c concentration of 18.56% compared with the placebo arm. There is no evidence that the LDL-c-lowering effect of ezetimibe differs across various patient subgroups such as women, the elderly and people with higher CVD risk factors. Although there are concerns regarding the relatively short periods of the studies, ezetimibe was generally considered to be well tolerated and the combination of ezetimibe plus a statin has a safety profile similar to that of a statin alone in the studies reviewed.

The evidence demonstrates the efficacy of ezetimibe in reducing LDL-c when administered as monotherapy and in combination with a statin. When used as monotherapy, ezetimibe's LDL-c-lowering ability is less than that of statins. However, ezetimibe has shown an additional LDL-c lowering effect when added to baseline statin therapy. The long-term efficacy and safety of ezetimibe alone or in combination with a statin are unknown. Effects on CV morbidity and mortality are also unknown.

Cost-effectiveness

Given the lack of detailed effectiveness data, there is a great deal of uncertainty in the cost-effectiveness of ezetimibe. The results suggest that depending on the comparator, ezetimibe could be a cost-effective treatment for diabetic patients, individuals with HeFH and those with high baseline LDL-c values.

The results generated are sensitive to changes in the parameters used to represent the relationship between reductions in LDL-c and events avoided. The results are also sensitive to changes in the effectiveness rates and the utility measures used. Due to a lack of detailed evidence on the effectiveness rates for ezetimibe co-administered with a statin compared with a more potent statin, the majority of results are governed by the costs of the treatment strategies being compared. Further research is urgently required to allow more precise estimates to be calculated.

Current ezetimibe prescribing is estimated to be around £37 million in 2006. It is estimated that approximately 50,000 additional patients will receive ezetimibe in 2007, incurring an incremental cost of approximately £14.2 million and bringing the estimated gross cost of ezetimibe to approximately £54.3 million in 2007.

Strengths and limitations of the assessment

Clinical effectiveness

The clinical effectiveness has several limitations, the foremost being the lack of RCT evidence for clinical outcomes. Trials reviewed in this report demonstrate the effectiveness of ezetimibe for surrogate outcomes only.

In terms of the methodology, all studies were described as being multi-centre, randomised trials, with treatment lasting for at least 12 weeks. Some important details of the randomisation method, such as allocation concealment, treatment allocation and assessment of blinding success, were omitted. However, power calculations and statistical analyses were considered to be adequate. Study groups were comparable at baseline and the overall likelihood of confounding bias was considered to be moderate to low.

There is insufficient evidence to demonstrate whether ezetimibe monotherapy and combination therapy differ in effectiveness in specific subgroups of patients, particularly those who are potentially more likely to benefit and require additional treatment to achieve target lipid levels, such as people with diabetes or HeFH.

It was not possible to differentiate the effectiveness between varying doses of different statins on the basis of the evidence; therefore, the statins were pooled across all doses and all types of statins and evaluated as a class drug. In particular, because of the complex administration, it was not possible to

establish in the titration studies how many patients reached the target LDL-c level at certain doses and how many were titrated to the next higher dose of statin.

No detailed information was given regarding the study population. It was not possible to establish whether the population was indeed intolerant or not adequately controlled by statin. Thus, most of the studies have not addressed the clinically important question of whether ezetimibe has incremental value when added in patients resistant to truly maximal statin treatment (i.e. 80 mg/day atorvastatin or a high dose of rosuvastatin).

Finally, the major limitation of the review was lack of data on key aspects of ezetimibe, that is, long-term information on safety and tolerability.

Cost-effectiveness

It is believed that a major strength of the economic evaluation is the use of UK-specific evidence used to generate transition rates and distribution of risks across events. A further strength is utilising the evidence from the CTTCs to translate the reductions in LDL-c to reductions in CVD risk as opposed to re-estimating changes in risk on an annual basis using the Anderson equations, which were not formulated to predict these changes.

The core limitation of the cost-effectiveness evaluation is the lack of RCT evidence on the effectiveness of ezetimibe in reducing CV events. Although the cost-effectiveness of ezetimibe monotherapy and combination therapy has been estimated using the available evidence on surrogate outcome measures, there remains a great deal of uncertainty surrounding the results.

The main areas of uncertainty are the relationship between ezetimibe-induced changes in lipids and reductions in CV events, extrapolating effectiveness rates well beyond RCT evidence and the generalisability of the short-term RCT effectiveness data into long-term effectiveness in reducing CV events in general clinical practice. An additional limitation is the lack of evidence on potential differences in effectiveness rates when combining ezetimibe with ongoing statin therapy.

An additional limitation is the lack of robust evidence which could be used to estimate cost-effectiveness results for subgroups who may potentially gain more benefit from ezetimibe treatment, such as those with higher than the norm baseline risk, which could include patients with diabetes, individuals with HeFH or ethnic subgroups such as South Asians.

Comparison of the results with other economic evaluations of ezetimibe treatment is not possible at present as the studies identified were all based on the Cook model. As described earlier, the reviewers do not consider that the results generated by the Cook model are robust owing to technical errors in the programming and several assumptions used in the modelling methodology. The Basic model submitted uses a similar methodology to that employed by the ScHARR analysts in that it bases effectiveness of treatments on published links between LDL-c reductions and CV risk. The results generated by this model are comparable to those generated by the ScHARR model, but the simplifying assumptions and the limited number of analyses reported make direct comparison difficult.

Uncertainties

The main area of clinical uncertainty concerns the association between the ezetimibe-induced reductions in LDL-c observed in the short-term RCTs and corresponding reductions in CV events. The long-term safety and adverse event profile, particularly when taken in combination with other treatments, is also unknown. The treatment effect in different populations, in particular those who have not achieved lipid targets on optimal statin, treatment or those who cannot tolerate statins is also uncertain. There are also limited data to confirm that the observed effectiveness of ezetimibe in the clinical trials transfers to produce corresponding reductions in lipids when prescribed in clinical practice. The proportion of individuals who are willing to switch from monotherapy to multi-drug therapies is unknown, and the associated impact on compliance to treatment when prescribing multi-lipid-lowering therapies for life is unknown.

All the above impact on the assumptions required to produce results from economic evaluations. As discussed elsewhere in the report, the three pivotal areas of uncertainty in the economic modelling are the assumption that changes in surrogate outcomes will provide corresponding reductions in CV events, the assumption that extremely short-term reductions in LDL-c levels will be maintained over very long time horizons and the lack of evidence on potential differences in effectiveness rates for different treatment strategies.

Other relevant factors

The majority of effectiveness from statins is gained from the initial dose, with each dose titration providing an approximate additional 6% reduction in LDL-c. Although guidelines for initiation of statin therapy recommend that treatment is prescribed based on the lowest acquisition cost, individuals may not achieve targets on this strategy. If the presenting baseline lipid profile is high, the initial statin dose may need titrating to achieve target levels.

The GMS contract currently provides an incentive for general practice to achieve targets which appears to be successful with 72% of CHD patients in the UK having Total-c measurements under 5.0 mmol/l.[45] Minor changes in this contract are expected, such as an increase in the expected percentage of patients to target (current = 60%). However, the expected restructuring of general practice organisation and PCTs could have a larger impact on the prescribing rates as it is expected that GPs will be encouraged to take responsibility for their total budget.[45] In addition, if blanket treatment policies are used, it has been suggested this could breach government agendas on patient choice and involvement.[45]

Chapter 7
Conclusions

The short-term RCT clinical evidence demonstrated that ezetimibe was effective in reducing LDL-c when administered as monotherapy or in combination with a statin. An additional LDL-c-lowering effect has been shown when ezetimibe is added to baseline statin therapy.

Given the lack of detailed effectiveness data, there is a great deal of uncertainty in the cost-effectiveness of ezetimibe. The results suggest that depending on the comparator, ezetimibe could be a cost-effective treatment for individuals with high baseline LDL-c values, for diabetic patients and for individuals with HeFH. Further research is urgently required to allow more precise estimates of cost-effectiveness to be calculated.

Implications for service provision

The growth rate on prescribing data for ezetimibe is increasing. Assuming that the current safety profile is maintained, there is no reason to suggest that the observed growth rate will not continue at least in the near future. There are no published data that suggest that clinicians are monitoring patients more closely when prescribing ezetimibe than when switching to any other lipid-lowering treatment or titrating to a more potent dose of statin. However, clinicians may increase the monitoring schedule offered to patients in comparison with that for other therapies until long-term data on ezetimibe emerges. However, if the observed reductions in LDL-c translate to reductions in CV events, the number of individuals requiring hospitalisation and specialist treatments should decrease.

Suggested research priorities

Clinical effectiveness

The most urgent need is for further research into the clinical effectiveness of ezetimibe in reducing CV events. There are currently three ongoing studies which should emerge in 2–4 years which will provide these data. Additional research into subgroup analyses in populations who are potentially more likely to benefit from the treatment are patients with diabetes, individuals with HeFH and ethnic minorities with higher baseline CHD/CVD risks such as South Asians.

There is also a need for the future research to produce the following:

- evidence on effectiveness, safety and tolerability of co-administration of ezetimibe with other lipid-lowering drugs
- evidence on effectiveness in patients who are on the treatment but have not reached target levels
- evidence of effectiveness in patients with very high baseline levels of plasma cholesterol
- long-term adverse events.

Cost-effectiveness

In addition to evidence on the effectiveness of ezetimibe in reducing CV events, robust evidence is required on the safety and adverse event profile of ezetimibe both as monotherapy and as combination therapy with both statins and other lipid lowering treatments. If ezetimibe reacts unfavourably with any of the lipid-lowering treatments currently prescribed, the costs and disutilities associated with the adverse events could alter the ICERs, particularly if the events are severe. Conversely, ezetimibe co-administered with a low-dose statin could have a better safety profile than the more potent statins.

Large outcome studies powered to identify differences in rates of CV events in subgroups would be useful to inform on the cost-effectiveness of treatment regimens for different subgroups. Studies exploring effectiveness in primary prevention, secondary prevention, diabetic patients, individuals with high baseline lipids and those with higher than normal risk by age such as South Asians would be particularly useful to inform future economic evaluations. In addition, studies recruiting individuals who are representative of the target populations, that is, individuals who do not achieve target levels on optimal statin treatment, and individuals in whom statins are contraindicated and those in whom statins are not tolerated would also be beneficial. Research on the attitudes of GPs to prescribing multi-drug therapies and on patients to switching to multi-drug therapies for life is also required.

Modelling the cost-effectiveness of treatments when only surrogate outcomes are available and extrapolating effectiveness data well beyond the evidence base increase the uncertainty surrounding the results of the evaluations. As such, the results presented should be interpreted with caution. The cost-effectiveness of ezetimibe should be re-evaluated when evidence becomes available on the effectiveness in reducing CV events.

To inform future economic evaluations, long-term RCT evidence of the safety profile of ezetimibe when prescribed as either monotherapy or combination therapy is required, particularly when combined with higher dose statins and lipid-lowering treatments generally prescribed to individuals in whom statins are contraindicated. Studies exploring the effectiveness of ezetimibe in the target population, that is, those not at target on current therapies, are also required, as is evidence of differential effectiveness in different subgroup populations, for example those with HeFH.

This review has been conducted at an early stage of ezetimibe's development. As a consequence the evidence available is limited. Both the clinical effectiveness and cost-effectiveness review will require updating as and when further evidence from clinical studies and clinical practice emerges.

Acknowledgements

Our thanks are due to Professor Paul Durrington, Professor of Medicine, University of Manchester, Professor David Wood, Garfield Weston Chair of Cardiovascular Medicine, Imperial College London, and Dr Wilf Yeo, Consultant Physician and Senior Lecturer in Clinical Pharmacology and Therapeutics, Royal Hallamshire Hospital, who provided clinical advice on this project. Thanks are also due to Dr Evan Stein, Director of the Metabolic and Atherosclerosis Research Center, Cincinnati, OH, USA, who provided additional data. We would also like to extend our thanks to Ms Rachel German for assistance in the use of the innovative problem structuring techniques employed in the cost-effectiveness review.

Andrea Shippam, Project Administrator, ScHARR, is also thanked for her help in the retrieval of papers and help in preparing and formatting the report.

This report was commissioned by the NHS R&D HTA Programme on behalf of the National Institute for Health and Clinical Excellence. The views expressed in this report are those of the authors and not necessarily those of the NHS R&D HTA Programme or the National Institute for Health and Clinical Excellence. The final report and any errors remain the responsibility of the University of Sheffield. Jim Chilcott and Eva Kaltenthaler, ScHARR, are guarantors.

Contribution of authors

Abdullah Pandor (Research Fellow) and Indra Tumur (Research Fellow) carried out the review of the background information and the clinical effectiveness review. Roberta Ara (Operational Research Analyst), Alejandra Duenas (Research Associate), Robert Williams (Placement Student) and Jim Chilcott (Technical Director, ScHARR TAG) carried out the cost-effectiveness review. Anna Wilkinson (Information Officer) and Suzy Paisley (Research Scientist) undertook the electronic literature searches. Suzy Paisley and Jim Chilcott investigated the role of problem structuring methods in the assessment.

References

1. Allender S, Peto V, Scarborough P, Boxer A, Rayner M. *Coronary heart disease statistics 2006 edition*. Oxford: British Heart Foundation Health Promotion Research Group, Department of Public Health, University of Oxford; 2006.
2. Peterson S, Peto V, Rayner M, Leal J, Luengo-Fernandez J, Gray A. *European cardiovascular disease statistics 2005 edition*. Oxford: British Heart Foundation; 2005.
3. British Cardiac Society, British Hypertension Society, Diabetes UK, HEART UK, Primary Care Cardiovascular Society, Stroke Association. JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. *Heart* 2005;**91**:v1–52.
4. Pullinger CR, Kane JP, Mallo MJ. Primary hypercholesterolemia: genetic causes and treatment of five monogenic disorders. *Expert Rev Cardiovasc Ther* 2003;**1**:107–19.
5. Durrington P. Dyslipidaemia. *Lancet* 2003;**362**: 717–31.
6. Reckless J, Morrell J. *Lipid disorders – your questions answered*. London: Elsevier; 2005
7. Thompson G, Morrell J, Wilson P. *Dyslipidaemia in clinical practice*. 2nd ed. Oxford: Oxford Informa Healthcare; 2006.
8. Durrington PN. *Hyperlipidaemia: diagnosis and management*. 2nd ed. Oxford: Butterworth-Heinemann; 1995.
9. NHS Centre for Reviews and Dissemination. Cholesterol and coronary heart disease: screening and treatment. *Effective Health Care Bull* 1998;**4**: 1–16.
10. Primatesta P, Poulter NR. Levels of dyslipidaemia and improvement in its management in England: results from the Health Survey for England 2003. *Clin Endocrinol* 2006;**64**:292–8.
11. World Health Organization. *Reducing risks, promoting healthy life*. The World Health Report 2002. Geneva: World Health Organization; 2002.
12. Joint Health Surveys Unit. *Health survey for England 2003: volume 2. Risk factors for cardiovascular disease*. London: The Stationery Office; 2004.
13 Joint Health Surveys Unit. *Health survey for England – the health of minority ethnic groups, 1999*. London: The Stationery Office; 2000.
14. Blake GH, Triplett LC, Blake GH, Triplett LC. Management of hypercholesterolemia. *Am Fam Physician* 2005;**51**:1157–66.
15. Rader DJ, Cohen J, Hobbs HH. Monogenic hypercholesterolemia: new insights in pathogenesis and treatment. *J Clin Invest* 2003;**111**:1795–803.
16. Bild DE, Williams RR, Brewer HB, Herd JA, Pearson TA, Stein E. Identification and management of heterozygous familial hypercholesterolaemia: summary and recommendations from NHLBI Workshop. *Am J Cardiol* 1993;**72**:1D–5D.
17. Civeira F, Pocovi M, Alegria E, Alonso R, Carmena R, Casasnovas JA, *et al*. Guidelines for the diagnosis and management of heterozygous familial hypercholesterolemia. *Atherosclerosis* 2004;**173**:55–68.
18. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;**106**:3143–421
19. Marks D, Thorogood M, Neil HAW, Humphries SE. A review on the diagnosis, natural history, and treatment of familial hypercholesterolaemia. *Atherosclerosis* 2003;**168**:1–14.
20. British Heart Foundation. *What part does cholesterol play in coronary heart disease?* URL: http://www.bhf.org.uk/hearthealth/index.asp?secID=1&secondlevel=78&thirdlevel=166&artID=443. Accessed 16 October 2006.
21. McPherson K, Britton A, Causer L. *CHD: estimating the impact of changes in risk factors*. London: National Heart Forum; 2002.
22. Lloyd-Jones DM, Wilson PW, Larson MG, Leip E, Beiser A, D'Agostino RB, *et al*. Lifetime risk of coronary heart disease by cholesterol levels at selected ages. *Arch Intern Med* 2003;**163**:1966–72.
23. Magnus P, Beaglehole R. The real contribution of the major risk factors to the coronary epidemics: time to end the "only-50%" myth. *Arch Intern Med* 2001;**161**:2657–60.
24. Luengo-Fernandez R, Leal J, Gray A, Petersen S, Rayner M. Cost of cardiovascular diseases in the United Kingdom. *Heart* 2006;**92**:1384–9.

25. Isles CG, Paterson JR. Identifying patients at risk for coronary heart disease: implications from trials of lipid-lowering drug therapy. *QJM* 2000;**93**: 567–74.

26. The Canadian Coordinating Office for Health Technology Assessment. Ezetimibe for lowering blood cholesterol. *Issues Emerg Health Technol* 2003;**49**:1–40.

27. Department of Health National Service Framework for Coronary Heart Disease. *Modern standards and service models*. London: Department of Health; 2000.

28. National Assembly for Wales. *Tackling CHD in Wales: implementing through evidence*. Cardiff: National Assembly for Wales; 2001.

29. Scottish Intercollegiate Guidelines Network (SIGN). *Lipids and the primary prevention of coronary heart disease. A national clinical guideline*. SIGN publication no. 40. Edinburgh: SIGN; 1999.

30. Scottish Intercollegiate Guidelines Network (SIGN). *Secondary prevention of coronary heart disease following myocardial infarction: a national clinical guideline*. SIGN publication no. 41. Edinburgh: SIGN; 2000.

31. Clinical Resource Efficiency Support Team (CREST). *Guidelines on the use of lipid lowering drugs*. Belfast: CREST; 2000.

32. British Medical Association (BMA). *Revisions to the GMS contract, 2006/07 – delivering investment in general practice*. London: BMA; 2006.

33. Grundy SM, Cleeman JI, Bairey Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, *et al*. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Arterioscler Thromb Vasc Biol* 2004;**24**:149–61.

34. Migoya EM, Bergman A, Hreniuk D, Matthews N, Yi B, Roadcap B, *et al*. Bioequivalence of an ezetimibe/simvastatin combination tablet and coadministration of ezetimibe and simvastatin as separate tablets in healthy subjects. *Int J Clin Pharmacol Ther* 2006;**44**:83–92.

35. De Backer G, Ambrosioni E, Borch-Johnsen K, Brotons C, Cifkova R, Dallongeville J, *et al*. *European guidelines on cardiovascular disease prevention in clinical practice*. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. *Eur Heart J* 2003;**24**:1601–10.

36. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;**106**:3143–21.

37. Edwards JE, Moore RA. Statins in hypercholesterolaemia: a dose-specific meta-analysis of lipid changes in randomised, double blind trials. *BMC Fam Pract* 2003;**4**:18.

38. Joint Formulary Committee. *British National Formulary*. 52nd. London: British Medical Association and Royal Pharmaceutical Society of Great Britain; 2006.

39. National Institute for Health and Clinical Excellence (NICE). *Statins for the prevention of cardiovascular events*. Technology Appraisal 94. London: NICE; 2006.

40. Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults and Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 2001;**285**: 2486–97.

41. Williams, H. Dyslipidaemia – drug treatment. *Hosp Pharm* 2005;**12**:177–81.

42. Williams H, Stevens M. Heart disease: (7) cholesterol control. *Pharma J* 2003;**270**:688–90.

43. Health and Social Care Information Centre. *Prescription cost analysis 2005*. URL: http://www.ic.nhs.uk/pubs/prescostanalysis2005. Accessed 9 October 2006.

44. Welsh Assembly Government. *Prescriptions dispensed in the community in Wales, 2000 to 2005 and prescription cost analysis (PCA) data*. URL: http://new.wales.gov.uk/topics/statistics/headlines/health-2006/hdw20060518/?lang=en. Accessed 9 October 2006.

45. Kirby M, Davis M, Drummond M, Findlay S, Schachter M, Adiseshiah M, *et al*. Switching statins: what are the issues and implications. *Br J Cardiol* 2006;**13**:S1–S12.

46. Walley T, Folino-Gallo P, Stephens P, Van Ganse E, EuroMedStat Group. Trends in prescribing and utilization of statins and other lipid lowering drugs across Europe. *Br J Clin Pharmacol* 2005;**60**:543–51.

47. Walley T, Folino-Gallo P, Schwabe U, Van Ganse E, EuroMedStat Group. Variations and increase in use of statins across Europe: data from administrative databases. *BMJ* 2004;**328**:385–6.

48. Majeed A, Moser K, Maxwell R. Age, sex and practice variations in the use of statins in general practice in England and Wales. *J Public Health Med* 2000;**22**:275–9.

49. Stocks NP, Ryan P, McElroy H, Allan J. Statin prescribing in Australia: socioeconomic and sex differences. A cross-sectional study. *Med J Aust* 2004;**180**:229–31.

50. Baxter C, Jones R, Corr L. Time trend analysis and variations in prescribing lipid lowering drugs in general practice. *BMJ* 1998;**317**:1134–5.

51. Packham C, Robinson J, Morris J, Richards C, Marks P, Gray D. Statin prescribing in Nottingham general practices: a cross-sectional study. *J Public Health Med* 1999;**21**:60–4.

52. Packham C, Pearson J, Robinson J, Gray D. Use of statins in general practices, 1996–8: cross sectional study. *BMJ* 2000;**320**:1583–4.

53. Danchin N, Grenier O, Ferrieres J, Cantet C, Cambou JP. Use of secondary preventive drugs in patients with acute coronary syndromes treated medically or with coronary angioplasty: results from the nationwide French PREVENIR survey. *Heart* 2002;**88**:159–62.

54. Hippisley-Cox J, Pringle M, Crown N, Meal A, Wynn A. Sex inequalities in ischaemic heart disease in general practice: cross sectional survey. *BMJ* 2001;**322**:832–4.

55. Reid FDA, Cook DG, Whincup PH. Use of statins in the secondary prevention of coronary heart disease: is treatment equitable? *Heart* 2002;**88**: 15–19.

56. Primatesta P, Poulter NR. Lipid concentrations and the use of lipid lowering drugs: evidence from a national cross sectional survey. *BMJ* 2000;**321**: 1322–5.

57. Patel MG, Wright DJ, Gill PS, Jerwood D, Silcock J, Chrystyn, H. Prescribing of lipid lowering drugs to South Asian patients: ecological study. *BMJ* 2002;**325**:25–26.

58. Gibson A, Asthana S, Brigham P, Moon G, Dicker J. Geographies of need and the new NHS: methodological issues in the definition and measurement of the health needs of local populations. *Health Place* 2002;**8**:47–60.

59. De Lusignan S, Hague N, Belsey J, Dhoul N, van Vlymen J. The 'rule of halves' still applies to the management of cholesterol in cardiovascular disease: 2002–2005. *Br J Cardiol* 2006;**13**:145–53.

60. Evans PH, Luthra M, Pike C, Round A, Salzmann M. NSF lipid targets in patients with CHD: are they achievable in a real-life primary care setting? *Br J Cardiol* 2004;**11**:71–4.

61. Hippisley-Cox J, Cater R, Pringle M, Coupland C. Cross-sectional survey of effectiveness of lipid lowering drugs in reducing serum cholesterol concentration in patients in 17 general practices. *BMJ* 2003:**326**:689–93.

62. Patel JV, Kirby M, Hughes EA. The lipid audit: analysis of lipid management in two centres in Britain 2003. *Br J Cardiol* 2004;**11**:214–17.

63. Whincup PH, Emberson JR, Lennon L, Walker M, Papacosta O, Thomson A. Low prevalence of lipid lowering drug use in older men with established coronary heart disease. *Heart* 2002;**88**:25–9.

64. Brady AJB, Norrie J, Ford I. Statin prescribing: is the reality meeting the expectations of primary care? *Br J Cardiol* 2005;**12**:397–400.

65. Baessler A, Fischer M, Huf V, Mell S, Hengstenberg C, Mayer B, *et al*. Failure to achieve recommended LDL cholesterol levels by suboptimal statin therapy relates to elevated cardiac event rates. *Int J Cardiol* 2005;**101**:293–8.

66. Frolkis JP, Pearce GL, Nambi V, Minor S, Sprecher DL. Statins do not meet expectations for lowering low-density lipoprotein cholesterol levels when used in clinical practice. *Am J Med* 2002;**113**:625–9.

67. Knopp RH. Drug therapy: drug treatment of lipid disorders. *N Engl J Med* 1999;**341**:498–511.

68. HEART UK. *The forgotten 50: "are we failing 50% of people with high cholesterol*". London: HEART UK; 2004.

69. Foley KA, Denke MA, Kamal-Bahl S, Simpson RJ Jr, Berra K, Sajjan S, *et al*. The impact of physician attitudes and beliefs on treatment decisions: lipid therapy in high-risk patients. *Med Care* 2006;**44**: 421–8.

70. Hobbs R. Can we do more to get patients to cholesterol targets? *Br J Cardiol* 2002;**9**:241–3.

71. HEART UK. *External submission to the National Institute for Health and Clinical Excellence Evidence for NICE Health Technology Assessment of Ezetimibe*. London: HEART UK; 2006.

72. Yang CC, Jick SS, Testa MA. Discontinuation and switching of therapy after initiation of lipid-lowering drugs: the effects of comorbidities and patient characteristics. *Br J Clin Pharmacol* 2003;**56**:84–91.

73. Ellis JJ, Erickson SR, Stevenson JG, Bernstein SJ, Stiles RA, Fendrick AM. Suboptimal statin adherence and discontinuation in primary and secondary prevention populations. *J Gen Intern Med* 2004;**19**:638–45.

74. Perreault S, Blais L, Dragomir A, Bouchard MH, Lalonde L, Laurier C, *et al*. Persistence and determinants of statin therapy among middle-aged patients free of cardiovascular disease. *Eur J Clin Pharmacol* 2005;**61**:667–74.

75. WHO-Human genetics DoNDP. Familial hypercholesterolaemia. *Report of a second WHO consultation*. Geneva: WHO; 1999. URL: http://whqlibdoc.who.int/hq/1999/WHO_HGN_FH_CONS_99.2.pdf. Accessed September 2006.

76. Majeed A, Aylin P, Williams S, Bottle A, Jarman B. Prescribing of lipid regulating drugs and admissions for myocardial infarction in England. *BMJ* 2004;645.

77. Anderson KM, Wilson PW, Odell PM, Kannel WB. An updated coronary risk profile. A statement for health professionals. *Circulation* 1991;**83**: 356–62.

78. Neaton JD, Blackburn H, Jacobs D, Kuller L, Lee DJ, Sherwin R, *et al*. Serum cholesterol level and mortality findings for men screened in the Multiple Risk Factor Intervention Trial. Multiple Risk Factor Intervention Trial Research Group. *Arch Intern Med* 1992;**152**:1490–500.

79. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, *et al*. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005;**366**: 1267–78.

80. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 1993;**16**:434–44.

81. Chen Z, Peto R, Collins R, MacMahon S, Lu J, Li W. Serum cholesterol concentration and coronary heart disease in population with low cholesterol concentrations. *BMJ* 1991;**303**:276–82.

82. Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, *et al*. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004:**110**:227–39.

83. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *BMJ* 2003;**326**:1423–7.

84. Gould AL, Rossouw JE, Santanello NC, Heyse J, Furberg CD. Cholesterol reduction yields clinical benefit: impact of statins. *Circulation* 1998;**97**: 946–52.

85. Robinson JG, Smith B, Maheshwari N, Schrott H. Pleiotropic effects of statins: Benefit beyond cholesterol reduction? a meta-regression analysis. *J Am Coll Cardiol* 2005;**46**:1855–62.

86. Stevens RJ, Kothari V, Adler AI, Stratton IM, Holman RR. The UKPDS risk engine: a model for the risk of coronary heart disease in type II diabetes (UKPDS 56). *Clin Sci* 2001;**101**:671–9.

87. D'Agostino RB, Russell MW, Huse DM, Ellison RC, Silbershatz H, Wilson PW, *et al*. Primary and subsequent coronary risk appraisal: new results from the Framingham study. *Am Heart J* 2000;**139**:272–81.

88. Cooper JA, Miller GJ, Humphries SE. A comparison of the PROCAM and Framingham point-scoring systems for estimation of individual risk of coronary heart disease in the Second Northwick Park Heart Study. *Atherosclerosis* 2005;**181**:93–100.

89. German, R. The role of problem structuring methods in the development of health technology assessment decision-analytic models: a pilot study. In press.

90. Grieve R, Hutton J, Green C. Selecting methods for the prediction of future events in cost-effectiveness models: a decision-framework and example from the cardiovascular field. *Health Policy* 2003;**64**:311–24.

91. University of Bristol. *Affairs of the heart*. URL: http://www.bris.ac.uk/researchreview/2004/1113901955. Accessed June 2006.

92. Brindle PM, Beswick AD, Fahey T, Ebrahim SB. The accuracy and impact of risk assessment in the primary prevention of cardiovascular disease: a systematic review. *Heart* 2006;**92**:1752–9

93. Brindle P, Emberson J, Lampe F, Walker M, Whincup P, Fahey T. Predictive accuracy of the Framingham coronary risk score in British men: prospective cohort study. *BMJ* 2003;**327**:1–6.

94. Empana JP, Ducimetiere P, Arveiler D, Ferrieres J, Evans A, Ruidavet JB. Are the Framingham and PROCAM coronary heart disease risk functions applicable to different European populations? The PRIME study. *Eur Heart J* 2003; **24**:1903–11.

95. Hense HW, Schulte H, Lowel H, Assmann G, Keil U. Framingham risk function overestimates risk of coronary heart disease in men and women from Germany – results from the MONICA Augsburg and the PROCAM cohorts. *Eur Heart J* 2003;**24**:937–45.

96. Thomsen TF, McGee D, Davidsen M, Jorgensen T, Menottis A. A cross validation of risk scores for coronary heart disease mortality based on data from the Glostrup Population studies and the Framingham Heart Study. *Int J Epidemiol* 2002;**31**: 817–22.

97. Jurgensen, J. S. The value of risk scores. *Heart* 2006;**92**:1713–14.

98. Brindle PM, McConnachie A, Upton MN, Hart CL, Davey Smith G, Watt GCM. The accuracy of the Framingham risk-score in different socioeconomic groups: a prospective study. *Br J Gen Pract* 2005;**55**:838–45.

99. Goldman L, Goldman PA, Williams LW, Weinstein MC. Cost-effectiveness considerations in the treatment of heterozygous familial hypercholesterolemia with medications. *Am J Cardiol* 1993;**72**:75D–79D.

100. Hjalte K, Lindgren B, Persson U, Hjalte K, Lindgren B, Persson U. Cost-effectiveness of simvastatin versus cholestyramine: results for Sweden. *Pharmacoeconomics* 1992;**1**:213–16.

101. Glick H, Kinosian B. Evaluating the efficiency of cholesterol modification for coronary heart disease with decision analytic models: a case study. *Drug Inf J* 1995;**29**:1441–57.

102. Sever PS, Dahlof B, Poulter NR, Wedel H, Beevers G, Caulfield M, *et al*. 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. *Drugs* 2004;**64**:43–60.

103. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HAW, Livingstone SJ, *et al*. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004;**364**:685–98.

104. WOSCOPS. Baseline risk factors and their association with outcome in the West of Scotland Coronary Prevention Study. The West of Scotland Coronary Prevention Study Group. *Am J Cardiol* 1997;**79**:756–62.

105. Law M, Singh D. Lipid lowering may reduce major cardiovascular events, regardless of pre-treatment cholesterol levels. *Evid Based Cardiovasc Med* 2006;**10**:8–10.

106. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement flow diagram. *Lancet* 1999;**354**:1896–900.

107. European Medicines Agency (EMEA) Committee for Medical Products for Human Use (CHMP). *Note for Guidance on Clinical Investigation of Medical Products in the Treatment of Lipid Disorders*. London: EMEA; 2004. pp. 1–7.

108. NHS Centre for Reviews and Dissemination. *Report 4: undertaking systematic reviews of research on effectiveness; CRD's guidance for those carrying out or commissioning reviews*. 2001. URL: www.york.ac.uk. Accessed September 2006.

109. Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions 4.2.6 [updated September 2006]. In *The Cochrane Library*, Issue 4, 2006. Chichester: Wiley; 2006.

110. Higgins JP, Thompson SG, Deeks JJ, Altman D. Measuring inconsistency in meta-analyses. BMJ 2003;**327**:557–60.

111. Bays HE, Ose L, Fraser N, Tribble DL, Quinto K, Reyes R, *et al*. A multicenter, randomized, double-blind, placebo-controlled, factorial design study to evaluate the lipid-altering efficacy and safety profile of the ezetimibe/simvastatin tablet compared with ezetimibe and simvastatin monotherapy in patients with primary hypercholesterolemia. *Clin Ther* 2004;**26**:1758–73.

112. Davidson MH, McGarry T, Bettis R, Melani L, Lipka LJ, LeBeaut AP, *et al*. Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. *J Am Coll Cardiol* 2002;**40**:2125–34.

113. Goldberg AC, Sapre A, Liu J, Capece R, Mitchel YB, Ezetimibe Study Group. Efficacy and safety of ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia: a randomized, double-blind, placebo-controlled trial. *Mayo Clin Proc* 2004;**79**:620–9.

114. Rodney RA, Sugimoto D, Wagman B, Zieve F, Kerzner B, Strony J, *et al*. Efficacy and safety of coadministration of ezetimibe and simvastatin in African-American patients with primary hypercholesterolemia. *J Natl Med Assoc* 2006;**98**: 772–8.

115. Ballantyne CM, Houri J, Notarbartolo A, Melani L, Lipka LJ, Suresh R, *et al*. Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. *Circulation* 2003;**107**:2409–15.

116. Melani L, Mills R, Hassman D, Lipetz R, Lipka L, LeBeaut A, *et al*. Efficacy and safety of ezetimibe coadministered with pravastatin in patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. *Eur Heart J* 2003;**24**:717–28.

117. Ballantyne CM, Lipka LJ, Sager PT, Strony J, Alizadeh J, Suresh R, *et al*. Long-term safety and tolerability profile of ezetimibe and atorvastatin coadministration therapy in patients with primary hypercholesterolaemia. *Int J Clin Pract* 2004;**58**: 653–8.

118. Stein E, Stender S, Mata P, Sager P, Ponsonnet D, Melani L, *et al*. Achieving lipoprotein goals in patients at high risk with severe hypercholesterolemia: efficacy and safety of ezetimibe co-administered with atorvastatin. *Am Heart J* 2004;**148**:447–55.

119. Ballantyne CM, Blazing MA, King TR, Brady WE, Palmisano J. Efficacy and safety of ezetimibe co-administered with simvastatin compared with atorvastatin in adults with hypercholesterolemia. *Am J Cardiol* 2004;**93**:1487–94.

120. Masana L, Mata P, Gagne C, Sirah W, Cho M, Johnson-Levonas AO, *et al*. Long-term safety and, tolerability profiles and lipid-modifying efficacy of ezetimibe coadministered with ongoing simvastatin treatment: a multicenter, randomized, double-blind, placebo-controlled, 48-week extension study. *Clin Ther* 2005;**27**:174–84.

121. McKenney JM, Jones PH, Bays HE, Knopp RH, Kashyap ML, Ruoff G, *et al*. Tu-W27:4 Comparative lipid effects of combination therapy with a statin and extended-release niacin versus statin plus ezetimibe versus a statin alone. *Atherosclerosis* 2006;**7**(Suppl.):174–5.

122. Dujovne CA, Ettinger MP, McNeer JF, Lipka LJ, LeBeaut AP, Suresh R, *et al*. Efficacy and safety of a potent new selective cholesterol absorption inhibitor, ezetimibe, in patients with primary hypercholesterolemia. *Am J Cardiol* 2002;**90**: 1092–7.

123. Knopp RH, Gitter H, Truitt T, Bays H, Manion CV, Lipka LJ, *et al*. Effects of ezetimibe, a new cholesterol absorption inhibitor, on plasma lipids in patients with primary hypercholesterolemia. *Eur Heart J* 2003;**24**:729–41.

124. Farnier M, Freeman MW, Macdonell G, Perevozskaya I, Davies MJ, Mitchel YB, *et al*. Efficacy and safety of the coadministration of ezetimibe with fenofibrate in patients with mixed hyperlipidaemia. *Eur Heart J* 2005;**26**:897–905.

125. Feldman T, Koren M, Insull W Jr, McKenney J, Schrott H, Lewin A, *et al*. Treatment of high-risk patients with ezetimibe plus simvastatin co-administration versus simvastatin alone to attain National Cholesterol Education Program Adult Treatment Panel III low-density lipoprotein cholesterol goals. *Am J Cardiol* 2004;**93**:1481–86.

126. Schering-Plough. IMPROVE-IT: examining outcomes in subjects with acute coronary syndrome: Vytorin (ezetimibe/simvastatin) vs simvastatin (Study P04103). URL: http://clinicaltrials.gov/show/NCT00202878?order=32. Accessed 31 October 2006.

127. Rossebo A, Pedersen T, Skjaerpe T. Design of the simvastatin and ezetimibe in aortic stenosis (SEAS) study. *Atherosclerosis* 2003;**170**:253.

128. Rossebo A. Increased cardiovascular risk factors in aortic stenosis – baseline characteristics of the simvastatin + ezetimibe in aortic stenosis study. Annual Meeting of the European Atherosclerosis Society (EAS), 24 April 2005. Poster presentation.

129. Baigent C, Laundry M. Study of heart and renal protection (SHARP). *Kidney Int* 2003;**63**:S207–10.

130. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischemic heart disease, and stroke: systematic review and meta-analysis. *BMJ* 2003;**326**:1423–7.

131. Knopp RH, Dujovne CA, LeBeaut A, Lipka LJ, Suresh R, Veltri, *et al*. Evaluation of the efficacy, safety, and tolerability of ezetimibe in primary hypercholesterolaemia: a pooled analysis from two controlled phase III clinical studies. *Int J Clin Pract* 2003;**57**:363–8.

132. Bays HE, Moore PB, Drehobl MA, Rosenblatt S, Toth PD, Dujovne CA, *et al*. Effectiveness and tolerability of ezetimibe in patients with primary hypercholesterolemia: pooled analysis of two phase II studies. *Clin Ther* 2001;**23**:1209–30.

133. Stein, E. Results of phase I/II clinical trials with ezetimibe, a novel selective cholesterol absorption inhibitor. *Eur Heart J* 2001;**3**:E11–16.

134. Leiv O, Arvind S, Davies MJ, Rotonda J, Maccubbin D, Tribble D, *et al*. Consistency of lipid-altering effects of ezetimibe/simvastatin across gender, race, age, baseline low density lipoprotein cholesterol levels, and coronary heart disease status: results of a pooled retrospective analysis. *Curr Med Res Opin* 2006;**22**:823–35.

135. Davidson MH, Ballantyne CM, Kerzner B, Melani L, Sager PT, Lipka L, *et al*. Efficacy and safety of ezetimibe coadministered with statins: randomised, placebo-controlled, blinded experience in 2382 patients with primary hypercholesterolemia. *Int J Clin Pract* 2004;**58**:746–55.

136. Davidson MH, MacCubbin D, Stepanavage M, Strony J, Musliner T. Striated muscle safety of ezetimibe/simvastatin (Vytorin). *Am J Cardiol* 2006; **97**:223–8.

137. McKenney JM, Davidson MH, Shear C, Revkin JH. Efficacy and safety of torcetrapib, a novel cholesteryl ester transfer protein inhibitor, in individuals with below-average high-density lipoprotein cholesterol levels on a background of atorvastatin. *J Am Coll Cardiol* 2006;**48**:1782–90.

138. Davidson MH, McKenney JM, Shear C, Revkin JH. Efficacy and safety of torcetrapib, a novel cholesteryl ester transfer protein inhibitor, in individuals with below-average high-density lipoprotein cholesterol levels. *J Am Coll Cardiol* 2006;**48**:1774–81.

139. Jensen G, Hampton J. Early termination of drug trials. *BMJ* 2007;**334**:326.

140. Wierzbicki AS. Statins: myalgia and myositis. *Br J Cardiol* 2002;**9**:193–4.

141. Eddy DM. *Technology assessment: the role of mathematical modelling in assessing medical technology*. Washington DC: National Academy Press; 1985. pp. 144–54.

142. Drummond M, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *BMJ* 1996;**313**:275–83.

143. Anon. Ezetimibe – a new cholesterol-lowering drug. *Drug Ther Bull* 2004;**42**:65–7.

144. Cook JR, Yin D, Alemao E, Davies G, Krobot KJ, Veltri E, *et al*. Cost-effectiveness of ezetimibe coadministration in statin-treated patients not at cholesterol goal: application to Germany, Spain and Norway. *Pharmacoeconomics* 2004;**22**:49–61.

145. Cook JR, Yin D, Alemao E, Drummond M. Development and validation of a model to project the long-term benefit and cost of alternative lipid-lowering strategies in patients with hypercholesterolaemia. *Pharmacoeconomics* 2004;**22**: 37–48.

146. Gryskiewicz KA, Coleman CI, Gillespie EL, White CM. Cost-effectiveness analysis of combination statin/ezetimibe therapy for the treatment of elevated low-density lipoprotein cholesterol. *Hosp Pharm* 2005;**40**:687–92.

147. Perkerson KA, Gillespie EL, Coleman CI. Cost-effectiveness of statin monotherapy and combination therapy with ezetimibe (structured abstract). *Conn Med* 2005;**69**:19–22.

148. Morris S, Tiller R. Ezetimibe for hypercholesterolemia. *Am Fam Physician* 2003;**68**: 1595–6.

149. Kohli M, Attard C, Lam A, Huse D, Cook J, Bourgault C, *et al*. Cost-effectiveness of adding ezetimibe to atorvastatin therapy in patients not at cholesterol treatment goal in Canada. *Pharmacoeconomics* 2006;**24**:815–30.

150. Draeger NM, Holm MV, Schwenkglenks NM, Szucs TD. Cost utility analysis: ezetimibe plus statin versus statin therapy under the Third Joint European Societies Taskforce Guideline in Coronary Heart Disease. Presented at the XIV International Symposium on Atherosclerosis, Rome, 2006.

151. Cook JR, Yin D, Alemao E, Drummond, M. The cost-effectiveness of ezetimibe in CHD and CHD equivalent patients not at total cholesterol goal on statin monotherapy in Scotland. *Abstracts, European Society of Cardiology Annual Meeting (ESC),* 28 August–1 September 2004, Munich, Germany.

152. Lee VWY, Alemao E, Yin D, Cook J, Lee KK. Cholesterol goal attainment among CHD patients in Hong Kong. Presented at the ISPOR 2nd Asia-Pacific Conference, 15–18 May 2005.

153. Organisation for Economic Cooperation and Development. *Purchasing power parities*. URL: http://www.oecd.org/department/. Accessed 3 July 2006.

154. Curtis L, Netten A. *Unit costs of health and social care*. Canterbury: PSSRU, University of Kent. URL: http://www.pssru.ac.uk/uc/uc2006contents.htm. Accessed 3 July 2006.

155. Clarke P, Gray A, Legood R, Briggs A, Holman R. The impact of diabetes-related complications on healthcare costs: results from the United Kingdom Prospective Diabetes Study (UKPDS Study No. 65). *Diabet Med* 2003;**20**:442–50.

156. Chekman IS, Angelutsa PA, Viktorov AP, Kalugin VE, Dutchak VA. Computer analysis of drug therapy in cardiac patients. Preliminary communication. *Cor et Vasa* 1991;**33**:322–6.

157. Kaplan NM. Treating hypertension to prevent coronary disease. *Cleve Clin J Med* 1991;**58**: 432–43.

158. Kothari V, Stevens RJ, Adler AI, Stratton IM, Manley SE, Neil HA, *et al*. UKPDS 60 – risk of stroke in type 2 diabetes estimated by the UK Prospective Diabetes Study risk engine. *Stroke* 2002;**33**:1776–81.

159. Chaturvedi N, Fuller JH. Ethnic differences in mortality from cardiovascular disease in the UK: do they persist in people with diabetes? *J Epidemiol Commun Health* 1996;**50**:137–9.

160. McKenney J. Combination therapy for elevated low-density lipoprotein cholesterol: the key to coronary artery disease risk reduction. *Am J Cardiol* 2002;**90**:8K–20K.

161. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;**344**:1383–9.

162. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, *et al*. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA* 1998;**279**:1615–22.

163. Vanderpump MP, Tunbridge WM, French JM, Appleton D, Bates D, Clark F, *et al*. The development of ischemic heart disease in relation to autoimmune thyroid disease in a 20-year follow-up study of an English community. *Thyroid* 1996;**6**:155–60.

164. Tunbridge WM, Evered DC, Hall R, Appleton D, Brewis M, Clark F, *et al*. Lipid profiles and cardiovascular disease in the Whickham area with particular reference to thyroid failure. *Clin Endocrinol (Oxf)* 1977;**7**:495–508.

165. Pearson TA, Laurora I, Chu H, Kafonek S. The Lipid Treatment Assessment (L-TAP) Project: a multicenter survey to evaluate the percentages of dyslipidemic patients receiving lipid-lowering therapy and achieving low-density lipoprotein cholesterol goals. *Arch Intern Med* 2000;**160**: 459–67.

166. NICE. *Cardiovascular risk assessment: the modification of blood lipids for the primary and secondary prevention of cardiovascular disease*. 2007. URL: http://guidance.nice.org.uk/page.aspx?o=438182. Accessed December 2007.

167. Bates MJ. The design of browsing and berrypicking techniques for the online search interface. *Online Rev* 1989;**13**:407–24.

168. The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. *JAMA* 1984;**251**:351–64.

169. Morris S. A comparison of economic modelling and clinical trials in the economic evaluation of cholesterol-modifying pharmacotherapy. *Health Econ* 1997;**6**:589–601.

170. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. *Med Dec Making* 1993;**13**:322–39.

171. Mueck AO, Seeger H. Statins and menopausal health. *J Br Menopause Soc* 2002;**8**:141–6.

172. National Institute for Health and Clinical Excellence (NICE). *Guide to the methods of technology appraisal (reference NO515)*. URL: www.nice.org.uk. Accessed September 2006.

173. Gagne C, Bays HE, Weiss SR, Mata P, Quinto K, Melino M, *et al*. Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. *Am J Cardiol* 2002;**90**:1084–91.

174. Health Survey for England. *Patient level data set; available*. 2006.

175. Sutcliffe SJ, Fox KF, Wood DA, Sutcliffe A, Stock K, Wright M, *et al*. Incidence of coronary heart disease in a health authority in London: review of a community register. *BMJ* 2003;**326**:20.

176. Dennis M, Bamford J, Sandercock P, Warlow C. Prognosis of transient ischemic attacks in the Oxfordshire Community Stroke Project. *Stroke* 1990;**21**:848–53.

177. Bamford J, Sandercock P, Dennis M, Warlow C, Jones L, McPherson K, *et al*. A prospective study of acute cerebrovascular disease in the community: the Oxfordshire Community Stroke Project 1981–86. I. Methodology, demography and incident cases of first-ever stroke. *J Neurol Neurosurg Psychiatry* 1988;**51**:1373–80.

178. British Heart Foundation. URL: http://www.heartstats.org. Accessed October 2006.

179. Bots AF, Kastelein JJ. Achieving lipid goals in real life: the Dutch DISCOVERY study. *Int J Clin Pract* 2005;**59**:1387–94.

180. Gray D, Hapton JR. Twenty years' experience of myocardial infarction: the value of a heart attack register. Nottingham Heart Attack Register. *Br J Clin Pharmacol* 1993;**47**:292–5.

181. Wolfe CDA, Rudd AG, Howard R, Coshall C, Stewart J, Lawrence E, *et al*. Incidence and case fatality rates of stroke subtypes in a multiethnic population: the South London Stroke Register. *J Neurol Neurosurg Psychiatry* 2002;**72**:211–16.

182. Rothwell PM, Coull AJ, Giles MF, Howard SC, Silver LE, Bull LM, *et al*. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). *Lancet* 2004;**363**:1925–33.

183. Juul-Moller S, Edvardsson N, Sorenson S, Jahnmatz B, Rosen A, Omblus R. Double-blind trial of aspirin in primary prevention of myocardial infarction in patients with stable chronic angina pectoris. *Lancet* 1992;**340**:1421–5.

184. National Institute for Health and Clinical Excellence. *Statins for the prevention of cardiovascular events*. Technology Appraisal 94. London: NICE; 2006.

185. Pedersen TR, Kjekshus J, Berg K, Haghfelt T, Faergeman O, Thorgeirsson G, *et al*. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S) (Reprinted from *Lancet* 1994;**344**:1383–9). *Atherosclerosis Suppl* 2004;**5**:81–87.

186. Sacks FM, Krukonis GP. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *Vasc Med* 1996;**1**:9–18.

187. Schwartz GG, Olsson AG, Ezekowitz MD, Ganz P, Oliver MF, Waters D, *et al*. Effects of atorvastatin on early recurrent ischaemic events in acute coronary syndromes. The MIRACL Study: a randomised controlled trial. *JAMA* 2001;**285**:1711–18.

188. Joint Formulary Committee. *British National Formulary*. URL: http://www.bnf.org/bnf. Accessed October 2006.

189. Curtis L, Netten, A. *Unit Costs of Health and Social Care*. Canterbury: PSSRU; 2005.

190. Palmer S, Sculpher M, Philips Z, Robinson M, Ginnelly L, Bakhai A, *et al*. A cost-effectiveness model comparing alternative management strategies for the use of glycoprotein IIb/IIIa antagonists in non-ST-elevation acute coronary syndrome. Report to the National Institute for Clinical Excellence. London: NICE; 2002. URL: http://www.nice.org.uk. Accessed September 2006.

191. Youman P, Wilson K, Harraf F, Kalra L. The economic burden of stroke in the United Kingdom. *Pharmacoeconomics* 2003;Suppl 1:43–50.

192. Department of Health. *NHS reference costs 2005*. URL: http://www.dh.gov.uk/en/Publicationsand statistics. Accessed September 2006.

193. Lenzen M, Scholte op Reimer W, Norekval TM, De Geest S, Fridlund B, Heikkila J, *et al*. Pharmacological treatment and perceived health status during 1-year follow up in patients diagnosed with coronary artery disease, but ineligible for revascularization, Results from the Euro Heart Survey on Coronary Revascularization. *Eur J Cardiovasc Nurs* 2006;**5**:115–21.

194. BARI Investigators. Protocol for the Bypass Angioplasty Revascularization Investigation. *Circulation* 1991;**84**:1–27.

195. Goodacre S, Nicholl J, Dixon S, Cross E, Angelini K, Arnold J, *et al*. Randomised controlled trial and economic evaluation of a chest pain observation unit compared with routine care. *BMJ* 2004;**328**:254–7.

196. Kim J, Henderson RA, Pocock SJ, Clayton T, Sculpher MJ, Fox KAA. Health-related quality of life after interventional or conservative strategy in patients with unstable angina or non-ST-segment elevation myocardial infarction: one year results of the third randomized intervention trial of unstable angina (RITA-3). *J Am Coll Cardiol* 2007;**45**:221–8.

197. Lacey EA, Walters SJ. Continuing inequality: gender and social class influences on self perceived health after a heart attack. *J Epidemiol Commun Health* 2003;**57**:622–7.

198. Haacke C, Althaus A, Spottke A, Siebert U, Back T, Dodel R. Long-term outcome after stroke: evaluating health-related quality of life using utility measurements. *Stroke* 2006;**37**:193–8.

199. Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey. *BMJ* 1998;**316**:736–41.

200. Tengs TO, Lin TH. A meta-analysis of quality of life estimates for stroke. *Pharmacoeconomics* 2003;**21**:191–200.

201. Van Exel NJA, Scholte op Reimer WJM, Koopmanschap MA. Assessment of post-stroke quality of life in cost-effectiveness studies: the usefulness of the Barthel Index and the EuroQol-5D. *Qual Life Res* 2004;**13**:427–33.

202. Leeds L, Meara J, Hobson P. The impact of discharge to a care home on longer term stroke outcomes. *Clin Rehabil* 2004;**18**:924–8.

203. Pickard AS, Johnson JA, Feeny DH. Responsiveness of generic health-related quality of life measures in stroke. *Qual Life Res* 2005;**14**: 207–19.

204. Hobbs R. Concordance with heart failure medications: what do patients think? *Fam Pract* 2006;**23**:607–8.

205. Anon. *Mortality statistics: cause. Review of the Registrar General on deaths by cause, sex and age, in England and Wales, 2001*. DH2 no. 28, London: Office for National Statistics; 2003.

206. Department of Health. *Prescription cost analysis 2003*. URL: http://www.dh.gov.uk/. Accessed September 2006.

207. Sproston K, Primatesta P (editors). *Unit Health Survey for England 2003: Volume 1 – cardiovascular disease*. London: The Stationery Office; 2004.

208. Anon. Study shows cholesterol absorption inhibitor is effective and safe. *Pharm J* 2001;**266**:740.

209. Anon. Statins plus cholesterol resorption inhibitor. LDL goal values attainable. *MMW Fortschr Med* 2002;**144**:56 (in German).

210. Anon. Lipid control in the double pack. Combined drugs to achieve the goal. *MMW Fortschr Med* 2002;**144**:53 (in German).

211. Anon. Ezetimib plus statin combination. A strong duo. *MMW Fortschr Med* 2002;**144**:53 (in German).

212. Anon. Combination provides more than twice the reduction of C-reactive protein. *Br J Diabetes Vasc Dis* 2003;**3**:442.

213. Anon. Lowering cholesterol becomes easier. Combining instead of increasing dosage. *MMW Fortschr Med* 2003;**145**:59 (in German).

214. Anon. Ezetimibe add-on to statin therapy for effectiveness trial (EASE). *ACC Curr J Rev* 2004;**13**:14–15.

215. Anon. Ezetimibe added to statin results in greater achievement of LDL goals. *Formulary* 2004;**39**:242.

216. Anon. Ezetimibe with simvastatin reduces LDL-C by 46-61%. *Br J Diabetes Vasc Dis* 2004;**4**:132.

217. Anon. Goal in hypercholesterolemia: lowering LDL cholesterol level by 50%. *MMW Fortschr Med* 2005;**147**:51 (in German).

218. Anon. Ezetimib and simvastatin. Cooperation at receptors of cholesterol metabolism. *MMW Fortschr Med* 2005;**147**:50 (in German).

219. Ballantyne CM, Abate N, Yuan Z, King TR, Palmisano J. Dose-comparison study of the combination of ezetimibe and simvastatin (Vytorin) versus atorvastatin in patients with hypercholesterolemia: the Vytorin Versus Atorvastatin (VYVA) study. *Am Heart J* 2005;**149**:464–73.

220. Ballantyne C, Sosef F, Duffield E; The EXPLORER Study Investigators. Efficacy and safety of rosuvastatin plus ezetimibe in high-risk patients: results from the EXPLORER study. *Atherosclerosis* 2006;**7**(Suppl.):552. Abstract Th-P16:270.

221. Ballantyne CM, Abate N, Yuan Z, Gazzara RA, Tershakovec AM. A 'step-up' dose comparison of the ezetimibe/simvastatin single tablet versus atorvastatin in patients with hypercholesterolemia. *Atherosclerosis* 2006;**7**(Suppl.):555. Abstract Th-P16:282.

222. Barrios V, Amabile N, Paganelli F, Chen J, Allen C, Johnson-Levonas AO, *et al*. Lipid-altering efficacy of switching from atorvastatin 10 mg/day to ezetimibe/simvastatin 10/20 mg/day compared to doubling the dose of atorvastatin in hypercholesterolaemic patients with atherosclerosis or coronary heart disease. *Int J Clin Pract* 2005;**59**:1377–86.

223. Brohet C, Banai S, Alings AM, Massaad R, Davies MJ, Allen C. LDL-C goal attainment with the addition of ezetimibe to ongoing simvastatin treatment in coronary heart disease patients with hypercholesterolemia. *Curr Med Res Opin* 2005;**21**:571–8.

224. Cruz-Fernandez JM, Bedarida GV, Adgey J, Allen C, Johnson-Levonas AO, Massaad R. Efficacy and safety of ezetimibe co-administered with ongoing atorvastatin therapy in achieving low-density lipoprotein goal in patients with hypercholesterolemia and coronary heart disease. *Int J Clin Pract* 2005;**59**:619–27.

225. Davidson MH, Catapano A, Ballantyne CM, Brady WE, Gazzara RA. Attainment of optimal NCEP ATP III treatment goals in high-risk patients: dose comparison of ezetimibe/simvastatin and rosuvastatin. *Atherosclerosis* 2006;**7**(Suppl.):555. Abstract Th-P16:280.

226. Davidson MH, Catapano A, Ballantyne CM, Brady WE, Gazzara RA. Lipid-altering efficacy and safety of ezetimibe/simvastatin versus rosuvastatin in patients with primary hypercholesterolemia. *Atherosclerosis* 2006;**7**(Suppl.):555. Abstract Th-P16:283.

227. Descamps O, Montant P, Chenot F, Boyasis P, Markovitch O. Co-administration of ezetimibe and simvastatin in acute myocardial infarction. *Atherosclerosis* 2006;**7**(Suppl.):553. Abstract Th-P16:274.

228. Dvorakova J, Taborsky L, Hyanek J, Dubska L. Fluvastatin-ezetimibe combination therapy. *Atherosclerosis* 2006;**7**(Suppl.):553. Abstract Th-P16:273.

229. Esteban-Salan M, Guimon-Bardesi A, Viuda-Unceta JM. Effectiveness of treatment with statins and ezetimibe in patients with hypercholesterolemia and mixed dyslipidemia. *Atherosclerosis* 2006;**7**(Suppl.):553. Abstract Th-P16:275.

230. Farnier M, Volpe M, Massaad R, Davies MJ, Allen C. Effect of co-administering ezetimibe with on-going simvastatin treatment on LDL-C goal attainment in hypercholesterolemic patients with coronary heart disease. *Int J Cardiol* 2005;**102**: 327–32.

231. Goldman-Levine JD, Bohlman LG. Ezetimibe/simvastatin (Vytorin) for hypercholesterolemia. *Am Fam Physician* 2005;**72**: 2081–2.

232. Jakulj L, Trip MD, Sudhop T, von Bergmann K, Kastelein JJ, Vissers MN. Inhibition of cholesterol absorption by the combination of dietary plant sterols and ezetimibe: effects on plasma lipid levels. *J Lipid Res* 2005;**46**:2692–8.

233. Jang-Whan Bae. The safety and efficacy of ezetimibe and simvastatin combination therapy in Korean patients with primary hypercholesterolemia. *Korean J Med* 2005;**68**: 487–97.

234. Kastelein JJ, Strony J, Sager PT, de Groot E, Veltri EP. The ENHANCE trial: ezetimibe and simvastatin in hypercholesterolemia enhances atherosclerosis regression. *Stroke* 2004;**35**: E258.

235. Kastelein JJ, Sager PT, de Groot E, Veltri E. Comparison of ezetimibe plus simvastatin versus simvastatin monotherapy on atherosclerosis progression in familial hypercholesterolemia. Design and rationale of the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial. *Am Heart J* 2005;**149**:234–9.

236. Leibovitz E, Gavish D, Bitzur R, Cohen A, Harats D. Efficacy and safety of rosuvastatin-ezetimibe combination for the treatment of severe hypercholesterolemia. *Atherosclerosis* 2006(Suppl.);**7**:554. Abstract Th-P16:276.

237. Madigosky WS, Kane KY. Ezetimibe plus atorvastatin lowers cholesterol. *J Fam Pract* 2003;**52**:671–2.

238. Maeder M, Blank R, Feucht J, Darioli R, Rickli H. Effect of ezetimibe co-administered with statin therapy in Swiss outpatients. *Kardiovask Med* 2005;**8**:399–409.

239. McKenney JM, Farnier M, Lo KW, Bays HE, Perevozkaya I, Carlson G, *et al*. Safety and efficacy of long-term co-administration of fenofibrate and ezetimibe in patients with mixed hyperlipidemia. *J Am Coll Cardiol* 2006;**47**:1584–7.

240. Melani L, Mills R, Hassman D, Lietz R, Stein EA. Combination ezetimibe plus pravastatin therapy is more effective than pravastatin monotherapy for the treatment of primary hypercholesterolaemia. *Evid Based Cardiovasc Med* 2003;**7**:179–80.

241. Ose L, Tonstad S, Harris S, Marotti M. Ezetimibe added to rosuvastatin for severely hypercholesterolemic patients: effects on lipid measures and C-reactive protein. *Atherosclerosis* 2005;**6** (Suppl):117.

242. Pearson TA, Denke M, McBride P, Battisti WP, Brady WE, Palmisano J. Effectiveness of the addition of ezetimibe to ongoing statin therapy in modifying lipid profiles and attaining low-density lipoprotein cholesterol goals in older and elderly patients: subanalyses of data from a randomized, double-blind, placebo-controlled trial. *Am J Geriatr Pharmacother* 2005;**3**:218–28.

243. Pearson TA, Denke MA, McBride PE, Battisti WP, Brady WE, Palmisano J. A community-based, randomized trial of ezetimibe added to statin therapy to attain NCEP ATP III goals for LDL cholesterol in hypercholesterolemic patients: the

ezetimibe add-on to statin for effectiveness (EASE) trial. *Mayo Clin Proc* 2005;**80**:587–95.

244. Pisciotta L, Masturzo P, Bellocchio A, Fresa R. Efficacy and safety of ezetimibe added to current therapy with statins in moleculary characterized FH patients. *Atherosclerosis* 2006;**7**(Suppl.):554. Abstract Th-P16:277.

245. Shepherd, J. Combined lipid lowering drug therapy for the effective treatment of hypercholesterolaemia. *Eur Heart Journal* 2003;**24**:685–9.

246. Simons L, Tonkon M, Masana L, Maccubbin D, Shah A, Lee M, *et al.*. Effects of ezetimibe added to on-going statin therapy on the lipid profile of hypercholesterolemic patients with diabetes mellitus or metabolic syndrome. *Curr Med Res Opin* 2004;**20**:1437–45.

247. Stein E, Harris S, Schleman M, Sager P. Ezetimibe added to rosuvastatin for severely hypercholesterolemic patients: effects on low-density lipoprotein cholesterol and C-reactive protein. *J Am Coll Cardiol* 2005;**45** (3 Suppl A): 392A.

248. Sudhop T, Lutjohann D, Kodal A, Igel M, Tribble DL, Shah S, *et al*. Inhibition of intestinal cholesterol absorption by ezetimibe in humans. *Circulation* 2002;**106**:1943–8.

249. Sudhop T, von Bergmann K. Ezetimib as combination partner in hypercholesteremia. Lowering LDL beyond the effect of statins. *MMW Fortschr Med* 2003;**145**:48–50 (in German).

250. van Heyningen, C. An evaluation of using ezetimibe and niaspan in a cardiovascular disease prevention clinic. *Atherosclerosis* 2006(Suppl.);**7**:122. Abstract Mo-P5:347.

251. Veltri E, Suresh R, Strony J. Safety and efficacy of long-term (up to 24 months) ezetimibe therapy in hypercholesterolemic patients. *Atherosclerosis* 2006;**7**(Suppl.):356. Abstract We-P11:49.

252. Vermaak W, Pinto X, Ponsonnet, D, Sager P, Lipka L, Suresh R, *et al*. Heterozygous familial hypercholesterolemia: coadministration of ezetimibe plus atorvastatin. *Atherosclerosis* 2002;**3**:230–1.

253. Wierzbicki A, Doherty E, Lumb PJ, Chik G, Crook MA. Efficacy of ezetimibe in patients with statin-resistant and statin-intolerant familial hyperlipidaemias. *Curr Med Res Opin* 2005;**21**: 333–8.

254. Stein EA. Managing dyslipidemia in the high-risk patient. *Am J Cardiol* 2002;**89**:50C–57C.

255. Rosenhead J, Mingers J. *Rational analysis for a problematic world revisited: problem structuring methods for complexity, uncertainty and conflict*. 2nd ed. Chichester: Wiley; 2001.

256. Pidd, M. *Tools for thinking: modelling in management science*. 2nd ed. Chichester: Wiley; 2003.

257. Assmann G, Schulte H. Modelling the Helsinki Heart Study by means of risk equations obtained from the PROCAM Study and the Framingham Heart Study. *Drugs* 1990; **40** Suppl 1:13–18.

258. Adult Treatment Panel. Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;**106**:3143–421.

259. Yeo WW, Yeo KR. Coronary risk versus cardiovascular risk for treatment decisions in mild hypertension. *J Cardiovasc Risk* 2002;**9**:275–80.

260. De Sauvage Nolting PR. Prevalence and significance of cardiovascular risk factors in a large cohort of patients with familial hypercholesterolaemia. *J Intern Med* 2003;**253**: 161–8.

261. Dennis MS, Burn JP, Sandercock PA, Bamford JM, Wade DT, Warlow CP. Long-term survival after first-ever stroke: the Oxfordshire Community Stroke Project. *Stroke* 1993;**24**:796–800.

262. Department of Health. *Our inheritance, our future: realising the potential of genetics in the NHS*. London: Department of Health; 2003.

263. Keiding N. Correction for measurement error. *Eur J Clin Nutr* 1993;**47**:S31–3.

264. Glick H, Kinosian B. Evaluating the efficiency of cholesterol modification for coronary heart disease with decision analytic models: a case study. *Drug Inf J* 1995;**29**:1441–57.

265. Joint Health Surveys. *Unit Health Survey for England 2003: Volume 1 – Cardiovascular Disease*. 2004.

266. Leren TP. Cascade genetic screening for familial hypercholesterolemia. *Clin Genet* 2004;**66**: 483–7.

267. Marks D, Wonderling D, Thorogood M, Lambert H, Humphries SE, Neil HA. Cost effectiveness analysis of different approaches of screening for familial hypercholesterolaemia (structured abstract). *BMJ* 2002;**324**:1303–6.

268. Marks D, Wonderling D, Thorogood M, Lambert H, Humphries SE, Neil HAW. Screening for hypercholesterolaemia versus case finding for familial hypercholesterolaemia: a systematic review and cost-effectiveness analysis. *Health Technol Assess* 2000(4).

269. Morris, S. A comparison of economic modelling and clinical trials in the economic evaluation of cholesterol-modifying pharmacotherapy. *Health Econ* 1997;**6**:589–601.

270. Newson AJ, Humphries SE. Cascade testing in familial hypercholesterolaemia: how should family

members be contacted? *Eur J Hum Genet* 2005;**13**:401–8.

271. Marang-van de Mheen PJ, ten Asbroek AH, Bonneux L, Bonsel GJ, Klazinga NS. Cost-effectiveness of a family and DNA based screening programme on familial hypercholesterolaemia in The Netherlands. *Eur Heart J* 2002;**23**:1922–30.

272. Sever PS, Dahlof B, Poulter NR, Wedel H, Beevers G, Caulfield M, *et al*. 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.

273. Steering Committee on behalf of the Simon Broome Register Group. Risk of fatal coronary heart disease in familial hypercholesterolaemia. *BMJ* 1991;**303**:893–6.

274. Tanne JH. Pfizer stops clinical trials of heart drug. *BMJ* 2006;**333**:1237.

275. Kerzner B, Corbelli J, Sharp S, Lipka LJ, Melani L, LeBeaut A, *et al*., Ezetimibe Study Group. Efficacy and safety of ezetimibe coadministered with lovastatin in primary hypercholesterolemia. *Am J Cardiol* 2003;**91**:418–24.

Appendix 1

Diagnostic criteria for FH as defined by the Simon Broome Register of Familial Hyperlipidaemia[19] and Dutch Lipid Network[17,19]

Simon Broome Register Group

Diagnostic criteria
A definite diagnosis of FH requires: 1. Total-c level above 7.5 mmol/l (290 mg/dl) in adults or a Total-c level above 6.7 mmol/l (260 mg/dl) for children under 16, **or** LDL-c level above 4.9 mmol/l (190 mg/dl) in adults (4.0 mmol/l in children) (either pretreatment or highest on treatment) PLUS 2. Tendon xanthomas (hard fatty lumps on the heels) in the patient or a relative (parent, child, sibling, grandparent, aunt, uncle) OR 3. DNA-based evidence of an LDL receptor mutation or familial defective apo B-100 **Possible FH is defined as (1) above plus one of the following:** 4. Family history of MI before age 50 years in grandparent, aunt, uncle or before age 60 years in parent, sibling or child 5. Family history of raised cholesterol in parent, sibling or child, or level above 7.5 mmol/l (290 mg/dl) in grandparent, aunt or uncle

Dutch Lipid Network

Diagnostic criteria	Score
Family history	
1. First-degree relative with known premature (male <55 years; female <60 years) coronary and vascular disease	1
2. First-degree relative with known LDL-cholesterol >95th percentile, and/or	2
1. First-degree relative with tendon xanthomata and/or arcus cornealis	2
2. Children below 18 years with LDL cholesterol >95th percentile	2
Clinical history	
1. Patient has premature (male <55 years; female <60 years) coronary artery disease	2
2. Patient has premature (male <55 years; female <60 years) cerebral or peripheral vascular disease	1
Physical examination	
1. Tendon xanthomata	6
2. Arcus cornealis below 45 years	4
Laboratory analysis (HDL-c and triglycerides are normal)	
1. LDL-c >8.5 mmol/l (330 mg/dl)	8
2. LDL-c 6.5–8.5 mmol/l (250–329 mg/dl)	5
3. LDL-c 5.0–6.4 (190–249 mg/dl)	3
4. LDL-c 4.0–4.9 (155–198 mg/dl)	1
DNA analysis	
1. Functional mutation in the LDL receptor present	8
Diagnostic total score: certain >8; probable 6 and 7; possible 3 and 5	

Appendix 2

Clinical effectiveness: literature search strategies

This appendix contains information on the sources searches and keyword strategies for the systematic review of clinical effectiveness.

The electronic databases searched are listed in *Table 52* and resources consulted via the Internet in *Table 53*.

TABLE 52 *Electronic databases searched*

BIOSIS Previews	Biological Abstracts
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Database of Controlled Trials
CINAHL	Cumulative Index of Nursing and Allied Health Literature
CRD Databases	Centre for Reviews and Dissemination Databases
DARE	NHS Database of Abstracts of Reviews of Effectiveness
HTA	NHS Health Technology Assessment Database
EMBASE	Excerpta Medica Database (EMBASE), EMBASE Drugs and Pharmacology (EMDP) and EMBASE Psychiatry (EMPS)
MEDLINE	The US National Library of Medicine's premier bibliographic database
MEDLINE In-Process and Other Non-Indexed Citations	The US National Library of Medicine's in-process database for Ovid MEDLINE
SCI and SSCI	Science and Social Sciences Citation Indexes

TABLE 53 *Other sources*

CCOHTA	Canadian Agency for Drugs and Technologies in Health
CCT	Current Controlled Trials Register
NRR	National Research Register
NCCHTA	National Coordinating Centre for Health Technology Assessment
NZHTA	New Zealand Health Technology Assessment
ReFeR	Research Finding Register
TRIP	Turning Research into Practice Database

Database keyword strategies

BIOSIS

1986–2005
WebSPIRS version
Search undertaken between April and June 2006

1 ezetimibe
2 (EZETIMIB) or (EZETIMIB-) or (EZETIMIBA) or (EZETIMIBA-) or (EZETIMIBE) or (EZETIMIBE-) or (EZETIMIBE-A) or (EZETIMIBE-ANALOG) or (EZETIMIBE-AND-SIMVASTATIN-IN-HYPERCHOLESTEROLEMIA-ENHANCES-ATHEROSCLEROSIS-REGRESSIO) or (EZETIMIBE-ATORVASTATIN) or (EZETIMIBE-BINDING) or (EZETIMIBE-CO-ADMINISTRATION) or (EZETIMIBE-GLUCURONIDE) or (EZETIMIBE-GLUCURONIDEOVERALL) or (EZETIMIBE-INDUCED-INCREMENTAL-REDUCTION) or (EZETIMIBE-LOWERING-EFFECT-CONSISTENCY) or (EZETIMIBE-POLICOSANOL) or (EZETIMIBE-SENSITIVE) or (EZETIMIBE-SIMVASTATIN) or (EZETIMIBE-STUDY-GROUP) or (EZETIMIBE-STUDY-GRP) or (EZETIMIBE-TREATED) or (EZETIMIBE-10) or (EZETIMIBES)
3 (EZETROL) or (EZETROL-)
4 (ZETIA) or (ZETIA-)
5 (VYTORIN) or (VYTORIN-) or (VYTORIN-VERSUS-ATORVASTATIN-STUDY)(2 records)
6 inegy
7 ((VYTORIN) or (VYTORIN-) or (VYTORIN-VERSUS-ATORVASTATIN-STUDY)) or ((ZETIA) or (ZETIA-)) or ((EZETROL) or (EZETROL-)) or ((EZETIMIB) or (EZETIMIB-) or (EZETIMIBA) or (EZETIMIBA-) or (EZETIMIBE) or (EZETIMIBE-) or (EZETIMIBE-A) or (EZETIMIBE-ANALOG) or (EZETIMIBE-AND-SIMVASTATIN-IN-HYPERCHOLESTEROLEMIA-ENHANCES-ATHEROSCLEROSIS-REGRESSIO) or (EZETIMIBE-ATORVASTATIN) or (EZETIMIBE-BINDING) or (EZETIMIBE-CO-ADMINISTRATION) or (EZETIMIBE-GLUCURONIDE) or (EZETIMIBE-GLUCURONIDEOVERALL) or (EZETIMIBE-INDUCED-INCREMENTAL-REDUCTION) or (EZETIMIBE-LOWERING-EFFECT-CONSISTENCY) or (EZETIMIBE-POLICOSANOL) or (EZETIMIBE-SENSITIVE) or (EZETIMIBE-SIMVASTATIN) or (EZETIMIBE-STUDY-GROUP) or (EZETIMIBE-STUDY-GRP) or (EZETIMIBE-TREATED) or (EZETIMIBE-10) or (EZETIMIBES)) or (ezetimibe)
8 HYPERCHOLESTEROLEMIA
9 hypercholesterolemia
10 hypercholesterolaemia
11 (hypercholesterolaemia) or (hypercholesterolemia) or (HYPERCHOLESTEROLEMIA)
12 ((hypercholesterolaemia) or (hypercholesterolemia) or (HYPERCHOLESTEROLEMIA)) and (((VYTORIN) or (VYTORIN-) or (VYTORIN-VERSUS-ATORVASTATIN-STUDY)) or ((ZETIA) or (ZETIA-)) or ((EZETROL) or (EZETROL-)) or ((EZETIMIB) or (EZETIMIB-) or (EZETIMIBA) or (EZETIMIBA-) or (EZETIMIBE) or (EZETIMIBE-) or (EZETIMIBE-A) or (EZETIMIBE-ANALOG) or (EZETIMIBE-AND-SIMVASTATIN-IN-HYPERCHOLESTEROLEMIA-ENHANCES-ATHEROSCLEROSIS-REGRESSIO) or (EZETIMIBE-ATORVASTATIN) or (EZETIMIBE-BINDING) or (EZETIMIBE-CO-ADMINISTRATION) or (EZETIMIBE-GLUCURONIDE) or (EZETIMIBE-GLUCURONIDEOVERALL) or (EZETIMIBE-INDUCED-INCREMENTAL-REDUCTION) or (EZETIMIBE-LOWERING-EFFECT-CONSISTENCY) or (EZETIMIBE-POLICOSANOL) or (EZETIMIBE-SENSITIVE) or (EZETIMIBE-SIMVASTATIN) or (EZETIMIBE-STUDY-GROUP) or (EZETIMIBE-STUDY-GRP) or (EZETIMIBE-TREATED) or (EZETIMIBE-10) or (EZETIMIBES)) or (ezetimibe))

Cochrane Library (CDSR, CENTRAL, DARE, HTA)

Issue 2, 2006
Wiley version
Search undertaken between April and June 2006

1 ezetimibe in All Fields in all products
2 ezetrol in All Fields in all products
3 zetia in All Fields in all products
4 vytorin in All Fields in all products
5 inegy in All Fields in all products
6 #1 OR #2 OR #3 OR #4 OR #5
7 hypercholesterolaemia or hypercholesterolemia in All Fields in all products
8 #6 AND #7

CINAHL

1982–2006
Ovid Online version
Search undertaken between April and June 2006

1 Ezetimibe/
2 ezetimibe.tw.
3 ezetrol.tw.

4 zetia.tw.
5 vytorin.tw.
6 inegy.tw.
7 1 or 2 or 4 or 5 or 6
8 Hypercholesterolemia/
9 hypercholesterolemia.af.
10 hypercholesterolaemia.af.
11 8 or 9 or 10
12 7 and 11
13 exp clinical trials/
14 Clinical trial.pt.
15 (clinic$ adj trial$1).tw.
16 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$3 or mask$3)).tw.
17 Randomi?ed control$ trial$.tw.
18 Random assignment/
19 Random$ allocat$.tw.
20 Placebo$.tw.
21 Placebos/
22 Quantitative studies/
23 Allocat$ random$.tw.
24 or/13-23
25 12 and 24

DARE-NHS EED-HTA

Data coverage not known (approximately 1994–2006)
CRD website version
Search undertaken between April and June 2006
((ezetimibe OR ezetrol OR zetia OR vytorin OR inegy) AND (hypercholesterolemia OR hypercholesterolaemia))

EMBASE

1980–2006
Ovid Online version
Search undertaken between April and June 2006
1 ezetimibe.tw.
2 ezetrol.tw.
3 zetia.tw.
4 vytorin.tw.
5 inegy.tw.
6 "163222-33-1.".rn.
7 Ezetimibe/
8 or/1-7
9 hypercholesterolaemia.mp. or hypercholesterolemia.af. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
10 8 and 9
11 clinical trial/
12 randomized controlled trial/
13 randomization/
14 single blind procedure/
15 double blind procedure/
16 crossover procedure/
17 placebo/
18 randomi?ed control$ trial$.tw.
19 rct.tw.
20 random allocation.tw.
21 randomly allocated.tw.
22 allocated randomly.tw.
23 (allocated adj2 random).tw.
24 single blind$.tw.
25 double blind$.tw.
26 ((treble or triple) adj blind$).tw.
27 placebo$.tw.
28 prospective study/
29 or/11-29
30 case study/
31 case report.tw.
32 abstract report/ or letter/
33 or/30-32
34 29 not 33
35 10 and 34

MEDLINE

1966–2006
Ovid Online
Search undertaken between April and June 2006
1 ezetimibe.tw.
2 ezetrol.tw.
3 zetia.tw.
4 vytorin.tw.
5 inegy.tw.
6 or/1-5
7 randomized controlled trial.pt.
8 controlled clinical trial.pt.
9 randomized controlled trials/
10 random allocation/
11 double blind method/
12 single blind method/
13 or/7-12
14 clinical trial.pt.
15 exp clinical trials/
16 (clin$ adj25 trial$).tw.
17 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).tw.
18 placebos/
19 placebo$.tw.
20 random$.tw.
21 research design/
22 or/14-21
23 "comparative study"/
24 exp evaluation studies/
25 follow-up studies/
26 prospective studies/
27 (control$ or prospectiv$ or volunteer$).tw.
28 (control$ or prospectiv$ or volunteer$).tw.
29 or/23-28
30 13 or 22 or 29
31 "animal"/
32 "human"/

33 31 not 32
34 30 not 33
35 34 and 6
36 hypercholesterolemia.af.
37 hypercholesterolaemia.af.
38 35 and (36 or 37)
39 "163222-33-1.".rn.
40 6 or 39
41 40 and 34 and (36 or 37)

MEDLINE In-Process and Other Non-Indexed Citations

Ovid Online version

Search undertaken between April and June 2006

1 ezetimibe.tw.
2 ezetrol.tw.
3 zetia.tw.
4 vytorin.tw.
5 inegy.tw.
6 or/1-5
7 hypercholesterolemia.af.
8 hypercholesterolaemia.af.
9 or/7-8
10 6 and 9

SCI and SSCI

1900–2006

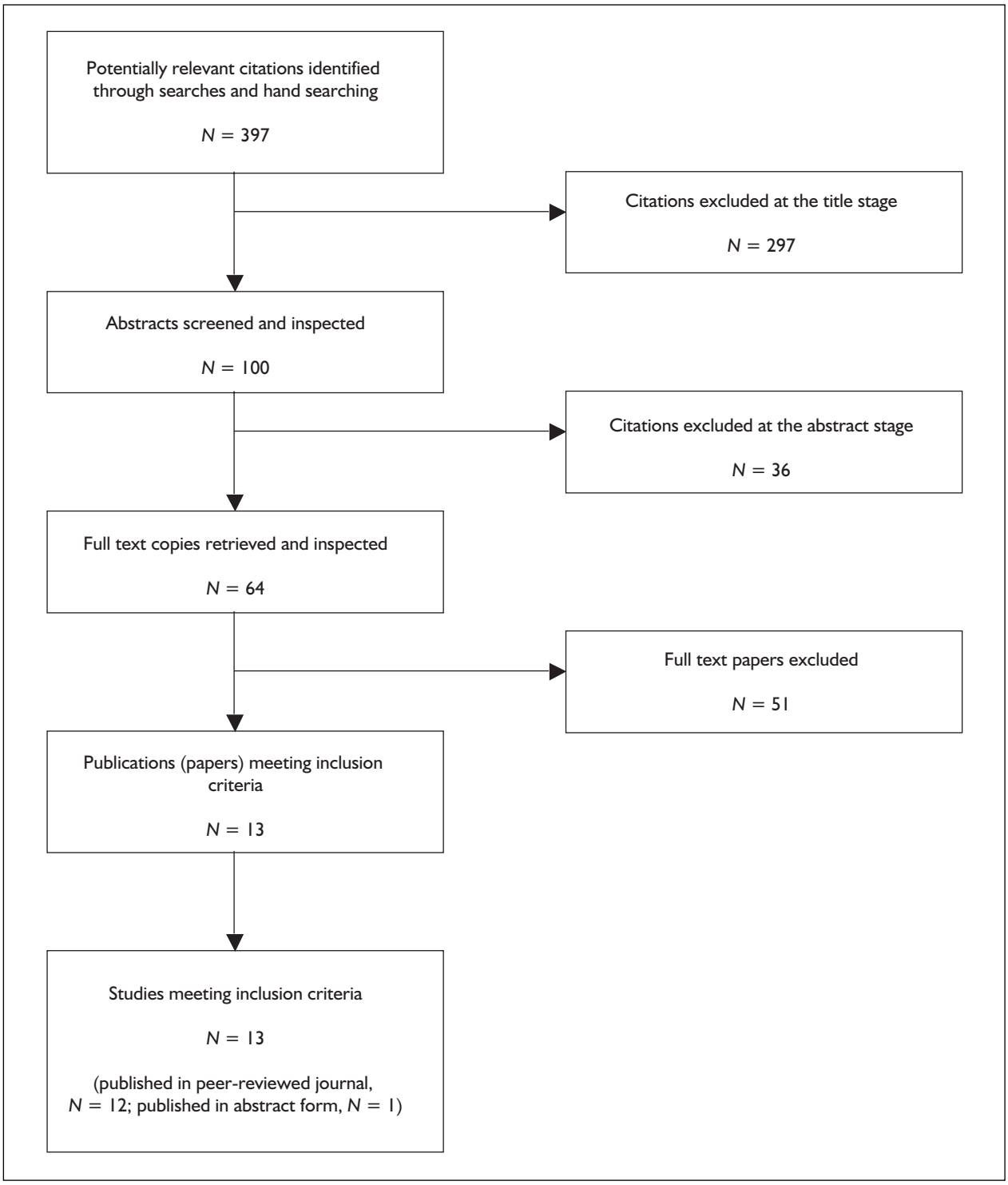
Web of Knowledge version

Search undertaken between April and June 2006

1 TS=(hypercholesterolemia OR hypercholesterolaeima) DocType=All document types; Language=All languages; Databases=SCI-EXPANDED, SSCI; Timespan=1900-2006
2 TS=(ezetimibe OR ezetrol OR zetia OR vytorin OR inegy) DocType=All document types; Language=All languages; Databases=SCI-EXPANDED, SSCI; Timespan=1900-2006
3 #1 AND #2 DocType=All document types; Language=All languages; Databases=SCI-EXPANDED, SSCI; Timespan=1900-2006

Appendix 3

Clinical effectiveness: QUOROM trial flow chart



Appendix 4

Summary of excluded studies with rationale (clinical effectiveness)

Reference	Reason for exclusion
Anon., 2001[208]	Letter/comment/editorial/report
Anon., 2002[209]	German (letter/comment/editorial/report)
Anon., 2002[210]	German (letter/comment/editorial/report)
Anon., 2002[211]	German (letter/comment/editorial/report)
Anon., 2003[212]	German (letter/comment/editorial/report)
Anon., 2003[213]	German (letter/comment/editorial/report)
Anon., 2004[214]	6-week study
Anon., 2004[215]	Letter/comment/editorial/report
Anon., 2004[216]	Letter/comment/editorial/report
Anon., 2005[217]	German (letter/comment/editorial/report)
Anon., 2005[218]	German (letter/comment/editorial/report)
Baigent and Laundry, 2003[129]	Ongoing trial
Ballantyne *et al*., 2005[219]	6-week study
Ballantyne *et al*., 2006[220] (abstract)	6-week study
Ballantyne *et al*., 2006[221] (abstract)	Same study as Ballantyne *et al*., 2006 (6-week study)
Barrios *et al*., 2005[222]	6-week study
Brohet *et al*., 2005[223]	6-week study
Cruz-Fernandez *et al*., 2005[224]	6-week study
Davidson *et al*., 2004[135]	Meta-analysis
Davidson *et al*., 2006[225] (abstract)	6-week study
Davidson *et al*., 2006[226] (abstract)	6-week study
Davidson *et al*., 2006[136]	Wrong intervention/comparator/outcome
Descamps *et al*., 2006[227] (abstract)	7-day study
Dvorakova *et al*., 2006[228] (abstract)	Non-RCT
Esteban-Salan *et al*., 2006[229] (abstract)	Non-RCT
Farnier *et al*., 2005[124]	Population with mixed hyperlipidaemia
Farnier *et al*., 2005[230]	6-week study
Feldman *et al*., 2004[125]	Results only for the first 5 weeks
Gagne *et al*., 2002[173]	8-week study
Goldman-Levine *et al*., 2005[231]	Review – not systematic
Jakulj *et al*., 2005[232]	Wrong intervention/comparator/outcome
Jang-Whan Bae, 2005[233]	The libraries were unable to trace this paper
Kastelein *et al*., 2004[234]	Ongoing
Kastelein *et al*., 2005[235]	Ongoing
Leibovitz *et al*., 2006[236] (abstract)	Non-RCT
Madigosky and Kane, 2003[237]	Letter/comment/editorial
Maeder *et al*., 2005[238]	Observational programme
McKenney *et al*., 2006[239]	Mixed hyperlipidaemia. Part of Farnier *et al*., 2005[124]
Melani *et al*., 2003[240]	Abstract, full results published by Melani *et al*., 2003[116]
Ose *et al*., 2005[241]	Single arm
Pearson *et al*., 2005[242]	Subgroup analysis (6-week study)
Pearson *et al*., 2005[243]	6-week study
Pisciotta *et al*., 2006[244] (abstract)	Non-RCT
Rossebo *et al*., 2003[127]	Ongoing trial
Rossebo, 2005[128]	Ongoing trial. Part of Rossebo *et al*., 2003[127]
Schering-Plough, 2006[126]	Ongoing trial
Shepherd, 2003[245]	Letter/comment/editorial
Simons *et al*., 2004[246]	*Post hoc* analysis of Gagne *et al*., 2002[173] (8-week study)
Stein *et al*., 2005[247]	Single arm study
Sudhop *et al*., 2002[248]	2-week study

continued

Reference	Reason for exclusion
Sudhop and von Bergmann, 2003[249]	German (letter/comment/editorial)
Van Heyningen, 2006[250] (abstract)	Non-RCT
Veltri *et al*., 2006[251] (abstract)	Review
Vermaak *et al*., 2002[252]	Abstract, no useful data. Email to authors
Wierzbicki *et al*., 2005[253]	Non-RCT

Appendix 5

Clinical effectiveness: quality assessment

	Ballantyne et *al.*, 2003[115]	Ballantyne et *al.*, 2004a[117]	Ballantyne et *al.*, 2004b[119]	Bays et *al.*, 2004[111]	Davidson et *al.*, 2002[112]	Dujovne et *al.*, 2002[122]	Goldberg et *al.*, 2004[113]	Knopp et *al.*, 2003[123]	Masana et *al.*, 2005[120]	McKenney et *al.*, 2006[121]	Melani et *al.*, 2003[116]	Rodney et *al.*, 2006[114]	Stein et *al.*, 2004[118]
Was the method used to assign participants to the treatment groups really random?	?	?	Y	?	Y	Y	Y	Y	?	?	Y	Y	?
What method of assignment was used?	?	?	CR	?	CG	CG	CG	CG	?	?	CG	CG	?
Was the allocation of treatment concealed?	?	?	?	?	?	?	?	?	?	?	?	?	?
What method was used to conceal treatment allocation?	?	?	?	?	?	?	?	?	?	?	?	?	?
Was the number of participants who were randomised stated?	Y	Y	Y	Y	Y	Y	Y	Y	Y	?	Y	Y	Y
Were details of baseline comparability presented?	Y	Y	Y	Y	Y	Y	Y	Y	Y	?	Y	Y	Y
Was baseline comparability achieved?	Y	Y	Y	Y	Y	Y	Y	Y	Y	?	Y	Y	Y
Were the eligibility criteria for study entry specified?	Y	Y	Y	Y	?	Y	Y	Y	Y	?	Y	Y	Y
Were any co-interventions identified that may influence the outcomes for each group?	?	Y	Y	Y	?	Y	Y	Y	Y	?	Y	Y	Y
Were the outcome assessors blinded to the treatment allocations?	Y	Y	Y	Y	Y	?	Y	?	?	?	Y	?	?
Were the individuals who administered the intervention blinded to the treatment allocation?	Y	Y	Y	Y	?	?	Y	Y	Y	?	Y	Y	Y
Were the participants who received the intervention blinded to the treatment allocation?	Y	Y	Y	Y	Y	Y	Y	Y	Y	?	Y	Y	Y
Was the success of the blinding procedure assessed?	?	?	?	?	?	?	?	?	?	?	?	?	?
Were at least 80% of the participants originally included in the randomised process followed up in the final analysis?	Y	Y	Y	Y	Y	Y	Y	Y	Y	?	Y	Y	Y
Were the reasons for withdrawal stated?	Y	Y	Y	Y	Y	Y	Y	Y	Y	?	Y	Y	Y
Was an ITT analysis included?	Y	Y	N	Y[a]	Y	Y	Y[a]	Y	Y	?	Y	Y[a]	N

CG, single computer generated; CR, central randomisation; N, no; Y, item addressed; ?, not enough information or not clear.
[a] Modified ITT.

Appendix 6

Patient demographics and baseline characteristics

Study	Patient characteristics								
	Mean age (range) (years)	Male (%)	BMI (kg/m^2), mean (range)	Physically active (%)	Smoker (%)	Ethnicity (%)	Lifestyle intervention	Concomitant therapy	History/risk factors/presence of CVD
Ballantyne *et al.*, 2003[115]	T1: 56.7 T2: 58.7 T3: 57.8 T4: 56.9	T1: 45 T2: 42 T3: 38 T4: 29	NR	T1: 49 T2: 50 T3: 48 T4: 55	T1: 17 T2: 14 T3: 13 T4: 15	White: T1: 88 T2: 87 T3: 83 T4: 82	The NCEP Step I or strict diet	NR	Mixed population of patients with family history of CHD (41%), history of hypertension (35%), DM (4%) and CHD including CHD risk factors (9%)
Ballantyne *et al.*, 2004a[117]	T1: 57.6 (26–86) T2: 58.5 (34–76) ⩾65 years: T1: 27% T2: 33%	T1: 39 T2: 51	NR	T1: 53 T2: 44	T1: 13 T2: 9	Caucasian: T1: 87; T2: 87 Black: T1: 6; T2: 4 Hispanic: T1: 4; T2: 9 Asian: T1: <1; T2: 0 American Indian: T1: <3; T2: 0	The NCEP Step I or strict diet	NR	Mixed population of patients with history of hypertension (38%), DM (4.5%), CHD including CHD risk factors (12.5%) and peripheral vascular disease (2.5%)
Ballantyne *et al.*, 2004b[119]	T1: 59.4 T2: 59.9 T3: 60.8	T1: 53.6 T2: 52.5 T3: 50	NR	NR	NR	White: T1: 92; T2: 89.7; T3: 89.3 Black: T1: 4.9; T2: 4.9; T3: 3.8 Hispanic: T1: 1.9; T2: 3; T3: 4.2 Asian: T1: 0.8; T2: 1.1; T3:1.9 Other: T1: 0.4; T2: 1.1; T3: 0.8	NR	NR	Patients with established CHD or its risk equivalent conferring a 10-year risk of >20% for CHD (Framingham score)

continued

Study	Patient characteristics								
	Mean age (range) (years)	**Male (%)**	**BMI (kg/m^2), mean (range)**	**Physically active (%)**	**Smoker (%)**	**Ethnicity (%)**	**Lifestyle intervention**	**Concomitant therapy**	**History/risk factors/presence of CVD**
Bays *et al.*, 2004[111]	T1: 55.5 T2: 56.4 T3: 54.9 T4: 56.0 ⩾65 years: T1: 22.8% T2: 23% T3: 21.1% T4: 24%	T1: 45.6 T2: 48.6 T3: 49.4 T4: 43.9	T1: 28.4 T2: 27.9 T3: 28.3 T4: 28.0	NR	NR	White: T1: 89.3; T2: 88.7 T3: 87; T4: 89.2 Black: T1: 2.7; T2: 3.1 T3: 3.4; T4: 3.4 Hispanic: T1: 2.7; T2: 1.3 T3: 2.7; T4: 1.4 Other: T1: 5.4; T2: 6.9 T3: 6.9; T4: 6.1	Cholesterol-lowering diet	NR	Includes patients with stable/controlled CVD, hypertension or DM
Davidson *et al.*, 2002[112]	T1: 60.3 (35–84) T2: 57.6 (27–83) T3: 56.4 (25–87) T4: 58.8 (25–84) ⩾65 years: T1: 34% T2: 31% T3: 28% T4: 33%	T1: 39 T2: 46 T3: 42 T4: 44	NR	NR	NR	White: T1: 95; T2: 91 T3: 90; T4: 96 Black: T1: 2; T2: 4 T3: 5; T4: 1 Hispanic: T1: 3; T2: 3 T3: 5; T4: 1 Asian: T1: 0; T2: 2 T3: <1; T4: 0 American Indian: T1: 0; T2: 0 T3: 0; T4: 1	NR	NR	Mixed population of patients with family history of CHD (45%), history of hypertension (30%), DM (6%) and CHD including CHD risk factors (6.5%)

continued

Study	Patient characteristics								
	Mean age (range) (years)	**Male (%)**	**BMI (kg/m^2), mean (range)**	**Physically active (%)**	**Smoker (%)**	**Ethnicity (%)**	**Lifestyle intervention**	**Concomitant therapy**	**History/risk factors/presence of CVD**
Dujovne *et al.*, 2002[122]	T1: 57.9 (18–85) T2: 58.1 (30–85) ⩾65 years: T1: 31% T2: 31%	T1: 50 T2: 45	T1: 28.6 (17.5–47.0) T2: 28.4 (19.4–49.5)	T1: 57 T2: 56	T1: 12 T2: 9	Caucasian: T1: 90; T2: 93 Black: T1: 5; T2: 4 American Indian: T1: <1; T2: 0 Asian: T1: 1; T2: 1 Hispanic: T1: 3; T2: 1 Pacific Islander: T1: <1; T2: 0	The NCEP Step 1 or strict diet	CVD drugs and aspirin (⩽325 mg/day) was permitted	One-third of patients had a known family history of CAD and one-third had some degree of hypertension. Other CVD risk factors were less frequent (⩽12% in either treatment group)
Goldberg *et al.*, 2004[113]	Age <65 years: T1: 79% T2: 75% T3: 77% T4: 71% Age ⩾65 years: T1: 21% T2: 25% T3: 23% T4: 29%	T1: 38 T2: 48 T3: 49 T4: 41	NR	NR	NR	White: T1: 77; T2: 83 T3: 79; T4: 81 Black: T1: 7; T2: 3 T3: 4; T4: 5 Hispanic: T1: 10; T2: 9 T3: 10; T4: 9 Other: T1: 7; T2: 5 T3: 7; T4: 5	The NCEP Step 1 or strict diet		Patients with hypertension, diabetes and CHD

continued

Study	Patient characteristics								
	Mean age (range) (years)	**Male (%)**	**BMI (kg/m^2), mean (range)**	**Physically active (%)**	**Smoker (%)**	**Ethnicity (%)**	**Lifestyle intervention**	**Concomitant therapy**	**History/risk factors/presence of CVD**
Knopp *et al.*, 2003[123]	T1: 58.3 (20–86) T2: 57.6 (24–79) ⩾65 years: T1: 33% T2: 32%	T1: 49 T2: 46	T1: 29.1 (17.8–49.6) T2: 29.6 (19.4–45.7)	T1: 50 T2: 48	T1: 15 T2: 11	White: T1: 91; T2: 88 Black: T1: 5; T2: 6 American Indian: T1: 0; T2: <1 Asian: T1: 1; T2: <1 Hispanic: T1: 2; T2: 5 Pacific Islander: T1: <1; T2: 0	The NCEP Step 1 or strict diet	CV drugs and aspirin (⩽350 mg/day) were permitted	One-third of patients had a known family history of CAD and one-third had some degree of hypertension
Masana *et al.*, 2005[120]	T1: 59 (22–84) T2: 61 (28–83) ⩾65 years: T1: 36% T2: 36%	T1: 57 T2: 55	T1: 29.2 T2: 29.6	NR	NR	White: T1: 91; T2: 94 Black: T1: 6; T2: 3 Hispanic: T1: 2; T2: 1 Asian 1: T1: <1; T2: 3 Other: T1: 1; T2: 0	Cholesterol-lowering diet	NR	Patients with established but stable CHD and CHD equivalents, including DM
McKenney *et al.*, 2006[121]	NR	50% women	NR	NR	NR	NR	NR	NR	NR

continued

Study	Patient characteristics								
	Mean age (range) (years)	**Male (%)**	**BMI (kg/m^2), mean (range)**	**Physically active (%)**	**Smoker (%)**	**Ethnicity (%)**	**Lifestyle intervention**	**Concomitant therapy**	**History/risk factors/presence of CVD**
Melani *et al.*, 2003[116]	T1: 52.0 (26–75) T2: 56.9 (20–86) T3: 55.1 (23–84) T4: 53.4 (32–76) ⩾65 years: T1: 16% T2: 25% T3: 26% T4: 17%	T1: 36 T2: 41 T3: 49 T4: 48	NR	T1: 52 T2: 62 T3: 52 T4: 58	T1: 23 T2: 11 T3: 15 T4: 15	Caucasian: T1: 94; T2: 86 T3: 85; T4: 80 Black: T1: 5; T2: 5 T3: 6; T4: 9 Hispanic: T1: 2; T2: 5 T3: 7; T4: 2 Asian: T1: 0; T2: 2 T3: 1; T4: 9 Pacific Islander: T1: 0; T2: 0 T3: <1; T4: 0 Other: T1: 0; T2: <1; T1: 0; T4: 0	NR	NR	40% of patients had a known family history of CHD, 29% had a history of hypertension, 4.2% had a DM, 5.5 had history of CHD, and 1.3% had a peripheral vascular disease
Rodney *et al.*, 2006[114]	T1: 55.2 T2: 53.7	T1: 39 T2: 38	T1: 31.3 T2: 31.0			All patients were African-Americans	The NCEP Step I diet	NR	21% in the ezetimibe + simvastatin arm and 16% in the simvastatin arm had DM. Patients with CHD were 10% vs 11% and CV risk ⩾2 were 49% vs 54%
Stein *et al.*, 2004[118]	T1: 53.0 T2: 51.6 ⩾65 years: T1: 21% T2: 16%	T1: 5 T2: 54	NR	NR	T1: 25 T2: 27	White: T1: 91 T2: 91 Non-white: T1: 9 T2: 9	NR	NR	HeFH was present in 58% of subjects (genotype confirmed in 30%) and the remaining subjects had CHD or at least 2 CVD risk factors (31%), history of hypertension (37%) and DM (6.5%)

NR, not reported.

Appendix 7

Data abstraction tables

Data are given in *Tables 54–57*.

TABLE 54 *LDL-c (mmol/l)*

Study	Pooled ezetimibe + statin				Ezetimibe				Pooled statin				Placebo			
	N	**Mean**	**SD**	**95% CI**	***N***	**Mean**	**SD**	**95% CI**	***N***	**Mean**	**SD**	**95% CI**	***N***	**Mean**	**SD**	**95% CI**
12-week studies																
Ballantyne et *al.*, 2003[115]																
Baseline	*255*	*4.65*	0.64	4.57 to 4.73	*65*	*4.53*	0.56	4.39 to 4.67	*248*	*4.65*	0.63	4.57 to 4.73	*60*	*4.60*	0.54	4.46 to 4.74
Mean % change	*255*	*–54.5*	15.01	–56.34 to –52.66	*65*	*–18.4*	14.92	–22.03 to –14.77	*248*	*–42.4*	14.96	–44.26 to –40.54	*60*	*5.9*	14.87	2.14 to 9.66
Bays et *al.*, 2004[111]																
Baseline	*609*	*4.58*	0.64	4.53 to 4.63	*149*	*4.68*	0.60	4.58 to 4.78	*622*	*4.62*	0.66	4.57 to 4.67	*148*	*4.63*	0.59	4.53 to 4.73
Mean % change	*604*	*–53.0*	14.75	–54.18 to –51.82	*148*	*–18.9*	14.60	–21.25 to –16.55	*612*	*–39.0*	14.84	–40.18 to –37.82	*146*	*–2.2*	14.50	–4.55 to 0.15
Davidson et *al.*, 2002[112]																
Baseline	*274*	*4.58*	*0.52*	4.52 to 4.64	*61*	*4.71*	*0.60*	4.56 to 4.86	*263*	*4.64*	*0.52*	4.54 to 4.68	*70*	*4.61*	*0.56*	4.48 to 4.74
Mean % change	*274*	*–49.9*	14.90	–51.66 to –48.14	*61*	*–18.1*	14.84	–21.82 to –14.38	*263*	*–36.1*	14.60	–37.86 to –34.34	*70*	*–1.3*	14.22	–4.63 to 2.03
Dujovne et *al.*, 2002[122]																
Baseline					*666*	*4.36*	NR	NA					*226*	*4.37*	NR	NA
Mean % change					*666*	*–16.86*	14.19	–17.94 to –15.78					*226*	*0.36*	12.48	–1.27 to 1.99
Goldberg et *al.*, 2004[113]																
Baseline	*353*	*4.55*	*0.68*	4.48 to 4.62	*92*	*4.58*	*0.68*	4.44 to 4.72	*349*	*4.55*	*0.65*	4.48 to 4.62	*93*	*4.52*	*0.73*	4.37 to 4.67
Mean % change	*353*	*–53.2*	*17.2*	–54.99 to –51.41	*89*	*–19.8*	*10.5*	–21.98 to –17.62	*345*	*–38.5*	*14.2*	–40.00 to –37.00	*92*	*2.7*	*13.3*	–0.02 to 5.42
Knopp et *al.*, 2003[123]																
Baseline					*622*	*4.27*	NR	NA					*205*	*4.25*	NR	NA
Mean % change					*621*	*–17.69*	14.70	–18.85 to –16.53					*204*	*0.79*	12.43	–0.92 to 2.50
Melani et *al.*, 2003[116]																
Baseline	*204*	*4.6*	0.5	4.53 to 4.67	*64*	*4.6*	0.6	4.45 to 4.75	*205*	*4.6*	0.6	4.52 to 4.68	*65*	*4.6*	0.5	4.48 to 4.72
Mean % change	*204*	*–37.7*	12.85	–39.46 to –35.94	*64*	*–18.7*	12.80	–21.84 to –15.56	*205*	*–24.3*	12.89	–26.06 to –22.54	*65*	*1.3*	12.90	–1.84 to 4.44
Rodney et *al.*, 2006[114]																
Baseline	*124*	*4.59*	*0.60*						*123*	*4.54*	*0.61*					
Mean % change	*124*	*–45.6*	15.8	–48.53 to –42.97					*123*	*–28.3*	15.7	–31.12 to –25.56				
Stein et *al.*, 2004[118]																
Baseline	*305*	*4.87*	1.22	4.73 to 5.0					*316*	*4.84*	1.24	4.70 to 4.98				
Mean % change	*293*	*–33.2*	11.98	–34.57 to –31.83					*303*	*–20.30*	15.67	–22.06 to –18.5				
23–48-week studies																
Ballantyne et *al.*, 2004a[117]																
Baseline	*201*	*4.7*	*0.6*	4.62 to 4.78					*45*	*4.8*	*0.6*	4.62 to 4.98				
Mean % change	*201*	*–48.4*	*18.8*	–51.00 to –45.80					*45*	*–38.6*	*12.4*	–42.22 to –34.98				

continued

TABLE 54 *LDL-c (mmol/l) (cont'd)*

Study	Pooled ezetimibe + statin				Ezetimibe				Pooled statin				Placebo			
	N	**Mean**	**SD**	**95% CI**	***N***	**Mean**	**SD**	**95% CI**	***N***	**Mean**	**SD**	**95% CI**	***N***	**Mean**	**SD**	**95% CI**
Masana et *al.*, 2005[120]																
Baseline	*355*	*3.55*	1.23	3.42 to 3.68					*78*	*3.42*	1.19	3.15 to 3.69				
Mean % change	*350*	*–23.7*	33.67	–27.23 to –20.17					*78*	*3.3*	22.96	–1.80 to 8.40				

NA, not applicable; NR, not reported; data in *italics*, reported data; other, calculated data.
To convert mg/dl of HDL-c or LDL-c to mmol/l, multiply by 0.02586; to convert mg/dl of TG to mmol/l, multiply by 0.01129.

Forced titration

Study	***N***	**Mean**	**SD**	**95% CI**	***N***	**Mean**	**SD**	**95% CI**	***N***	**Mean**	**SD**	**95% CI**
Ballantyne et *al.*, 2004b[119]												
	Ezetimibe + statin 10/10 (T1)				**Ezetimibe + statin 10/20 (T2)**				**Atorvastatin 10 (T3)**			
Baseline	*263*	*4.68*	1.07	4.55 to 4.81	*263*	*4.66*	1.08	4.53 to 4.79	*262*	*4.70*	1.19	4.56 to 4.84
Mean % change at 6 weeks	*263*	*–46.1*	12.97	–47.67 to –44.53	*263*	*–50.3*	12.97	–51.87 to –48.73	*262*	*–37.2*	12.95	–38.77 to –35.63
	Ezetimibe + statin 10/20				**Ezetimibe + statin 10/40**				**Atorvastatin 10**			
Mean % change at 12 weeks	*250*	*–50.2*	12.65	–51.77 to –48.63	*252*	*–54.3*	12.70	–55.87 to –52.73	*246*	*–44.3*	14.12	–46.06 to –42.54
	Ezetimibe + statin 10/40				**Ezetimibe + statin 10/40**				**Atorvastatin 40**			
Mean % change at 18 weeks	*242*	*–55.6*	9.31	–56.78 to –54.42	*240*	*–55.6*[a]	9.31[a]	–56.78 to –54.42[a]	*237*	*–49.1*	13.86	–50.86 to –47.34
	Ezetimibe + statin 10/80				**Ezetimibe + statin 10/80**				**Atorvastatin 80**			
Mean % change at 24 weeks (end-point)	*232*	*–59.4*	10.62	–60.77 to –58.03	*227*	*–59.4*[a]	10.62[a]	–60.77 to –58.03[a]	*228*	*–52.5*	15.10	–54.46 to –50.54

To convert mg/dl of HDL-c or LDL-c to mmol/l, multiply by 0.02586; to convert mg/dl of TG to mmol/l, multiply by 0.01129.
Data in *italics*, reported data; others, calculated data.
[a] Data pooled for common doses of ezetimibe + simvastatin at weeks 18 and 24 (based on the mean sample size of the two arms).

TABLE 55 *Total-c (mmol/l)*

Study	Pooled ezetimibe + statin				Ezetimibe				Pooled statin				Placebo			
	N	Mean	SD	95% CI	*N*	Mean	SD	95% CI	*N*	Mean	SD	95% CI	*N*	Mean	SD	95% CI
12-week studies																
Ballantyne et *al.*, 2003[115]																
Baseline	*255*	*6.91*	0.64	6.83 to 6.99	*65*	*6.70*	0.73	6.52 to 6.88	*248*	*6.95*	0.63	6.87 to 7.03	*60*	*6.77*	0.70	6.59 to 6.95
Mean % change	*255*	*–41.1*	11.82	–42.55 to –39.65	*65*	*–13.5*	12.34	–16,50 to –10.50	*248*	*–32.1*	11.81	–33.57 to –30.63	*60*	*3.5*	11.85	0.50 to 6.50
Bays et *al.*, 2004[111]																
Baseline	*609*	*6.78*	0.73	6.72 to 6.84	*149*	*6.88*	0.68	6.77 to 6.99	*622*	*6.80*	0.75	6.74 to 6.86	*148*	*6.80*	0.74	6.68 to 6.92
Mean % change	*604*	*–37.6*	12.29	–38.58 to –36.62	*148*	*–13.3*	10.95	–15.06 to –11.54	*612*	*–27.7*	12.37	–28.68 to –26.72	*146*	*–1.4*	10.87	–3.16 to 0.36
Davidson et *al.*, 2002[112]																
Baseline	*274*	*6.86*	NR	NA	*61*	*7.07*	NR	NA	*263*	*6.89*	NR	NA	*70*	*6.89*	NR	NA
Mean % change	*274*	*–36.6*	11.59	–37.97 to –35.23	*61*	*–13.3*	11.72	–16.24 to –10.36	*263*	*–25.8*	11.35	–27.17 to –24.43	*70*	*–0.6*	11.71	–3.34 to 2.14
Dujovne et *al.*, 2002[122]																
Baseline					*666*	*6.57*	NR	NA					*226*	*6.62*	NR	NA
Mean % change					*666*	*12.48*	9.81	11.74 to 13.22					*226*	*0.84*	8.42	–0.26 to 1.94
Goldberg et *al.*, 2004[113]																
Baseline	*353*	*6.76*	*0.78*	6.68 to 6.84	*92*	*6.81*	*0.78*	6.65 to 6.97	*349*	*6.73*	*0.78*	6.65 to 6.81	*93*	*6.71*	*0.83*	6.54 to 6.88
Mean % change	*353*	*–37.7*	*13.3*	–39.09 to –36.31	*90*	*–13.7*	*7.9*	–15.33 to –12.07	*345*	*–26.4*	*11.3*	–27.59 to –25.21	*92*	*2.2*	*9.9*	0.18 to 4.22
Knopp et *al.*, 2003[123]																
Baseline					*621*	*6.44*	NR	NA					*204*	*6.43*	NR	NA
Mean % change					*621*	*–12.40*	9.47	–13.14 to –11.66					*204*	*0.57*	8.57	–0.61 to 1.75
Melani et *al.*, 2003[116]																
Baseline	*204*	*6.8*	NR	NA	*64*	*6.9*	NR	NA	*205*	*6.8*	NR	NA	*65*	*6.8*	NR	NA
Mean % change	*204*	*–27.1*	8.57	–28.28 to –25.92	*64*	*–13.2*	9.60	–15.55 to –10.85	*205*	*–17.2*	8.59	–18.38 to –16.02	*65*	*0.2*	9.67	–2.15 to 2.55
Rodney et *al.*, 2006[114]																
Baseline	*124*	*6.66*	*0.70*						*123*	*6.59*	*0.70*					
Mean % change	*124*	*–33*	9.0	–35.19 to –32.02					*123*	*21*	8.9	–22.44 to –19.26				
Stein et *al.*, 2004[118]																
Baseline	*305*	*6.81*	1.22	6.67 to 6.95					*316*	*6.87*	1.24	6.73 to 7.00				
Mean % change	*293*	*–26.1*	11.98	–27.47 to –24.73					*303*	*–16*	12.18	–17.37 to –14.63				
23–48-week studies																
Ballantyne et *al.*, 2004a[117]																
Baseline	*201*	*6.9*	*0.7*	6.80 to 7.00					*45*	*7.0*	*0.7*	6.80 to 7.20				
Mean % change	*201*	*–35.4*	*14.0*	–37.34 to –33.46					*45*	*–27.5*	*10.4*	–30.54 to –24.46				

continued

TABLE 55 *Total-c (mmol/l) (cont'd)*

Study	Pooled ezetimibe + statin				Ezetimibe				Pooled statin				Placebo			
	N	**Mean**	**SD**	**95% CI**	***N***	**Mean**	**SD**	**95% CI**	***N***	**Mean**	**SD**	**95% CI**	***N***	**Mean**	**SD**	**95% CI**
Masana et *al.*, 2005[120]																
Baseline	*355*	*5.62*	1.27	5.49 to 5.75					*78*	*5.49*	1.26	5.21 to 5.77				
Mean % change	*350*	*–15.9*	22.45	–18.25 to –13.55					*78*	*2.5*	15.90	–1.03 to 6.03				

NA, not applicable; NR, not reported; data in *italics*, reported data; others, calculated data.
To convert mg/dl of HDL-c or LDL-c to mmol/l, multiply by 0.02586; to convert mg/dl of TG to mmol/l, multiply by 0.01129.

Forced titration

Study	***N***	**Mean**	**SD**	**95% CI**	***N***	**Mean**	**SD**	**95% CI**	***N***	**Mean**	**SD**	**95% CI**
Ballantyne et *al.*, 2004b[119]												
	Ezetimibe + statin 10/10				**Ezetimibe + statin 10/20**				**Atorvastatin 10**			
Baseline	*263*	*6.90*	1.19	6.76 to 7.04	*263*	*6.86*	1.14	6.72 to 6.99	*262*	*6.93*	1.29	6.77 to 7.09
Mean % change at 6 weeks	*263*	*–33.9*	9.73	–35.08 to –32.72	*263*	*–36.2*	9.73	–37.38 to –35.02	*262*	*–28.1*	9.71	–29.28 to –26.92
	Ezetimibe + statin 10/20				**Ezetimibe + statin 10/40**				**Atorvastatin 20**			
Mean % change at 12 weeks	*250*	*–36.5*	9.49	–37.68 to –35.32	*252*	*–39.2*	9.52	–40.38 to –38.02	*246*	*–33.1*	9.41	–34.28 to –31.92
	Ezetimibe + statin 10/40				**Ezetimibe + statin 10/40**				**Atorvastatin 40**			
Mean % change at 18 weeks	*242*	*–40.5*	7.76	–41.48 to –39.52	*240*	*–40.5*[a]	7.76[a]	–41.48 to –39.52[a]	*237*	*–37.0*	10.78	–38.37 to –35.63
	Ezetimibe + statin 10/80				**Ezetimibe + statin 10/80**				**Atorvastatin 80**			
Mean % change at 24 weeks (end-point)	*232*	*–43.3*	7.58	–44.28 to –42.32	*227*	*–43.3*[a]	7.58[a]	–44.28 to –42.32[a]	*228*	*–40.2*	10.57	–41.57 to –38.83

To convert mg/dl of HDL-c or LDL-c to mmol/l, multiply by 0.02586; to convert mg/dl of TG to mmol/l, multiply by 0.01129.
Data in *italics*, reported data; others, calculated data.
[a] Data pooled for common doses of ezetimibe + simvastatin at weeks 18 and 24 (based on the mean sample size of the two arms).

TABLE 56 *HDL-c (mmol/l)*

Study	Pooled ezetimibe + statin				Ezetimibe				Pooled statin				Placebo			
	N	Mean	SD	95% CI	*N*	Mean	SD	95% CI	*N*	Mean	SD	95% CI	*N*	Mean	SD	95% CI
12-week studies																
Ballantyne *et al.*, 2003[115]																
Baseline	*255*	*1.31*	0.32	1.27 to 1.35	*65*	*1.31*	0.32	1.23 to 1.39	*248*	*1.39*	0.32	1.35 to 1.43	*60*	*1.30*	0.31	1.22 to 1.38
Mean % change	*255*	*7.3*	11.66	5.87 to 8.73	*62*	*4.2*	11.53	1.40 to 7.0	*248*	*4.3*	11.65	2.85 to 5.75	*60*	*3.7*	11.54	0.78 to 6.62
Bays *et al.*, 2004[111]																
Baseline	*609*	*1.35*	0.34	1.32 to 1.38	*149*	*1.36*	0.33	1.31 to 1.41	*622*	*1.33*	0.32	1.30 to 1.36	*148*	*1.38*	0.34	1.32 to 1.44
Mean % change	*604*	*7.2*	12.29	6.22 to 8.18	*148*	*5.0*	13.38	2.84 to 7.16	*612*	*6.8*	12.37	5.82 to 7.78	*146*	*–0.3*	13.29	–2.46 to 1.86
Davidson *et al.*, 2002[112]																
Baseline	*274*	*1.31*	*0.32*	1.27 to 1.35	*61*	*1.33*	*0.30*	1.25 to 1.41	*263*	*1.33*	*0.28*	1.32 to 1.40	*70*	*1.36*	*0.31*	1.29 to 1.43
Mean % change	*274*	*9.3*	13.24	7.73 to 10.87	*61*	*5.1*	12.50	1.96 to 8.24	*263*	*6.9*	12.97	5.33 to 8.47	*70*	*0.9*	12.55	–2.04 to 3.84
Dujovne *et al.*, 2002[122]																
Baseline					*666*	*1.35*	NR	NA					*226*	*1.36*	NR	NA
Mean % change					*666*	*1.31*	12.65	0.35 to 2.27					*226*	*–1.60*	10.97	–3.03 to –0.17
Goldberg *et al.*, 2004[113]																
Baseline	*353*	*1.33*	*0.34*	1.29 to 1.37	*92*	*1.33*	*0.34*	1.26 to 1.40	*349*	*1.27*	*0.31*	1.24 to 1.30	*93*	*1.30*	*0.31*	1.24 to 1.36
Mean % change	*353*	*8.2*	*13.1*	6.83 to 9.57	*90*	*7.0*	*12.6*	4.40 to 9.60	*345*	*7.6*	*11.9*	6.34 to 8.86	*92*	*2.3*	*10.8*	0.09 to 4.51
Knopp *et al.*, **2003**[123]																
Baseline					*621*	*1.35*	NR	NA					*204*	*1.32*	NR	NA
Mean % change					*621*	*1.01*	12.46	0.03 to 1.99					*204*	*–1.26*	11.14	–2.79 to 0.27
Melani *et al.*, 2003[116]																
Baseline	*204*	*1.3*	0.3	1.26 to 1.34	*64*	*1.3*	0.3	1.23 to 1.38	*205*	*1.3*	0.3	1.26 to 1.34	*65*	*1.3*	0.3	1.23 to 1.37
Mean % change	*204*	*8.1*	11.43	6.53 to 9.67	*64*	*4.1*	12.0	1.16 to 7.04	*205*	*6.7*	11.45	5.13 to 8.27	*65*	*2.0*	12.09	–0.94 to 4.94
Rodney *et al.*, 2006[114]																
Baseline	*124*	*1.38*	*0.35*						*123*	*1.31*	*0.35*					
Mean % change	*124*	*1.0*	–11.27	3.40 to –0.57					*123*	*2.0*	–8.9	3.81 to 0.64				
Stein *et al.*, 2004[118]																
Baseline	*305*	*3.7*	11.98	2.33 to 5.07					*316*	*1.0*	12.18	–0.37 to 2.37				
Mean % change	*293*	*2.1*	10.27	0.92 to 3.28					*303*	*1.3*	10.44	0.12 to 2.48				
23–48-week studies																
Ballantyne *et al.*, 2004a[117]																
Baseline	*201*	*1.4*	*0.4*	1.34 to 1.46					*45*	*1.3*	*0.3*	1.21 to 1.39				
Mean % change	*201*	*6.3*	*13.4*	4.45 to 8.15					*45*	*5.4*	*3.13*	4.49 to 6.31				

continued

TABLE 56 *HDL-c (mmol/l) (cont'd)*

Study	Pooled ezetimibe + statin				Ezetimibe				Pooled statin				Placebo			
	N	**Mean**	**SD**	**95% CI**	***N***	**Mean**	**SD**	**95% CI**	***N***	**Mean**	**SD**	**95% CI**	***N***	**Mean**	**SD**	**95 % CI**
Masana et *al.*, 2005[120]																
Baseline	*355*	*1.30*	0.31	1.27 to 1.33					*78*	*1.33*	0.35	1.25 to 1.41				
Mean % change	*350*	*2.0*	20.58	–0.16 to 4.16					*78*	*–0.6*	14.13	–3.74 to 2.54				

NA, not applicable; NR, not reported; data in *italics*, reported data; others, calculated data.
To convert mg/dl of HDL-c or LDL-c to mmol/l, multiply by 0.02586; to convert mg/dl of TG to mmol/l, multiply by 0.01129.

Forced titration

Study	***N***	**Mean**	**SD**	**95% CI**	***N***	**Mean**	**SD**	**95% CI**	***N***	**Mean**	**SD**	**95% CI**
Ballantyne et *al.*, 2004b[119]												
	Ezetimibe + statin 10/10 (T1)				**Ezetimibe + statin 10/20 (T2)**				**Atorvastatin (T3)**			
Baseline	*263*	*1.21*	0.32	1.17 to 1.25	*263*	*1.22*	0.28	1.19 to 1.25	*262*	*1.22*	0.30	1.18 to 1.26
Mean % change at 6 weeks	*263*	*8.0*	12.97	6.43 to 9.57	*263*	*9.5*	12.97	7.93 to 11.07	*262*	*5.1*	12.95	3.53 to 6.67
	Ezetimibe + statin 10/20				**Ezetimibe + statin 10/40**				**Atorvastatin 20**			
Mean % change at 12 weeks	*250*	*9.0*	14.23	7.24 to 10.76	*252*	*12.4*	14.29	10.64 to 14.16	*246*	*6.9*	14.12	5.14 to 8.66
	Ezetimibe + statin 10/40				**Ezetimibe + statin 10/40**				**Atorvastatin 40**			
Mean % change at 18 weeks	*242*	*11.4*	10.87	10.03 to 12.77	*240*	*11.4*[a]	10.87[a]	10.03 to 12.77[a]	*237*	*7.8*	15.39	5.84 to 9.76
	Ezetimibe + statin 10/80				**Ezetimibe + statin 10/80**				**Atorvastatin 80**			
Mean % change at 24 weeks (end-point)	*232*	*12.3*	10.62	10.93 to 13.67	*227*	*12.3*[a]	10.62[a]	10.93 to 13.67[a]	228	6.5	15.10	4.54 to 8.46

To convert mg/dl of HDL-c or LDL-c to mmol/l, multiply by 0.02586; to convert mg/dl of TG to mmol/l, multiply by 0.01129.
Data in *italics*, reported data; others, calculated data.
[a] Data pooled for common doses of ezetimibe + simvastatin at weeks 18 and 24 (based on the mean sample size of the two arms).

TABLE 57 *TG (mmol/l)*

Study	Pooled ezetimibe + statin				Ezetimibe				Pooled statin				Placebo			
	N	**Mean**	**SD**	**95% CI**	***N***	**Mean**	**SD**	**95% CI**	***N***	**Mean**	**SD**	**95% CI**	***N***	**Mean**	**SD**	**95 % CI**
12-week studies																
Ballantyne et *al.*, 2003[115]																
Baseline	*255*	*1.9*	NA	NA	*65*	*1.6*	NA	NA	*248*	*1.7*	NA	NA	*60*	*1.6*	NA	NA
Median % change	*255*	*–32.8*	NA	NA	*65*	*–5.1*	NA	NA	*248*	*–24.5*	NA	NA	*60*	*–6.4*	NA	NA
Bays et *al.*, 2004[111]																
			(SE)													
Baseline	*609*	*1.69*	*0.92*	NA	*149*	*1.60*	*0.87*	NA	*622*	*1.71*	*0.83*	NA	*148*	*1.57*	*0.69*	NA
Median % change	*604*	*–24.3*	*1.1*	NA	*148*	*–10.7*	*2.6*	NA	*612*	*–20.8*	*1.2*	NA	*146*	*–1.9*	*2.6*	NA
Davidson et *al.*, 2002[112]																
Baseline	*274*	*1.97*	*0.72*	1.88 to 2.06	*61*	*2.09*	*0.75*	1.90 to 2.28	*263*	*1.86*	*0.66*	1.79 to 1.97	*70*	*1.88*	*0.75*	1.70 to 2.06
Mean % change	*274*	*–24.1*	23.17	–26.84 to –21.36	*61*	*–8.3*	23.43	–14.18 to –2.42	*263*	*–16.6*	22.70	–19.34 to –13.86	*70*	*2.4*	23.43	–3.09 to 7.89
Dujovne et *al.*, 2002[122]																
Baseline					*666*	*1.86*	NA	NA					*226*	*1.92*	NA	NA
Mean % change					*666*	*–5.65*	33.81	–8.22 to –3.08					*226*	*5.74*	29.62	1.88 to 9.60
Goldberg et *al.*, 2004[113]																
Baseline	*353*	*1.86*	*1.02*	NA	*92*	*1.79*	*1.14*	NA	*349*	*1.84*	*0.98*	NA	*93*	*1.78*	*0.91*	NA
Median % change	*353*	*–28.0*	*28.0*	NA	*90*	*–13.2*	*27.8*	NA	*345*	*–15.2*	*34.1*	NA	*93*	*–2.2*	*33.0*	NA
Knopp et *al.*, 2003[123]																
Baseline					*621*	*1.84*	NA	NA					*204*	*1.93*	NA	NA
Mean % change					*621*	*–1.71*	35.64	–4.51 to –68.42					*204*	*2.43*	31.99	–1.96 to –60.47
Melani et *al.*, 2003[116]																
Baseline	*204*	*2.0*	0.7	1.90 to 2.10	*64*	*2.0*	0.7	1.83 to 2.17	*205*	*2.0*	0.7	1.90 to 2.10	*65*	*1.8*	0.7	1.63 to 1.97
Mean % change	*204*	*–17.6*	29.99	–21.72 to –13.48	*64*	*–2.1*	30.40	–9.55 to –55.78	*205*	*–7.6*	30.07	–11.72 to –3.48	*65*	*2.0*	30.64	–5.45 to –56.25
Rodney et *al.*, 2006[114]																
Baseline	*124*	*1.37*	*0.11*						*123*	*1.38*	*0.64*					
Median % change	*124*	*–22*							*123*	*–15*						
Stein et *al.*, 2004[118]																
			(SE)													
Baseline	*305*	*1.29*	*0.042*	NA					*316*	*1.31*	*0.046*	NA				
Median % change	*293*	*–19.7*	1.6	NA					*303*	*–11.3*	1.7	NA				

continued

TABLE 57 *TG (mmol/l) (cont'd)*

Study	Pooled ezetimibe + statin				Ezetimibe				Pooled statin				Placebo			
	N	Mean	SD	95% CI	*N*	Mean	SD	95% CI	*N*	Mean	SD	95% CI	*N*	Mean	SD	95 % CI
23–48-week studies																
Ballantyne et *al.*, 2004a[117]																
Baseline	*201*	*1.8*	NA	*1.4 to 2.4*					*45*	*1.8*	NA	*1.3 to 2.3*				
Median % change	*201*	*–29.6*	NR	NR					*45*	*–16.9*	NR	NR				
Masana et *al.*, 2005[120]																
Baseline	*355*	*1.44*	*0.05*	NR					*78*	*1.41*	*0.09*	NR				
Median % change	*350*	*–8.2*	*1.7*	NR					*78*	*5.4*	*3.4*	NR				

NA, not applicable; NR, not reported; SE, standard error; data in *italics*, reported data; others, calculated data.
To convert mg/dl of HDL-c or LDL-c to mmol/l, multiply by 0.02586; to convert mg/dl of TG to mmol/l, multiply by 0.01129.

Forced titration

Study	*N*	Median	IQR/1,075	*N*	Median	IQR/1,075	*N*	Median	IQR/1,075
Ballantyne et *al.*, 2004b[119]									
	Ezetimibe + statin 10/10			**Ezetimibe + statin 10/20**			**Atorvastatin 10**		
Baseline	*263*	*1.92*	*1.03*	*263*	*1.94*	*1.20*	*262*	*1.89*	*1.03*
Median % change at 6 weeks	*263*	*–26.3*	*1.5*	*263*	*–24.6*	*2.0*	*262*	*–22.5*	*1.8*
	Ezetimibe + statin 10/20			**Ezetimibe + statin 10/40**			**Atorvastatin 20**		
Median % change at 12 weeks	*250*	*–27.7*	*1.9*	*252*	*–30.8*	*1.7*	*246*	*–28.4*	*1.7*
	Ezetimibe + statin 10/40			**Ezetimibe + statin 10/40**			**Atorvastatin 40**		
Median % change at 18 weeks	*242*	*–32.0*	*1.3*	*240*	*–32.0*[a]	*1.3*[a]	*237*	*–31.2*	*1.8*
	Ezetimibe + statin 10/80			**Ezetimibe + statin 10/80**			**Atorvastatin 80**		
Median % change at 24 weeks (end-point)	*232*	*–35.3*	*1.2*	*227*	*–35.3*[a]	*1.2*[a]	*228*	*–34.8*	*1.9*

To convert mg/dl of HDL-c or LDL-c to mmol/l, multiply by 0.02586; to convert mg/dl of TG to mmol/l, multiply by 0.01129.
[a] Data pooled for common doses of ezetimibe + simvastatin at weeks 18 and 24 (based on the mean sample size of the two arms).

Appendix 8

Meta-analyses

Results are reported in *Figures 9* and *10*, *Table 58* and *Figures 11* and *12*.

Review: Ezetimibe
Comparison: 01 Ezetimibe + statin versus statin alone
Outcome: 03 High density lipoprotein cholesterol (HDL-c) non-titrated 12-week studies

Study or subcategory	Ezetimibe + statin N	Ezetimibe + statin Mean (SD)	Statin N	Statin Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) (95% CI)
01 Ezetimibe + simvastatin versus simvastatin							
Bays[111]	604	7.20 (12.29)	612	6.80 (12.37)		35.69	0.40 (–0.99 to 1.79)
Davidson[112]	274	9.30 (13.24)	263	6.90 (12.97)		13.95	2.40 (0.18 to 4.62)
Goldberg[113]	353	8.20 (13.10)	345	7.60 (11.90)		19.90	0.60 (–1.26 to 2.46)
Subtotal (95% CI)	1231		1220			69.54	0.86 (–0.13 to 1.85)
Test for heterogeneity: $\chi^2 = 2.35$, df = 2 ($p = 0.31$), $I^2 = 15.0\%$							
Test for overall effect: $Z = 1.69$ ($p = 0.09$)							
02 Ezetimibe + atorvastatin versus atorvastatin							
Ballantyne[115]	255	7.30 (11.66)	248	4.30 (11.65)		16.52	3.00 (0.96 to 5.04)
Subtotal (95% CI)	255		248			16.52	3.00 (0.96 to 5.04)
Test for heterogeneity: not applicable							
Test for overall effect: $Z = 2.89$ ($p = 0.004$)							
03 Ezetimibe + pravastatin versus pravastatin							
Melani[116]	204	8.10 (11.43)	205	6.70 (11.45)		13.94	1.40 (–0.82 to 3.62)
Subtotal (95% CI)	204		205			13.94	1.40 (–0.82 to 3.62)
Test for heterogeneity: not applicable							
Test for overall effect: $Z = 1.24$ ($p = 0.22$)							
Total (95% CI)	1690		1673			100.00	1.29 (0.46 to 2.12)
Test for heterogeneity: $\chi^2 = 5.79$, df = 4 ($p = 0.22$), $I^2 = 31.0\%$							
Test for overall effect: $Z = 3.05$ ($p = 0.002$)							

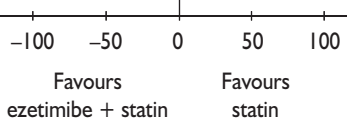


FIGURE 9 *For patients whose condition is not adequately controlled with a statin alone: fixed-dose studies*

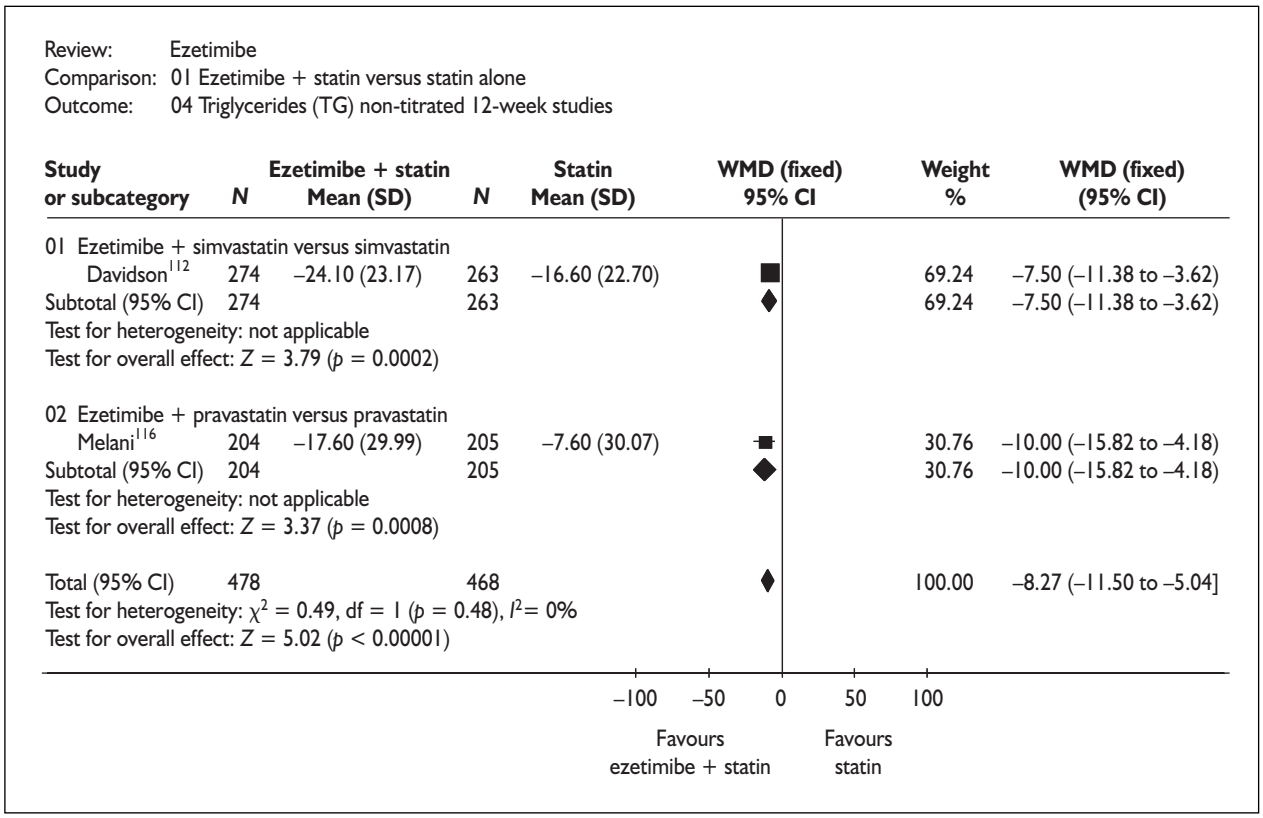


FIGURE 10 *For patients whose condition is not adequately controlled with a statin alone: fixed-dose studies*

TABLE 58 *For patients whose condition is not adequately controlled with a statin alone: summary of titrated studies*

	End-point mean % change (SD)		
	Ezetimibe + pooled statin	**Pooled statin**	***p*-Value**
HDL-c			
Ballantyne *et al.*, 2004a[117]	6.3 (13.4)	5.4 (3.13)	NS
Ballantyne *et al.*, 2004b[119]	12.3 (10.62)	6.5 (15.10)	≤0.05
Masana *et al.*, 2005[120]	2.0 (20.58)	–0.6 (14.13)	0.07
Stein *et al.*, 2004[118]	2.1 (10.27)	1.3 (10.44)	NS
TG (median)			
Ballantyne *et al.*, 2004a[117]	–29.6 (NR)	–16.9 (NR)	<0.01
Ballantyne *et al.*, 2004b[119]	–35.3 (NR)	–34.8 (NR)	NS
Masana *et al.*, 2005[120]	–8.2 (1.7)	5.4 (3.4)	<0.001
Stein *et al.*, 2004[118]	–9.3 (NR)	–3.9 (NR)	<0.01

NR, not reported; NS, not significant.

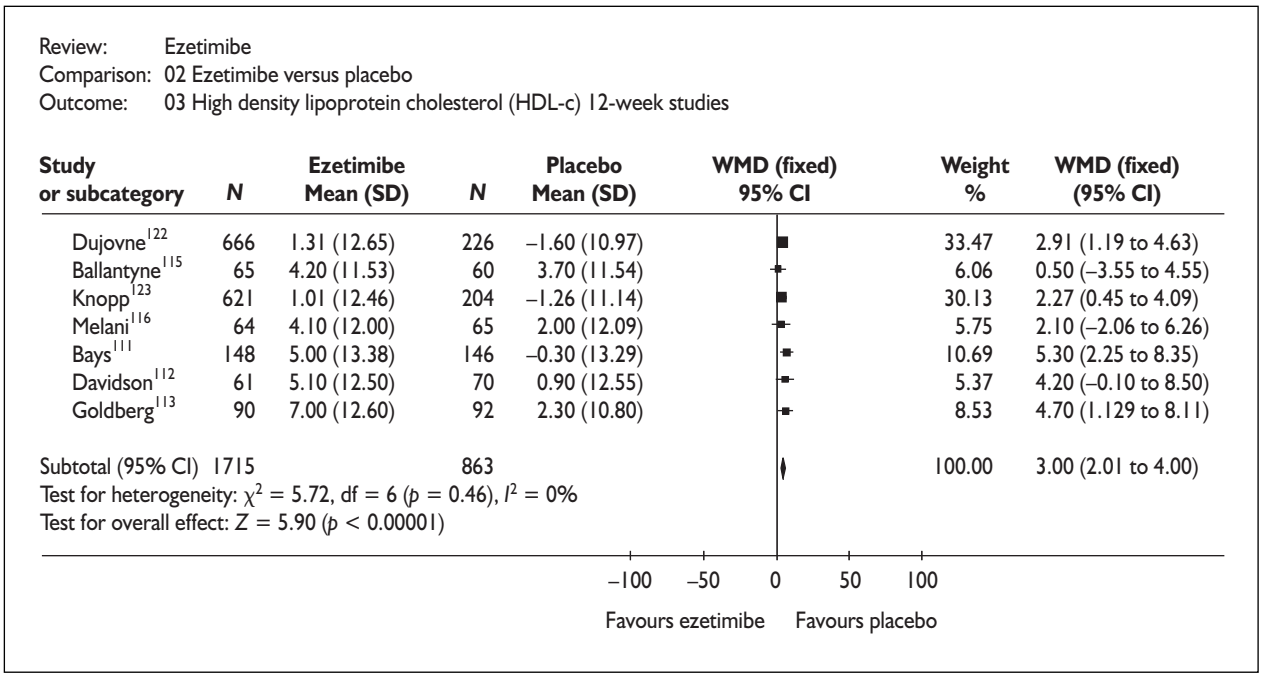


FIGURE 11 *For patients in whom a statin is considered inappropriate, or is not tolerated*

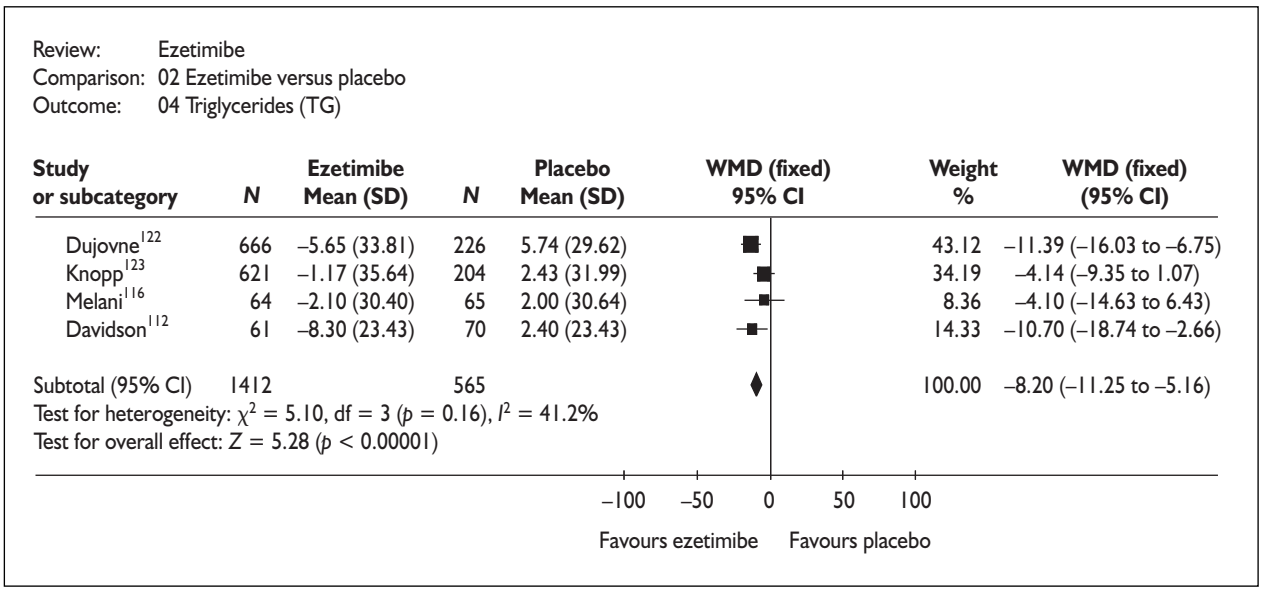


FIGURE 12 *For patients in whom a statin is considered inappropriate, or is not tolerated*

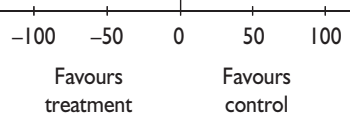
Appendix 9

Clinical effectiveness: LDL-c reduction in HeFH versus non-HeFH group of patients (mmol/l)

Review: WMD
Comparison: 01 HeFH
Outcome: 01 LDL-c

Study or subcategory	N	Ezetimibe + atorvastatin Mean (SD)	N	Atorvastatin Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) (95% CI)
Genetic group	181	–34.60 (16.14)	181	–20.10 (16.14)		55.90	–14.50 (–17.83 to –11.17)
Non-genetic group	124	–31.10 (15.59)	135	–20.50 (15.10)		44.10	–10.60 (–14.34 to –6.86)
Total (95% CI)	305		316			100.00	–12.78 (–15.27 to –10.29)

Test for heterogeneity: $\chi^2 = 2.33$, df = 1 ($p = 0.13$), $I^2 = 57.1\%$
Test for overall effect: $Z = 10.07$ ($p < 0.00001$)



Appendix 10

Changes in plasma lipid/lipoprotein concentrations in HeFH versus non-HeFH patients after addition of ezetimibe to atorvastatin 10 mg/day or doubling the dose of atorvastatin to 20 mg/day

		HeFH group						Non-HeFH group					
		Ezetimibe 10 mg + atorvastatin 10/20/40 mg (*n* = 181)		Atorvastatin 20/40/80 mg (*n* = 181)		Between-group % change	p-Value	Ezetimibe 10 mg + atorvastatin 10/20/40 mg (*n* = 124)		Atorvastatin 20/40/80 mg (*n* = 135)		Between-group % change	p-Value
		Absolute change (mmol/l)	Mean % change (SD)	Absolute change (mmol/l)	Mean % change (SD)			Absolute change (mmol/l)	Mean % change (SD)	Absolute change (mmol/l)	Mean % change (SD)		
Week 4/5	LDL-c	–1.21	–23.6 (12.11)	–0.39	–7.4 (13.45)	–16.2	<0.01	–0.93	–21.5 (13.36)	–0.45	–10.0 (12.78)	–11.5	<0.01
	Total-c	–1.28	–18.1 (9.42)	–0.40	–5.5 (9.42)	–12.6	<0.01	–1.04	–16.2 (10.02)	–0.45	–6.8 (9.30)	–9.3	<0.01
	HDL-c	0.02	1.9 (9.42)	0.01	0.8 (10.76)	1.2	NS	0.03	2.5 (10.02)	0.02	1.9 (10.46)	0.6	NS
	TG (median)	–0.09	–9.3	–0.05	–3.8	–5.5	0.01	–0.15	–9.3	–0.06	–3.9	–5.4	0.02
Week 9/10	LDL-c	–1.55	–30.1 (14.80)	–0.75	–14.7 (14.80)	–15.4	<0.01	–1.25	–28.7 (14.48)	–0.69	–14.9 (13.94)	–13.9	<0.01
	Total-c	–1.65	–23.1 (12.11)	–0.82	–11.6 (12.11)	–11.5	<0.01	–1.41 (11.14)	–22.0	–0.74 (10.46)	–11.0	–11.1	<0.01
	HDL-c	0.03	2.3 (10.76)	–0.01	–0.4 (10.76)	2.7	0.02	0.02	2.5 (11.14)	0.01	1.3 (10.46)	1.2	NS
	TG (median)	–0.11	–10.2	–0.07	–6.4	–3.8	0.02	–0.20	–14.0	–0.11	–9.1	–5.0	0.03
Week 14	LDL-c	–1.78	–34.6 (16.14)	–1.04	–20.1 (16.14)	–14.5	<0.01	–1.39	–31.1 (15.59)	–0.94	–20.5 (15.10)	–10.5	<0.01
	Total-c	–1.93	–27.0 (12.11)	–1.15	–16.2 (13.45)	–10.8	<0.01	–1.61	–24.7 (11.14)	–1.04	–15.7 (10.46)	–9.0	<0.01
	HDL-c	0.04	3.5 (12.11)	–0.01	–0.3 (12.11)	3.8	<0.01	0.04	4.1 (13.36)	0.03	2.8 (12.78)	1.3	NS
	TG (median)	–0.18	–16.3	–0.12	–11.2	–5.1	0.04	–0.38	–23.7	–0.22	–13.1	–10.6	<0.01

NS, not significant.
Data obtained by personal communication from Dr Evan Stein, Director of the Metabolic and Atherosclerosis Research Center, Cincinnati, OH, USA, 30 October 2006.

Appendix 11

Adverse events

Data are given in *Table 59*.

TABLE 59 *Adverse events*

Placebo and ezetimibe arms[a]

	Placebo (%)							Ezetimibe (%)						
	Ballantyne *et al.*, 2003[115]	Bays *et al.*, 2004[111]	Davidson *et al.*, 2002[112]	Dujovne *et al.*, 2002[122]	Goldberg *et al.*, 2004[113]	Knopp *et al.*, 2003[123]	Melani *et al.*, 2003[116]	Ballantyne *et al.*, 2003[115]	Bays *et al.*, 2004[111]	Davidson *et al.*, 2002[112]	Dujovne *et al.*, 2002[122]	Goldberg *et al.*, 2004[113]	Knopp *et al.*, 2003[123]	Melani *et al.*, 2003[116]
N	60	148	70	226	93	205	65	65	149	61	666	92	622	64
General adverse events														
Headache				8		11					9		4	
Nausea														
Gastrointestinal adverse events	10		10					6		5				
Constipation														
Musculoskeletal disorders	5		4	4		4		5		2	5		2	
Myopathy		0				4			0				3	
Back pain				5		4					5		4	
Arthralgia				5							4			
Rhabdomyolysis														
Respiratory system disorders														
Upper respiratory infection				11		7					9		8	
Liver function tests ⩾3× ULN (ALT and/or AST)		0.7			0				0.7			0		
ALT	0		0			0	0	0		0			<1	0
AST	0		0			0	0	0		0			<1	0
CPK ⩾10× ULN	0	0.7	0		1	0	0	0	0	0		0	0	0
All adverse events	57	54.1	70		66		57	63	53	74		57		70
Treatment-related adverse events	20	8.1	24		9		11	18	12.8	18		9		9
Serious adverse events		1.4			1				1.3			0		
Serious treatment-related adverse events		0			0				0			0		
Discontinuation due to adverse events	5	1.4	4		2		8	5	1.3	8		3		3
Discontinuation due to treatment-related adverse events		1.4			0				0.7			2		
Death	0	0	0	0	0	0	0	0	0	0	0	0	0.2	0

continued

TABLE 59 *Adverse events (cont'd)*

Statin and ezetimibe + statin arms[b]

	Pooled statin (%)									Ezetimibe + pooled statin (%)								
	Ballantyne *et al.*, 2003[115]	Ballantyne *et al.*, 2004a[117]	Bays *et al.*, 2004[111]	Davidson *et al.*, 2002[112]	Goldberg *et al.*, 2004[113]	Masana *et al.*, 2005[120]	Melani *et al.*, 2003[116]	Rodney *et al.*, 2006[114]	Stein *et al.*, 2004[118]	Ballantyne *et al.*, 2003[115]	Ballantyne *et al.*, 2004a[117]	Bays *et al.*, 2004[111]	Davidson *et al.*, 2002[112]	Goldberg *et al.*, 2004[113]	Masana *et al.*, 2005[120]	Melani *et al.*, 2003[116]	Rodney *et al.*, 2006[114]	Stein *et al.*, 2004[118]
N	248	45	622	263	349	355	205	124	316	255	201	609	274	353	78	204	123	305
General adverse events																		
Headache				9					6				7					7
Nausea				6									4					
Gastrointestinal adverse events	5			6		9				8			4	6				
Abdominal pain									5									6
Musculoskeletal disorders	6			3						8			2					
Myopathy			0.2			0			9			0			0			8
Back pain																		
Arthralgia									5									5
Rhabdomyolysis						0	0								0			0
Respiratory system disorders																		
Upper respiratory infection				14					8				15					9
Liver function tests ⩾3× ULN (ALT and/or AST)		0	1.1		0				<1		0	1.5		2				1
ALT	<1			<1		0	<1	0		2			2		0.3	<1	0	
AST	<1			<1		0	<1	0		<1			<1		0.3	<1	0	
CPK ⩾10× ULN	0	0	0.2	<1	0.3	0	<1	0	<1	<1	0	0	0	0.6	0	0	1	0
All adverse events	59	67	53.4	72	63	72	63		58	58	71	57.5	69	61	75	66		63
Treatment-related adverse events	17	27	14.8	19	13	17	15	19		23	22	15.1	20	14	19	17	17	
Serious adverse events		11	1.8		1	17		2	3		8	1.5		0.9	12		1	4
Serious treatment-related adverse events		4	0.2		0			0			<1	0		0			0	
Discontinuation due to adverse events	5	7	5	5	2	10	1	2	4	6	9	5.1	7	5	7	4	3	4
Discontinuation due to treatment-related adverse events		7	3.4		1	4		2			6	4.4		3	4		1	
Death	0	0	0	0	0	0	0		0	0	0	0.2	2.7	0	0	0		0

[a] Knopp *et al.*, 2003 – 1 patient died (drowned) in the ezetimibe arm; investigators considered not related to treatment.
[b] Bays *et al.*, 2004 – 1 patient died of cardiac arrest (ezetimibe/simvastatin) – investigators considered not related to treatment. Davidson *et al.*, 2002 – 1 patient died of respiratory failure (ezetimibe/simvastatin) – investigators considered not related to treatment. Masana *et al.*, 2005 – 1 patient died of motor vehicle accident – investigators considered not related to treatment (not clear in which arm). Stein *et al.*, 2004 – 1 patient in statin group died of MI – investigators considered not related to treatment.

TABLE 59 *Adverse events (cont'd)*

Statin and ezetimibe + statin arms

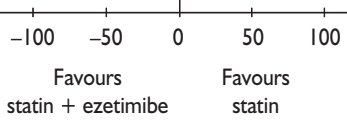
	Statin (%)		Statin + ezetimibe (%)				
	Balantyne et *al.*, 2004b[119]	Feldman et *al.*, 2004[125]	Balantyne et *al.*, 2004b[119]		Feldman et *al.*, 2004[125]		
	Atorvastatin	Simvastatin 20	Ezetimibe + simvastatin 10	Ezetimibe + simvastatin 20	Ezetimibe + simvastatin 10	Ezetimibe + simvastatin 20	Ezetimibe + simvastatin 40
N	262	253	263	263	251	109	97
General adverse events							
Headache							
Nausea							
Gastrointestinal adverse events							
Constipation							
Musculoskeletal disorders							
Myopathy							
Back pain							
Arthralgia							
Rhabdomyolysis	0	0	0	0	0	0	0
Respiratory system disorders							
Upper respiratory infection							
Liver function tests ⩾3× ULN (ALT and/or AST)		0			0.4	0	1.0
ALT	2.4		2.3	2.0			
AST	0.8		1.2	0			
CPK ⩾10× ULN	0	0.8	0.4	0.4	0	0	1.0
All adverse events	71.4	66	70	62.7	56	68	65
Treatment-related adverse events	16	7.5	16	13.7	9.6	14	10
Serious adverse events		4.7			8.0	2.8	4.1
Serious treatment-related adverse events		0			0	0	0
Discontinuation due to adverse events	3.8	5.5	5.7	5.7	4.4	6.4	5.2
Discontinuation due to treatment-related adverse events		0.8			2.0	2.8	1.0
Death	0	0	0	0	0	0	0

Appendix 12

Meta-analysis of 6–8-week studies

Review: Ezetimibe
Comparison: 07 Ezetimibe + statin versus statin alone (LDL-c) 6-week studies
Outcome: 01 Low density lipoprotein cholesterol (LDL-c)

Study or subcategory	N	Statin + ezetimibe Mean (SD)	N	Statin Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) (95% CI)
01 6–8-week studies							
Gagne[173]	379	–25.00 (13.63)	390	–3.70 (13.82)		31.31	–21.30 (–23.24 to –19.36)
Brohet[223]	208	–27.10 (15.45)	210	–4.10 (14.78)		14.02	–23.00 (–25.90 to –20.10)
Cruz-Femandez[224]	219	–31.10 (15.50)	225	–4.20 (15.60)		14.08	–26.90 (–29.79 to –24.01)
Farnier[230]	179	–25.20 (15.25)	186	–0.90 (18.28)		9.91	–24.30 (–27.75 to –20.85)
Pearson[243]	1940	–25.80 (35.24)	968	–2.70 (18.67)		30.67	–23.10 (–25.06 to –21.14)
Subtotal (95% CI)	2925		1979			100.00	–23.18 (–24.26 to –22.09)
Test for heterogeneity: $\chi^2 = 10.39$, df = 4 ($p = 0.03$), $I^2 = 61.5\%$							
Test for overall effect: $Z = 41.84$ ($p < 0.00001$)							
Total (95% CI)	2925		1979			100.00	–23.18 (–24.26 to –22.09)
Test for heterogeneity: $\chi^2 = 10.39$, df = 4 ($p = 0.03$), $I^2 = 61.5\%$							
Test for overall effect: $Z = 41.84$ ($p < 0.00001$)							



Appendix 13

Soft OR techniques used to identify the methodology used to link changes in surrogate measures to clinical outcomes

Strategic Choice Approach

The Strategic Choice Approach (SCA) allows one to "make more confident progress towards decisions by focusing our attention on possible ways of managing uncertainty as to what we should do next".[255] It allows a decision to be reached in real time for problems where strategic decisions are complexly interconnected, while considering the areas of uncertainty surrounding the problem. SCA classes the areas of uncertainty into three groups: uncertainties about the working environment, uncertainties about the guiding values and uncertainties about choices on related agendas.

The SCA is seen as strategic decision-making, considering problems of a short- and long-term nature, but essentially it is a methodology to address problems which are continuously changing. SCA develops the problem as it changes, resulting in a transparent decision-making process, often using graphical methods for clarity. The SCA considers each area of uncertainty, the potential outcomes and the information required to make this area less uncertain. The SCA aids confidence in decision-making as the outcomes of each uncertainty area are considered against each other.

Cognitive mapping

Cognitive maps are used to clarify thought processes and, when constructed by an independent body, they tend to be objective and consequently are a useful method to illustrate any issues identified for a particular problem. Methods include:

1. Oval maps, which are used to answer the question, *what do we think*? By identifying clusters of issues from an initial brainstorming session, this method capture views, ideas and issues related to a problem and illustrates these using a map which shows how the concepts are linked together. Key issues and action plans can then readily identified.
2. Soda maps I and II, which are used when an action plan is required and particularly when dealing with areas of uncertainty which involve groups of people. Soda I uses individual cognitive maps (obtained from each person involved), which are merged to create one large strategic map. This is then analysed by a facilitator to identify the goals of the team and action to proceed.[256] Soda II uses a similar methodology and the main difference is that the whole group works together to create one strategic map, with the outcome being a strategic plan for solving the problem.

Identifying the methodology to link cholesterol and CV events using problem structuring methods

A brief summary of the full report[89] of the PSM used to identify the methodology used to link cholesterol and CV events is provided below.

An electronic literature search was undertaken to identify papers which could be used to link surrogate outcomes to CV events. Of the 634 papers identified, 25 were retained from the titles and abstracts and six were reviewed in more detail, namely Framingham Anderson,[77] Framingham D'Agostino,[87] UKPDS,[86] WOSCOPS,[104] Lancet[79] and PROCAM.[257]

The assumptions required for each of the methods are provided in *Table 60*.

SCA techniques were used to explore the decision options available and an overview is provided below.

1. Define the options graph using the options identified in *Table 61*.

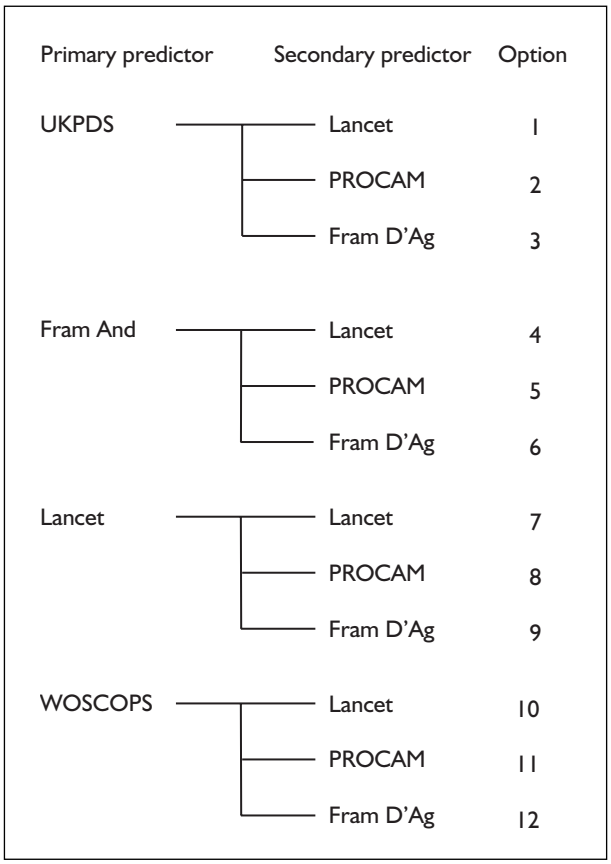
TABLE 60 *The assumptions necessary if the studies' methodologies were to be incorporated to the ezetimibe treatment*

Study	Assumption
Framingham Anderson	Equations are applicable to predict the risk of an event for a patient whose cholesterol profile has been chemically changed
Framingham D'Agostino	Equations are applicable to predict a risk of an event for a patient whose cholesterol profile has been chemically changed
UKPDS	Prediction of events for patients with type 2 diabetes is transferable to patients with primary hypercholesterolaemia
WOSCOPS	Predictions of events for mixed hypercholesterolaemic middle-aged men will be equal or close to primary, mixed age and sex hypercholesterolaemic patients
Lancet	The number of events after *x* change in LDL which is statin induced corresponds to the same number of events with the same change *x* in LDL which is ezetimibe induced
PROCAM	Predictions of only MI can be extrapolated to reveal other events. Events are equally distributed from the German, male participants to the ezetimibe population

TABLE 61 *The options associated with each decision area*

Methodology	Options	Abbreviation
Framingham Anderson	Do not use	0
	Primary prediction	1
Framingham D'Agostino	Do not use	0
	Subsequent predictions	2
UKPDS	Do not use	0
	Primary prediction	1
WOSCOPS	Do not use	0
	Primary prediction	1
Lancet	Do not use	0
	Primary prediction	1
	Subsequent predictions	2
PROCAM	Do not use	0
	Subsequent prediction	2

2. Devise a list of comparison areas to evaluate and distinguish between the methodologies:
   (a) Are published statistical relationships between risk factors and events available?
   (b) (i) Are the characteristics of the target population comparable to those of the population on which the methods are based?
   (b) (ii) Is the population hypercholesterolaemic?
   (b) (iii) Is the population UK based?
   (b) (iv) Is the population of a broad age range?
   (c) Is the population of mixed sex?
   (d) Do the range of events projected and the periods of the projection meet the needs of the model?
   (e) Are trial data available for the risk factors on which the projections are based?



OPTIONS GRAPH *Flow diagram showing the decision schemes available when choosing the modelling methodology*

   (f) Will the methods, data and results be readily understood and accepted by the key decision-makers?
   (g) Size of study.
   (h) Prediction period.
3. Rate the comparison areas against the decision schemes using a binary highest/lowest to grade each comparison area with each decision

TABLE 62 *Showing the results of the decision schemes when compared with the comparison areas*

Option	(a)	(b)(i)	(b)(ii)	(b)(iii)	(b)(iv)	(c)	(d)	(e)	(f)	(g)
1	= H	= H	= L		= H					= H
2	= H	= H	= L		= L		L		L	= H
3	= H	= H	= L		= H			= H		= H
4	= H	= L	= H		= H	= H	= H			= H
5	= H	= L	= H		= L				L	= H
6	= H	= L	= H		= H		= H	= H		= H
7	= H	= L	= H	H	= H	= H	= H		H	= L
8	= H	= L	= H		= L			L		= L
9	= H	= L	= H		= H		= H			= L
10	= L	= H	= H		= L		= H			= L
11	= L	= H	= H	L	= L	L	= H		L	= L
12	= L	+H	= H		= L		= H	= H		= L

H represents the highest result in the comparison area and L the lowest.

scheme (*Table 62*). This is used to highlight dominant decision schemes.

4. Implement the comparisons in a cyclic format until all aspects under considerations have been applied (*Table 63*).
5. Readjust the remaining strategies by reconsidering the uncertainties:
   (a) How confident the modeller would feel using the methodologies should this decision strategy be chosen.
   (b) How adaptable the methodology would be to a change in the time lag as defined in the methodology to the extended time lags that would be needed for the ezetimibe model.
   (c) The acceptance of the methodology within the clinical community should the decision strategy be chosen.
   (d) How easily and accurately the methodology would be adapted from the current circumstances and assumptions on which the methodology is based to the ezetimibe community.
6. The uncertainties were also classified into uncertainties about our working environment (UE), uncertainties about our guiding values (UV) and uncertainties about choices on related agendas (UR) groups (*Table 64*).
7. Cognitive mapping was used to explore the remaining uncertainties in the two optimal strategies identified from the earlier stages (*Figures 13* and *14*).

TABLE 63 *Showing which decision schemes are dominated*

Option	Dominated	Example dominator
1	Yes	3
2	Yes	1
3	No	–
4	No	–
5	Yes	6
6	No	–
7	No	–
8	Yes	7
9	Yes	7
10	Yes	12
11	Yes	12
12	No	–

Hard OR techniques

Two simple models were constructed to assess the predictive accuracy of using (a) the changes in LDL-c measurements (CTTC method) and (b) the changes in Total-c and HDL-c lipids (Framingham method).

The CTTC method uses the published RR of events: non-fatal MI = 0.74, non-fatal Str = 0.83 and fatal CHD = 0.81 for each 1 mmol/l reduction in LDL-c.

TABLE 64 *Classifications of uncertainties*

Uncertainty	Classification
Confidence in using the methodology	UV
Number of events within a time horizon	UE
Methodology's acceptance within the clinical community	UV
Adaptability of the methodology to ezetimibe	UV

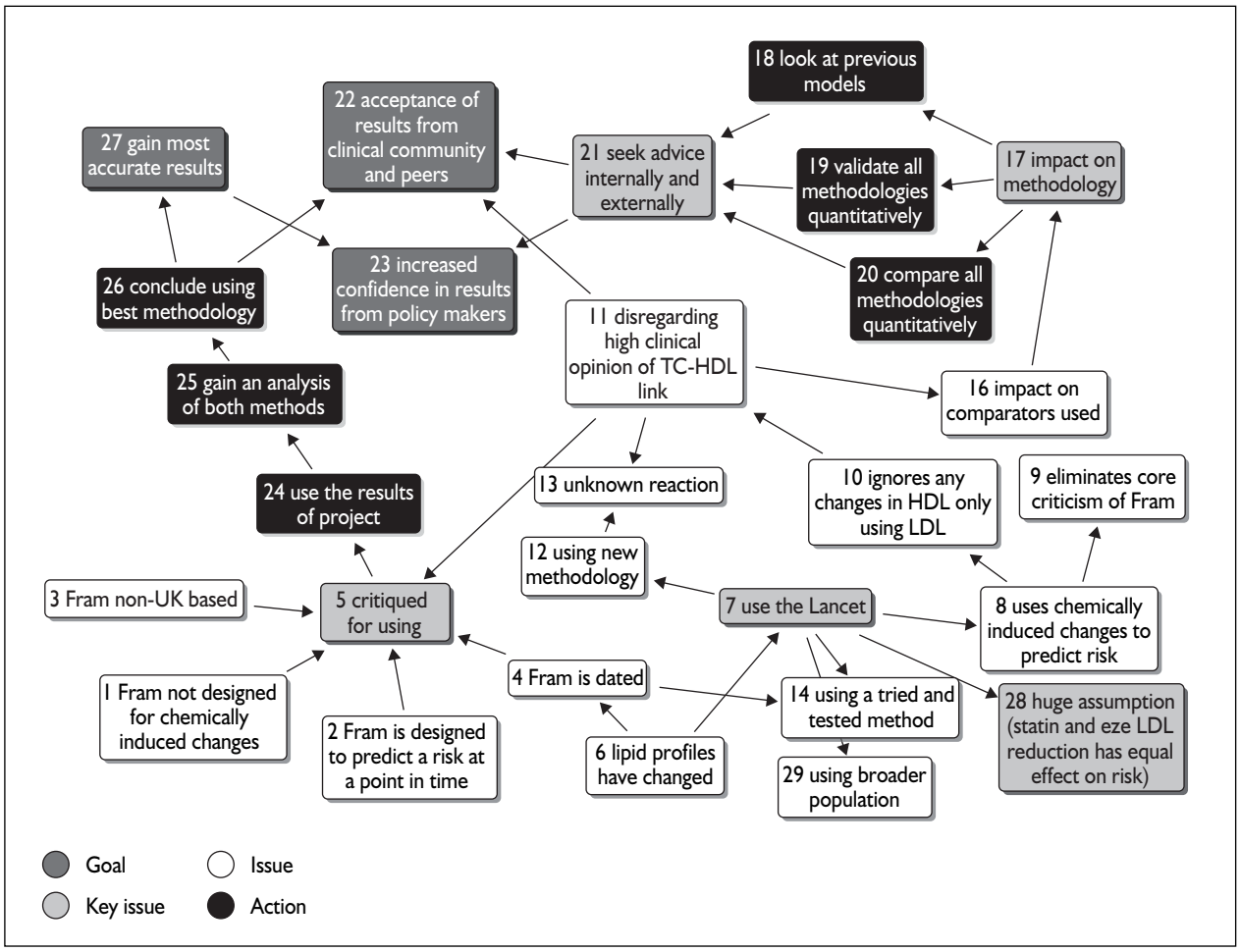


FIGURE 13 *Cognitive map of Miss R Ara of the issues surrounding the use of Framingham or Lancet as the key methodology*

The Framingham method recalculates the probability of an event on an annual basis using the observed changes in Total-c and HDL-c using the CHD and CVD equations from Anderson and colleagues.[77] Published incidence rates are used to distribute the proportion of risk predicted to event type (either a non-fatal MI, a fatal CHD event or a non-fatal Str).

The baseline data and the changes in lipids observed in the CTTC study are used in the models. The models were run for 5 years and the predicted event rates were compared with the numbers and proportions reported in the CTTC article.

Over a 5-year period, the CTTC model over-predicts the number of primary events in both the treatment and comparator arms (*Table 65*). However, the difference in the proportion of events predicted for the treatment and comparator arms using the CTTC model is very close (predicted: non-fatal MI = 1.03 versus 1.24%; non-fatal Str = 0.53 versus 0.45%; fatal CHD = 0.40 versus 0.37%; and all CHD events = 1.42 versus 1.62%).

Over a 5-year period, the Framingham model under-predicts the number of primary events in both the treatment and comparator arms. The difference in the proportion of events predicted for the treatment and comparator arms using the Framingham model is also less accurate (predicted: non-fatal MI = 0.81 versus 1.24%; non-fatal Str = 0.21 versus 0.45% ; fatal CHD = 0.21 versus 0.37% and all CHD events = 1.01 versus 1.62%).

For the secondary events (*Table 66*), the Framingham model uses the D'Agostino equation to predict a secondary CHD risk and then derives a corresponding CVD risk using a methodology published by Yeo and colleagues.[259]

Over a 5-year period, the CTTC model over-predicts the number of secondary events in both

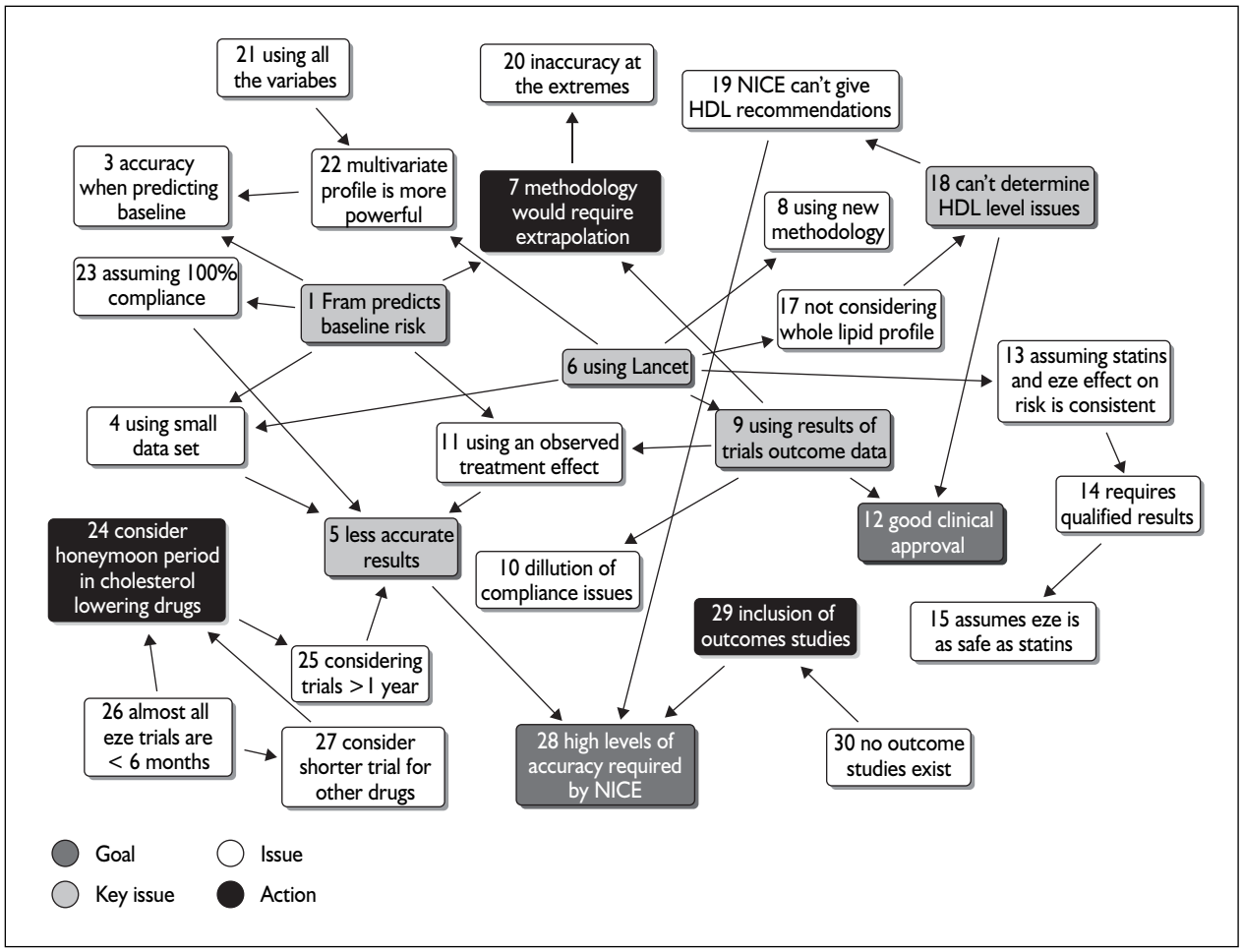


FIGURE 14 *Cognitive Map of Dr W Yeo of the issues surrounding the use of Framingham or Lancet as the key methodology*

TABLE 65 *Comparing the number of primary events predicted by the CTTC and Framingham models compared with the number observed in the CTTC data*

	Non-fatal MI	Non-fatal Str	Fatal CHD	All CHD events
Treatment arm				
Observed	656	656	432	1088
	2.73%	2.74%	1.80%	4.54%
CTTC	787	705	477	1264
	3.27%	2.93%	1.98%	5.26%
Framingham	513	347	138	652
	2.13%	1.44%	0.57%	2.71%
Comparator arm				
Observed	950	761	519	1469
	3.97%	3.19%	2.17%	6.16%
CTTC	1031	829	571	1602
	4.30%	3.46%	2.38%	6.68%
Framingham	704	396	187	891
	2.94%	1.65%	0.78%	3.72%
Difference				
Observed	1.24%	0.45%	0.37%	1.62%
CTTC	1.03%	0.53%	0.40%	1.42%
Framingham	0.81%	0.21%	0.21%	1.01%

TABLE 66 *Comparing the number of secondary events predicted by the CTTC and Framingham models compared with the number observed in the CTTC data*

	Non-fatal MI	Non-fatal Str	Fatal CHD	All CHD events
Treatment arm				
Observed	1133	684	1116	2249
	5.51%	3.45%	5.40%	10.98%
CTTC	1203	765	1237	2440
	5.82%	3.86%	5.99%	11.81%
Framingham	1516	2003	425	1941
	7.34%	10.10%	2.06%	9.40%
Comparator arm				
Observed	1510	856	1441	2951
	7.35%	4.31%	6.98%	14.4%
CTTC	1594	910	1491	3086
	7.72%	4.58%	7.22%	14.9%
Framingham	1778	2203	496	2274
	8.66%	11.10%	2.41%	11.07%
Difference				
Observed	1.84%	0.86%	1.58%	3.42%
CTTC	1.90%	0.72%	1.23%	3.09%
Framingham	1.32%	1.00%	0.35%	1.67%

the treatment and comparator arms. However, the difference in the proportion of events predicted for the treatment and comparator arms using the CTTC model is slightly under-predicted (predicted: non-fatal MI = 1.90 versus 1.84%; non-fatal Str = 0.72 versus 0.86%; fatal CHD = 1.23 versus 1.58%; and all CHD events = 3.09 versus 3.42%).

Over a 5-year period, the Framingham model over-predicts the number of secondary events in both the treatment and comparator arms. The difference in the proportion of events predicted for the treatment and comparator arms using the Framingham model is also less accurate (predicted: non-fatal MI = 1.32 versus 1.84%; non-fatal Str = 1.00 versus 0.86%; fatal CHD = 0.35 versus 1.58%; and all CHD events = 1.67 versus 3.42%).

Appendix 14

Eddy/BMJ checklists for the published cost-effectiveness studies

Checklists are shown in *Tables 67* and *68*.

TABLE 67 *Eddy/BMJ checklist for quality of studies*

Item	Cook *et al.*[144]	Kohli *et al.*[149]
A statement of the problem	Y	Y
A discussion of the need for modelling vs alternative methodologies	Y	Y
A description of the relevant factors and outcomes (disease-specific)	Y	Y
A description of the model including reasons for this type of model and a specification of the scope including: time frame, perspective, comparators and setting. Note: *n* = number of health states within sub-model	Y	Y
A description of data sources (including subjective estimates), with a description of the strengths and weaknesses of each source, with reference to a specific classification or hierarchy of evidence	Y for data sources N for description of strengths and weaknesses	Y for data sources N for description of strengths and weaknesses
A list of assumptions pertaining to the structure of the model (e.g. factors included, relationships, and distributions) and the data	Y It is not clear in some cases	Y
A list of parameter values that will be used for a base-case analysis, and a list of the ranges in those values that represent appropriate confidence limits and that will be used in a sensitivity analysis	Y The base case is not defined in terms of age and gender	Y
The results derived from applying the model for the base case	Y The results are not presented by age and gender	Y
"The results of the sensitivity analyses; unidimensional; best/worst case; multidimensional (Monte Carlo/parametric); threshold"	Y One-way sensitivity analyses were performed	Y One-way sensitivity analyses were performed
A discussion of how the modelling assumptions might affect the results, indicating both the direction of the bias and the approximate magnitude of the effect	Y One-way sensitivity analyses are not optimal	Y
"A description of the validation undertaken including: concurrence of experts; internal consistency; external consistency; predictive validity"	NA	NA
A description of the settings to which the results of the analysis can be applied and a list of factors that could limit the applicability of the results	Y for the description of the settings N for the factors that could limit the applicability	Y Results are not transferable to other statins
A description of research in progress that could yield new data that could alter the results of the analysis	N	N

N, no; NA, not applicable; Y, yes.

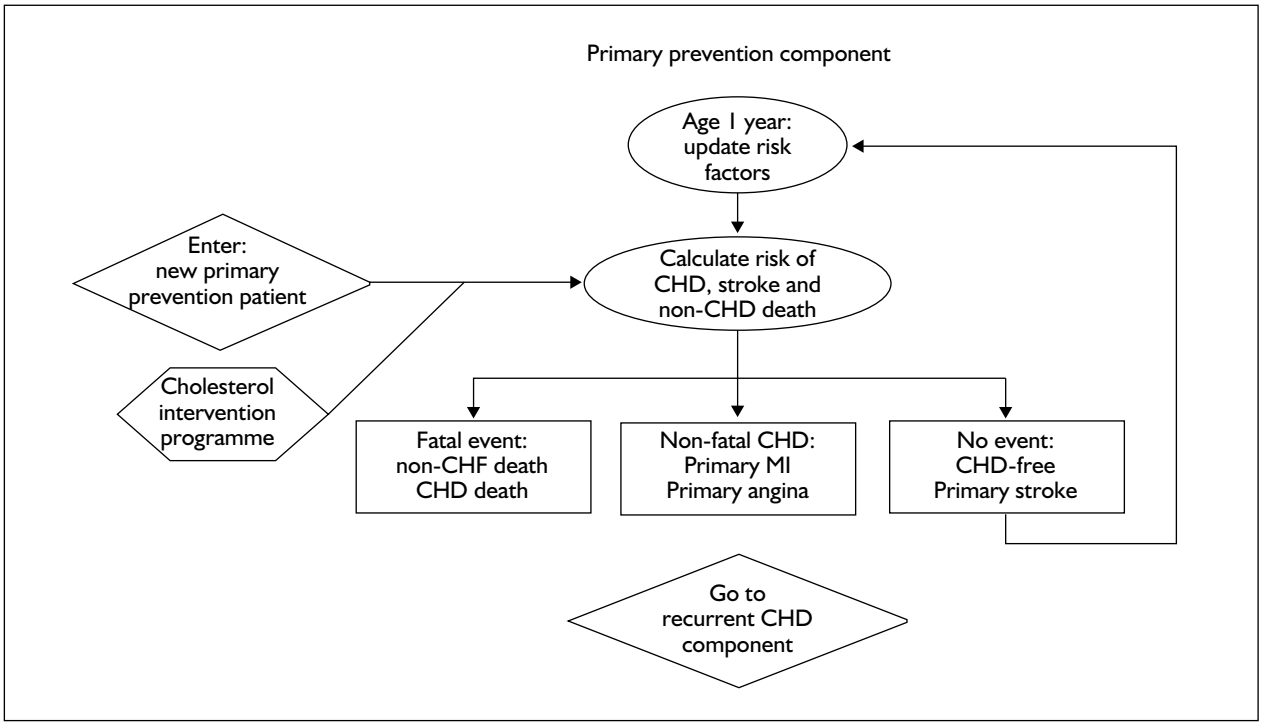
TABLE 68 *Eddy/BMJ checklist for modelling assessment*

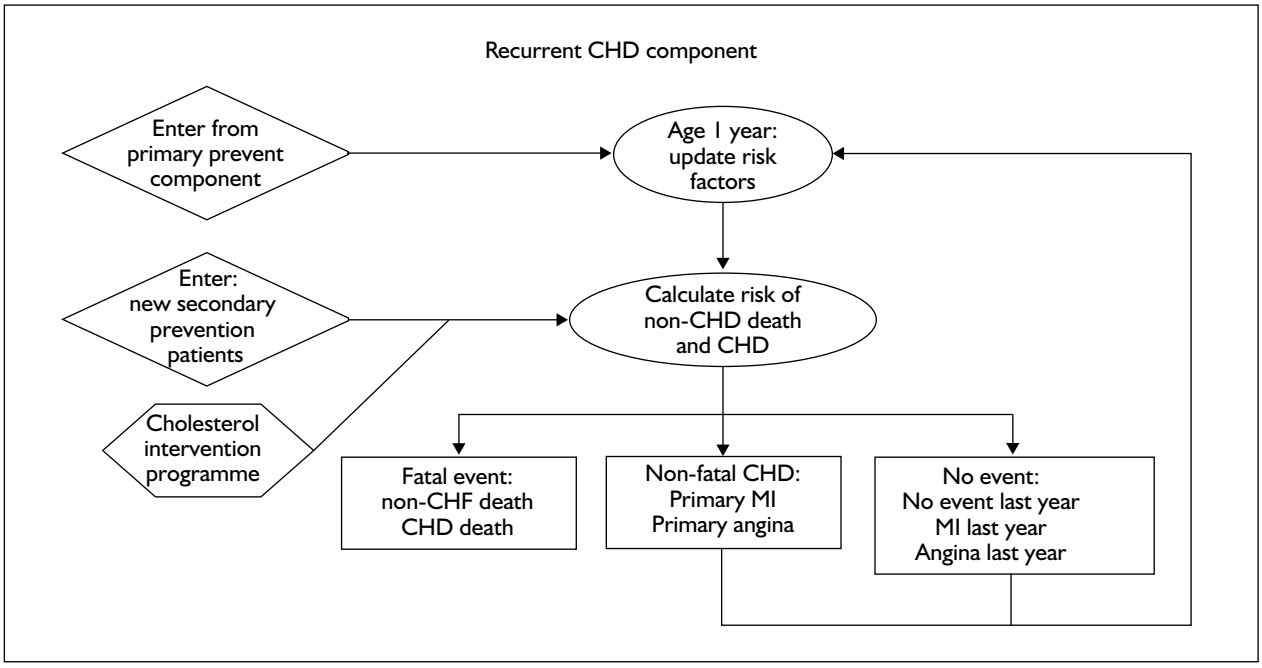
Item	MSD/SP
A statement of the problem	Y
A discussion of the need for modelling vs alternative methodologies	N
A description of the relevant factors and outcomes (disease-specific)	Y
A description of the model including reasons for this type of model and a specification of the scope including: time frame, perspective, comparators and setting. Note: *n* = number of health states within sub-model	Y The authors compare their model with a simple model, although the models might not be comparable
A description of data sources (including subjective estimates), with a description of the strengths and weaknesses of each source, with reference to a specific classification or hierarchy of evidence	Y
A list of assumptions pertaining to: the structure of the model (e.g. factors included, relationships and distributions) and the data	Y It is not clear in some cases
A list of parameter values that will be used for a base-case analysis, and a list of the ranges in those values that represent appropriate confidence limits and that will be used in a sensitivity analysis	Y
The results derived from applying the model for the base case	Y The base case (age) varies depending on the analysis
"The results of the sensitivity analyses; unidimensional; best/worst case; multidimensional (Monte Carlo/parametric); threshold"	Y Univariate sensitivity analyses were performed
A discussion of how the modelling assumptions might affect the results, indicating both the direction of the bias and the approximate magnitude of the effect	Y
"A description of the validation undertaken including: concurrence of experts; internal consistency; external consistency; predictive validity"	NA
A description of the settings to which the results of the analysis can be applied and a list of factors that could limit the applicability of the results	Y for the description of the settings N for the factors that could limit the applicability
A description of research in progress that could yield new data that could alter the results of the analysis	N

N, no; NA, not applicable; Y, yes.

Appendix 15

Schematic models of primary and secondary prevention from the MSD/SP submission





Appendix 16

Costs of treatments used in the MSD/SP Cook evaluation

Cost are given in *Table 69* and the current statin market share in the UK in *Table 70*.

TABLE 69 *Cost per pack of 28 tablets of treatments used in MSD/SP*

Drug	Drug tariff price (£)[a]	Drug	Drug tariff price (£)[a]
Simvastatin		Fluvastatin	
20 mg	1.89	40 mg	13.99
40 mg	4.17	80 mg	17.60
10 mg	1.97	20 mg	13.99
80 mg	26.42	Zocor®	
Atorvastatin		20 mg	29.69
10 mg	18.03	40 mg	29.69
20 mg	24.64	10 mg	18.03
40 mg	28.21	80 mg	29.69
80 mg	28.21	Lipostat®	
Pravastatin		40 mg	27.61
40 mg	4.57	20 mg	27.61
20 mg	2.94	10 mg	15.05
10 mg	2.49	Simvador®	
Rosuvastatin		40 mg	4.17
10 mg	18.03	20 mg	1.89
20 mg	29.69	10 mg	1.97
40 mg	29.69	Ezetimibe	
5 mg	18.03	10 mg	26.31

[a] Based on eMIMs, July 2006.

TABLE 70 *Current statin market share in the UK (from MSD/SP report)*
[Confidential information removed].

Appendix 17

Health state utility values used in the Cook model

Data are given in *Table 71*.

TABLE 71 *Health state utility values used in the Cook model*

Health state	Utility value
Angina	0.79
MI	0.75
Age adjusted	Various (Kind and Dolan)[199]

Appendix 18

Meta-analyses percentage change in TC and HDL-c

Effectiveness data for ezetimibe + statin combination treatment used in MSD/SP cost-effectiveness model

Percentage change in TC

Review: Ezetimibe review
Comparison: 03 2nd line ezetimibe/statin combination therapy – fixed effects models
Outcome: 03 % Total cholesterol change from base line – EZ/ST vs PO/ST

Study or subcategory	N	Ezetimibe/statin Mean (SD)	N	Placebo/statin Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) (95% CI)
01 TC change from base line – EZ/ST vs PO/ST							
Gagne[173]	379	−17.00 (11.68)	390	−2.30 (9.87)	■	23.44	−14.70 (−16.23 to −13.17)
Pearson[243]	1942	−18.20 (22.03)	969	−2.90 (15.56)	■	28.59	−15.30 (−16.69 to −13.91)
Subtotal (95% CI)	2321		1359		◆	52.03	−15.03 (−16.06 to −14.00)
Test for heterogeneity: $\chi^2 = 0.32$, df = 1 ($p = 0.57$), $I^2 = 0\%$							
Test for overall effect: $Z = 28.68$ ($p < 0.00001$)							
02 TC change from base line – EZ/SI vs PO/SI in CHD patients							
Farnier[230]	179	−16.73 (11.37)	186	0.36 (0.82)	■	19.69	−17.09 (−18.76 to −15.42)
Cruz-Fernandez[224]	219	−19.90 (10.95)	225	−2.70 (11.02)	■	13.14	−17.70 (−19.74 to −15.56)
Brohet[223]	208	−17.80 (10.24)	210	−1.80 (9.61)	■	15.14	−16.00 (−17.90 to −14.10)
Subtotal (95% CI)	606		621		◆	47.97	−16.91 (−17.98 to −15.84)
Test for heterogeneity: $\chi^2 = 1.50$, df = 2 ($p = 0.47$), $I^2 = 0\%$							
Test for overall effect: $Z = 30.99$ ($p < 0.00001$)							
Total (95% CI)	2927		1980		◆	100.00	−15.93 (−16.67 to −15.19)
Test for heterogeneity: $\chi^2 = 8.02$, df = 4 ($p = 0.09$), $I^2 = 50.1\%$							
Test for overall effect: $Z = 42.15$ ($p < 0.00001$)							

−100 −50 0 50 100

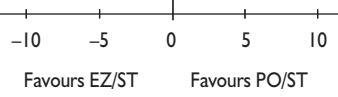
Favours EZ/ST Favours PO/ST

Effectiveness data for ezetimibe + statin combination treatment used in MSD/SP cost-effectiveness model

Percentage change in HDL-c[a]

Review: Ezetimibe review
Comparison: 03 2nd line ezetimibe/statin combination therapy – fixed effects models
Outcome: 04 % HDL-c change from base line – EZ/ST vs PO/ST

Study or subcategory	Placebo/statin N	Placebo/statin Mean (SD)	Ezetimibe/statin N	Ezetimibe/statin Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) (95% CI)
01 % HDL-c change from base line – EZ/ST vs PO/ST							
Gagne[173]	390	1.00 (9.87)	379	2.70 (9.73)		32.19	–1.70 (–3.09 to –0.31)
Pearson[243]	969	–0.80 (15.56)	1942	1.30 (17.63)		39.24	–2.10 (–3.25 to –0.85)
Subtotal (95% CI)	1359		2321			71.43	–1.92 (–2.85 to –0.99)
Test for heterogeneity: $\chi^2 = 0.18$, df = 1 ($p = 0.67$), $I^2 = 0\%$							
Test for overall effect: $Z = 4.05$ ($p < 0.0001$)							
02 % HDL-c change from base line – EZ/SI vs PO/SI in CHD patients							
Farnier[230]	186	1.52 (14.46)	179	2.23 (12.31)		8.16	–0.71 (–3.46 to 2.04)
Cruz-Fernandez[224]	225	0.13 (12.86)	219	2.90 (12.76)		10.86	–2.77 [a]5.15 to –0.39)
Brohet[223]	210	1.40 (13.31)	208	1.00 (13.25)		9.53	0.40 (–2.15 to 2.95)
Subtotal (95% CI)	621		606			28.57	–1.12 (–2.59 to 0.35)
Test for heterogeneity: $\chi^2 = 3.30$, df = 2 ($p = 0.19$), $I^2 = 39.3\%$							
Test for overall effect: $Z = 1.50$ ($p = 0.13$)							
Total (95% CI)	1980		2927			100.00	–1.69 (–2.48 to –0.91)
Test for heterogeneity: $\chi^2 = 4.27$, df = 4 ($p = 0.37$), $I^2 = 6.4\%$							
Test for overall effect: $Z = 4.22$ ($p < 0.0001$)							



[a] Keeping with the convention of meta-analysis, HDL-c was modelled placebo – ezetimibe and hence the '–' sign with HDL-c increase with ezetimibe

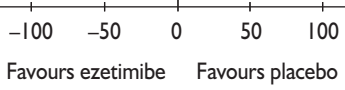
Effectiveness data for ezetimibe monotherapy treatment used in MSD/SP cost-effectiveness model

Percentage change in TC

Review: Ezetimibe review
Comparison: 01 1st line ezetimibe monotherapy
Outcome: 02 % TC change from base line – EZ vs PO

Study or subcategory	N	Ezetimibe Mean (SD)	N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) (95% CI)
Dujovne[122]	666	–12.48 (9.81)	226	0.84 (8.42)		32.11	–13.32 (–14.65 to –11.99)
Davidson[112]	61	–13.30 (11.72)	70	–0.60 (11.71)		3.49	–12.70 (–16.72 to –8.68)
Ballantyne[115]	65	–13.50 (12.34)	60	3.50 (11.85)		3.14	–17.00 (–21.24 to –12.76)
Knopp[123]	621	–12.40 (9.47)	204	0.57 (8.57)		29.17	–12.97 (–14.36 to –11.59)
Melani[116]	64	–13.20 (9.60)	65	0.20 (9.67)		5.11	–13.40 (–16.73 to –10.07)
Kerzner[275]	72	–13.00 (8.49)	64	1.00 (8.00)		7.35	–14.00 (–16.77 to –11.23)
Bays[111]	143	–13.30 (10.76)	140	–1.40 (10.65)		9.08	–11.90 (–16.77 to –11.23)
Goldberg[113]	90	–13.70 (11.62)	92	2.20 (11.26)		5.11	–15.90 (–19.23 to –12.57)
Farnier[230]	173	–11.80 (10.74)	61	0.20 (11.16)		5.43	–12.00 (–15.23 to –8.77)
Subtotal (95% CI)	1953		982			100.00	–13.30 (–14.05 to –12.55)

Test for heterogeneity: $\chi^2 = 7.66$, df = 8 ($p = 0.47$), $I^2 = 0\%$
Test for overall effect: $Z = 34.67$ ($p < 0.00001$)



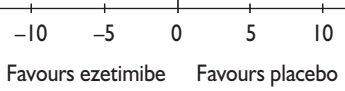
Effectiveness data for ezetimibe monotherapy treatment used in MSD/SP cost-effectiveness model

Percentage change in HDL-c[a]

Review: Ezetimibe review
Comparison: 01 1st line ezetimibe monotherapy
Outcome: 03 % HDL-c change from base line – EZ vs PO

Study or subcategory	N	Ezetimibe Mean (SD)	N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) (95% CI)
Dujovne[122]	226	–1.60 (10.97)	666	1.33 (15.23)		26.14	–2.91 (–4.75 to –1.07)
Davidson[112]	70	0.90 (12.55)	61	5.10 (12.50)		4.78	–4.20 (–8.50 to 0.10)
Ballantyne[115]	60	3.70 (11.54)	65	4.20 (11.53)		5.40	–0.50 (–4.55 to 3.55)
Knopp[123]	204	–1.26 (11.14)	621	1.01 (12.46)		26.82	–2.27 (–4.09 to –0.45)
Melani[116]	65	2.00 (12.09)	64	4.10 (12.00)		5.12	–2.10 (–6.26 to 2.06)
Kerzner[275]	64	0.00 (8.00)	72	3.00 (8.49)		11.50	–3.00 (–5.77 to –0.23)
Bays[111]	140	–0.30 (13.02)	143	5.00 (13.15)		9.51	–5.30 (–8.35 to –2.25)
Goldberg[113]	92	2.30 (12.23)	90	7.00 (12.58)		6.80	–4.70 (–8.31 to –1.09)
Farnier[230]	61	3.20 (16.34)	173	3.90 (16.11)		3.92	–0.70 (–5.45 to 4.05)
Subtotal (95% CI)	982		1955			100.00	–2.90 (–3.84 to –1.96)

Test for heterogeneity: $\chi^2 = 6.47$, df = 8 ($p = 0.59$), $I^2 = 0\%$
Test for overall effect: $Z = 6.05$ ($p < 0.00001$)



[a] Keeping with the convention of meta-analysis, HDL-c was modelled placebo – ezetimibe and hence the '–' sign with HDL-c increase with ezetimibe

Appendix 19

Summary of results from the MSD/SP Cook model

Results are presented in *Table 72*.

TABLE 72 *Summary of MSD/SP cost-effectiveness results from the Cook model*

Population	Patient profile: M/F, age (years), Total-c (mmol/l)	Discounted ICER: (£000): min. (max.)	MSD/SP report/ Appendix M
Basecase (a): ezetimibe plus current statin vs current statin titration			
Males with history of CVD	M, 50, 6.5	15.8	3.11, p. 45
	M, 80, 4.5	(31.3)	3.11, p. 45
Females with history of CVD	F, 60, 6.5	26.3	26.1, p. 226
	F, 80, 4.5	(45.2)	26.1, p. 226
Result used to evaluate the impact of univariate Sa	M, 70, 5.5	21.4	3.15, p. 49
Sa: baseline utility = 1 plus 10% on health state utility	M, 70, 5.5	14.	3.35, p. 49
Sa: discount costs and benefits at 6%	M, 70, 5.5	24.2	3.35, p. 49
Male diabetic patients with no history of CVD	M, 70, 6.5	11.3	3.12, p. 46
	M, 50, 4.5	(18.5)	3.12, p. 46
Female diabetic patients with no history of CVD	F, 70, 6.5	15.5	26.4, p. 228
	F, 50, 4.5	(26.9)	26.4, p. 228
Result used to evaluate the impact of univariate Sa	M, 70, 5.5	13.1	3.15, p. 49
Sa: baseline utility = 1 minus 1% on HS utility	M, 70, 5.5	9.3	3.15, p. 49
Sa: 5-year time frame	M, 70, 5.5	18.4	3.15, p. 49
Males with no history of CVD	M, 60, 6.5	11.9	3.13, p. 46
	M, 50, 4.5	(18.5)	3.13, p. 46
Females with no history of CVD	F, 50, 6.5	33.7	26.7, p. 229
	F, 80, 4.5	(121.9)	26.7, p. 229
Result used to evaluate the impact of univariate Sa	M, 70, 5.5	13.6	3.15, p. 49
Sa: baseline utility = 1 minus 1% on HS utility	M, 70, 5.5	9.4	3.15, p. 49
Sa: Brindle's correction	M, 70, 5.5	17.3	3.15, p. 49
South Asian males at high risk	M, 60, 6.5	8.8	3.14, p. 47
	M, 50, 4.5	(12.9)	3.14, p. 47
South Asian females at high risk	F, 50, 6.5	21.5	26.1, p. 231
	F, 80, 4.5	(81.2)	26.1, p. 231
Base-case result (provided for comparison only) (Sa not reported for this population)	M, 70, 5.5	1.0	3.14, p. 47
Basecase (b): ezetimibe plus current statin vs current statin without titration[a]			
History of CVD	M, 50, 6.5	14.1	26.2, p. 227
	F, 80, 4.5	(41.3)	26.3, p. 227
Diabetes, no history of CVD	M. 70, 6.5	1.1	26.5, p. 228
	F, 50, 4.5	(23.7)	26.6, p. 229
No history of CVD	M, 60, 6.5	1.6	26.8, p. 23
	F, 80, 4.5	(11.)	26.9, p. 23
South Asians at high risk	M, 60, 6.5	7.9	26.11, p. 231
	F, 80, 4.5	73.2	26.12, p. 232

continued

TABLE 72 *Summary of MSD/SP cost-effectiveness results from the Cook model (cont'd)*

Population	Patient profile: M/F, age (years), Total-c (mmol/l)	Discounted ICER: (£000): min. (max.)	MSD/SP report/ Appendix M
Ezetimibe monotherapy vs no treatment[a]			
History of CVD	M, 50, 6.5 F, 80, 4.5	17.4 (5.6)	3.17, p. 51 26.13, p. 233
Diabetes, no history of CVD	M, 70, 6.5 F, 50, 4.5	12.4 (28.)	3.18, p. 52 26.14, p. 233
No history of CVD	M, 60, 6.5 F, 80, 4.5	13.2 (131.1)	3.19, p. 52 26.15, p. 234
South Asians at high risk	M, 60, 6.5 F, 80, 4.5	9.9 (87.3)	3.2, p. 53 26.16, p. 234
Alternative scenario 1: ezetimibe plus low-cost statin vs switch to more potent high-cost statin[a]			
History of CVD	M, 50, 6.5 F, 80, 4.5	2.5 (6.4)	26.17, p. 235 26.2, p. 236
Diabetes, no history of CVD	M, 70, 6.5 F, 50, 4.5	1.5 (3.7)	26.18, p. 235 26.21, p. 237
No history of CVD	M, 80, 6.5 F, 80, 4.5	1. (15.6)	26.19, p. 236 26.22, p. 237
Alternative scenario 2: titrate high-cost statin vs switch to low-cost statin plus ezetimibe[a]			
History of CVD	M, 50, 6.5 F, 80, 4.5	2.4 (6.1)	26.23, p. 238 26.26, p. 239
Diabetes, no history of CVD	M, 80, 6.5 F, 50, 4.5	1.4 (3.6)	26.24, p. 238 26.27, p. 24
No history of CVD	M, 80, 6.5 F, 80, 4.5	1. (14.9)	26.25, p. 239 26.28, p. 24

F, female; M, male; Sa, sensitivity analysis.
[a] Range is presented for males and females combined, for brevity.

Appendix 20

ScHARR's initial queries on the MSD/SP economic evaluation and the responses received

Query 1

In the cost-effectiveness section of the main report, the alternative Scenarios 1 and 2 are described (p. 40) as follows:

For Scenario 1, the current therapy is assumed to be:
50% on simvastatin 20 mg and 50% on simvastatin 40 mg

The addition of ezetimibe to this therapy is then compared with switching to atorvastatin of the same dose.

Hence the comparators modelled are:
Treatment 1: (50% simvastatin 20 mg and 50% simvastatin 40 mg) plus ezetimibe 10 mg
Treatment 2: (50% atorvastatin 20 mg and 50% atorvastatin 40 mg)

For Scenario 2, the therapy is assumed to be:
50% on atorvastatin 10 mg and 50% on atorvastatin 20 mg

The analysis compares titrating atorvastatin by one dose (i.e. from atorvastatin 10 mg to 20 mg or from atorvastatin 20 mg to 40 mg) with switching to equipotent simvastatin (i.e. from atorvastatin 10 mg to simvastatin 20 mg or from atorvastatin 20 mg to simvastatin 40 mg) plus Ezetimibe 10 mg.

Hence the comparators modelled are:
Treatment 1: (50% atorvastatin 20 mg and 50% atorvastatin 40 mg)
Treatment 2: (50% simvastatin 20 mg and 50% simvastatin 40 mg) plus ezetimibe 10 mg

Assuming that patients remain on these doses, unless we are misinterpreting the description provided, these alternatives look identical. However, the results provided for the two analyses are slightly different. *Table 1* provides the range of discounted ICERs with the corresponding table and page numbers from the MSD/SP Appendices.

Response to Query 1

We agree with the statement that the two alternative scenarios are equivalent. The incremental QALYs, as reported in the Appendix Tables 26.17 and 26.23, 26.19 and 26.25, 26.20 and 26.26, and 26.22 and 26.28 (Tables 26.17 and 26.23 from the Appendix are copied overleaf), are the same for the two scenarios, since these alternative scenarios have similar efficacy. However, the incremental costs are slightly different (undiscounted £10–35 higher for Scenario 1). The reason for this slight difference in cost is due to the rounding of the drug cost in one of the scenarios and not in the other, that is, in alternative Scenario 1 the average cost of statin titration used was £0.94, whereas in alternative Scenario 2 the average cost of titration used was £0.9438. We realised this lack of rounding in one of the scenarios towards the

TABLE 1 *Extract from results tables for alternative Scenarios 1 and 2*

Table	Page	Gender	CVD	Range of discounted ICER for alternative Scenario 1
26.17	235	Male	Secondary	£2.5 (TC 6.5, age 50) to £4.3 (TC 4.5, age 80)
26.19	236	Male	Primary	£1.0 (TC 6.5, age 80) to £2.1 (TC 4.5, age 50)
26.20	236	Female	Secondary	£3.9 (TC 6.5, age 60) to £6.4 (TC 4.5, age 80)
26.22	237	Female	Primary	£4.1 (TC 6.5, age 50) to £15.6 (TC 4.5, age 80)
				Range of discounted ICER for alternative Scenario 2
26.23	238	Male	Secondary	£2.4 (TC 6.5, age 50) to £4.1 (TC 4.5, age 80)
26.25	239	Male	Primary	£1.0 (TC 6.5, age 80) to £2.0 (TC 4.5, age 50)
26.26	239	Female	Secondary	£3.8 (TC 6.5, age 60) to £6.1 (TC 4.5, age 80)
26.28	240	Female	Primary	£3.9 (TC 6.5, age 50) to £14.9 (TC 4.5, age 80)

RESPONSE TABLE 1 *Copy of Appendix Table 26.17 (ezetimibe co-administration with simvastatin vs switch to atorvastatin in 1000 men with history of CVD who are not appropriately controlled with statin alone)*

		Undiscounted			Discounted		
Total cholesterol (mmol/l)	**Age (years)**	**Incremental cost (£)**	**Incremental QALY**	**Incremental cost/QALY (£)**	**Incremental cost (£)**	**Incremental QALY**	**Incremental cost/QALY (£)**
4.5	*50*	*1072)*	*417*	*2.6*	*605*	*191*	*3.2*
	60	*747*	*278*	*2.7*	*482*	*153*	*3.2*
	70	*466*	*152*	*3.1*	*342*	*97*	*3.5*
	80	*263*	*69*	*3.8*	*215*	*50*	*4.3*
5.5	*50*	*1077*	*469*	*2.3*	*606*	*220*	*2.8*
	60	*743*	*305*	*2.4*	*480*	*170*	*2.8*
	70	*461*	*165*	*2.8*	*338*	*107*	*3.2*
	80	*259*	*75*	*3.4*	*211*	*55*	*3.8*
6.5	*50*	*1078*	*508*	*2.1*	*607*	*243*	*2.5*
	60	*739*	*325*	*2.3*	*477*	*184*	*2.6*
	70	*456*	*176*	*2.6*	*334*	*115*	*2.9*
	80	*255*	*80*	*3.2*	*208*	*59*	*3.5*

RESPONSE TABLE 2 *Copy of Appendix Table 26.23 (ezetimibe co-administration with simvastatin vs titration on atorvastatin in 1000 men with history of CVD who are not appropriately controlled with atorvastatin alone)*

		Undiscounted			Discounted		
Total cholesterol (mmol/l)	**Age (years)**	**Incremental cost (£)**	**Incremental QALY**	**Incremental cost/QALY (£)**	**Incremental cost (£)**	**Incremental QALY**	**Incremental cost/QALY (£)**
4.5	*50*	*1037*	*417*	*2.5*	*582*	*191*	*3.0*
	60	*722*	*278*	*2.6*	*465*	*153*	*3.0*
	70	*449*	*152*	*3.0*	*329*	*97*	*3.4*
	80	*253*	*69*	*3.7*	*206*	*50*	*4.1*
5.5	*50*	*1044*	*469*	*2.2*	*585*	*220*	*2.7*
	60	*720*	*305*	*2.4*	*463*	*170*	*2.7*
	70	*445*	*165*	*2.7*	*325*	*107*	*3.0*
	80	*249*	*75*	*3.3*	*203*	*55*	*3.7*
6.5	*50*	*1047*	*508*	*2.1*	*586*	*243*	*2.4*
	60	*717*	*325*	*2.2*	*461*	*184*	*2.5*
	70	*441*	*176*	*2.5*	*322*	*115*	*2.8*
	80	*245*	*80*	*3.1*	*200*	*59*	*3.4*

end of the submission process. In Table 1 on p. 11 of the user guide we did provide cost of Statin Dose 2 = 0.94 (for alternative Scenario 1) and Statin Dose 2 = 0.9438 (for alternative Scenario 2) so that one could replicate the results. The use of rounding in alternative Scenario 1 does not have a substantial impact on the overall ICERs and is slightly conservative in that it increases the incremental daily cost of ezetimibe arm.

Query 2

The ICERs for the females are much larger than those for the equivalent analyses for males. One would expect some difference in the results for the secondary CVD analyses due to the difference in the distribution across events for males and females and for age. The results for the primary CVD analyses are not directly comparable by gender and age as, owing to the methodology employed, similar baseline characteristics give very different risks for males and females of the same age. However, the predicted risk could be used to compare results. If ICERs are compared using this method, some of the results are vastly different. The summary table (Table 3.10, p. 44, main MSD/SP report) lists ICERs as high as £122,000, £110,000 and £131,000 per QALY for females. Conversely, the highest equivalents for the males are £31,000, £29,000 and £36,000 per QALY.

The model used in the industry submission was previously used to evaluate the cost-effectiveness of ezetimibe in Canada (by Kohli and colleagues[149]) and three European countries (by Cook and colleagues[144]). Looking at Table VI in the study by Kohli and colleagues,[149] the ICERs for males and females are very similar for diabetic patients (male diabetic: Can$ 25,000–27,000 and female diabetic Can$ 25,000–27,000) and secondary CVD analyses (male approximately Can$ 21,000; female approximately Can$ 25,000). For male primary CVD analyses the ICERs reported range from Can$ 19,000–20,000. However, the corresponding ICERs for females at high risk of CVD are not reported. The difference in the ICERs for the male and female analyses are briefly discussed on p. 826 and it is suggested this is due to the events predicted using the Framingham equations. Based on this, the events were recalibrated.

The results presented in the study by Cook and colleagues[144] are not reported for males and females separately, and they are not provided for non-diabetic individuals with primary CVD who are at high risk of a CHD event. Hence it is not possible to establish if the huge differences in the ICERs for males and females are seen in this evaluation.

We have been unable to establish a reasonable explanation for the difference in the primary CVD ICERs for males and females in the MSD/SP submission report. Can you please provide a detailed rationale for the difference in results, both for the secondary CVD analyses and the primary CVD analyses?

Response to Query 2

The ICERs for male and female diabetic patients and CVD patients in the study by Kohli and colleagues are similar because the risks predicted by the model in that analysis were recalibrated as stated in the manuscript. In addition, on p. 826 of the manuscript the authors state: "the noticeable difference in the cost effectiveness results of lipid-lowering therapy for men and women in the Russell analysis is because the ***Framingham risk equations predict many more CAD events among men than women****. In the Canadian population, there is not such a stark difference in the number of events experienced by men and women and our calibration exercise has corrected for this.* ***Prior to calibration, the cost-effectiveness ratios for women would have been of a similar magnitude to those reported by Russell and colleagues****."*

The Russell analysis reports ratios for women that are three times those for men (94,732 versus 30,055 at a baseline LDL-c level of 4.14 mmol/l). In our submission for ezetimibe co-administration vs statin titration, the increases in ICERs for females compared with male CVD patients are 40–100% greater and for female diabetic patients compared with males the ICERs are 30–45% greater. For female patients with a 10-year risk of 20% or greater, the increases in ICERs range from 3.4 to 6.7 times compared with male patients.

To confirm that the gender differences in the ICER are due to differences in the Framingham risk, we also evaluated the 10-year fatal and total CHD event risk for the three patients groups: (1) patients with existing CVD, (2) non-CVD patients with diabetes and (3) non-CVD, non-diabetic patients with 10-year risk of 20% or greater. Based on the results reported in Response Table 3, through Table 5 below it can be seen that:

(i) Baseline risk for fatal CHD and also total CHD for male patients is greater compared with female patients – the largest differences are seen in Table 5 with the non-CVD, non-diabetic patients, where the risk of fatal and total CHD for females is as much as 1/5th that of the risk for men.

(ii) Correspondingly, the incremental benefit (reduction in risk) of ezetimibe co-administration versus statin titration is greater for male patients compared with female patients as represented by the greater delta for male patients compared with females – again, the largest differences between men and women in risk reduction are seen in the non-CVD, non-diabetic patients (i.e. the total CHD risk reduction for 70-year-old patients differs by 0.038 – 0.008 = 0.030). Therefore, it would seem that the difference in the primary CVD ICERs for males and females is primarily driven by the large difference in the baseline risk and corresponding difference in the absolute risk reduction. Females, as predicted by the Framingham risk equations, have a lower baseline risk that results in a smaller opportunity to lower risk with treatment. As a consequence, the QALY gains are much smaller and the resulting ICERs are much higher for women compared with men. This general pattern was also observed in Canada prior to adjusting the risk for women upward as a result of the calibration to Canadian data.

RESPONSE TABLE 3 *Predicted 10-year fatal and total CHD event rates for CVD group (cholesterol level 5.5 mmol)*

Age (years)	Baseline risk		Statin titration		Delta (difference between ezetimibe co-administration and statin titration)	
	Males	Females	Males	Females	Males	Females
Fatal CHD event rate						
50	*0.113*	*0.034*	*0.105*	*0.031*	*0.014*	*0.005*
70	*0.235*	*0.145*	*0.224*	*0.138*	*0.020*	*0.014*
Total CHD event rate						
50	*0.327*	*0.153*	*0.317*	*0.147*	*0.019*	*0.011*
70	*0.374*	*0.211*	*0.363*	*0.203*	*0.020*	*0.015*

RESPONSE TABLE 4 *Predicted 10-year fatal and total CHD event rates for non-CVD diabetic group (cholesterol level 5.5 mmol)*

Age (years)	Baseline risk		Statin titration		Deltas (difference between ezetimibe co-administration and statin titration)	
	Males	Females	Males	Females	Males	Females
Fatal CHD event rate						
50	*0.065*	*0.034*	*0.061*	*0.032*	*0.008*	*0.004*
70	*0.225*	*0.134*	*0.212*	*0.126*	*0.024*	*0.015*
Total CHD event rate						
50	*0.118*	*0.064*	*0.111*	*0.060*	*0.013*	*0.007*
70	*0.294*	*0.178*	*0.278*	*0.167*	*0.030*	*0.020*

RESPONSE TABLE 5 *Predicted 10-year fatal and non-fatal CHD event rates for non-CVD, non-diabetic group with 20% or greater 20-year risk of developing CVD (cholesterol level 5.5 mmol)*

Age (years)	Baseline risk		Statin titration		Deltas (difference between ezetimibe co-administration and statin titration)	
	Males	Females	Males	Females	Males	Females
Fatal CHD event rate						
50	*0.054*	*0.011*	*0.050*	*0.010*	*0.008*	*0.002*
70	*0.186*	*0.032*	*0.174*	*0.029*	*0.021*	*0.004*
Total CHD event rate						
50	*0.208*	*0.093*	*0.196*	*0.088*	*0.021*	*0.010*
70	*0.432*	*0.076*	*0.411*	*0.071*	*0.038*	*0.008*

Query 3

We note that a number of the Anderson equations are used to derive a distribution for the type of event which is then applied *pro rata* to the predicted D'Agostino risk for the primary analyses. In theory, the balance should provide the proportion of risk attributable to angina. Looking at the code, the authors are obviously aware that this methodology can sometimes produce results which are inaccurate, particularly when including Str. A function is included within the code to set zeros to the angina health state if the sum of the probabilities is greater than the predicted total risk.

When generating results for males in the primary CVD analyses, the Markov trace for the 'no treatment' arm has zero individuals in the primary angina health state – presumably due to the summed probabilities being greater than the predicted total risk. However, both the ezetimibe (plus statin) and the statin monotherapy Markov traces have individuals in the primary angina health state. This implies that individuals who receive treatment are more likely to have angina than individuals who do not receive any treatment. Is our interpretation of the code and the Markov traces correct? If not, can you please provide a detailed explanation for this?

Response to Query 3

Your interpretation of the code is correct. There is no inherent constraint on the Anderson risk equations that guarantees the combined risk of CHD death and MI will not exceed the estimated risk for total CHD. Because we use these estimates to calculate the risk of angina, when a negative result does occur, we set the risk of angina to 0 and determine the relative likelihood of CHD death and MI based on their calculated risks. Based on what you are describing above, you must have uncovered a situation in which a reduction in Total/HDL ratio (either by statin titration or the addition of ezetimibe) lowered the calculated risk for CHD, CHD death and MI such that the sum of the CHD death and MI risks was no longer greater than the total CHD risk estimate.

Query 4

Some of the CEAC plots [e.g. Fig. 3.4, p. 47, Fig. 3.4, p. 48; Fig. 3.5, p. 49; Fig. 3.8, p. 55 (please note there are two figures numbered 3.4)] are described as the results for 'people' as opposed to 'male' or 'female'. Is this correct? Are the results weighted in some way using results from both male and female analyses. If the titles are correct, can you please provide an explanation for the results presented. If the titles should read 'male' as opposed to 'people', can you please provide corresponding CEACs for the female evaluations.

Response to Query 4

We are sorry about the typo in numbering the CEAC plots. The plots provided were those for males only. Please find below the plots for females and in these plots the scales on the x-axes are different for the different plots; in the keys, TC = total cholesterol (mmol/l).

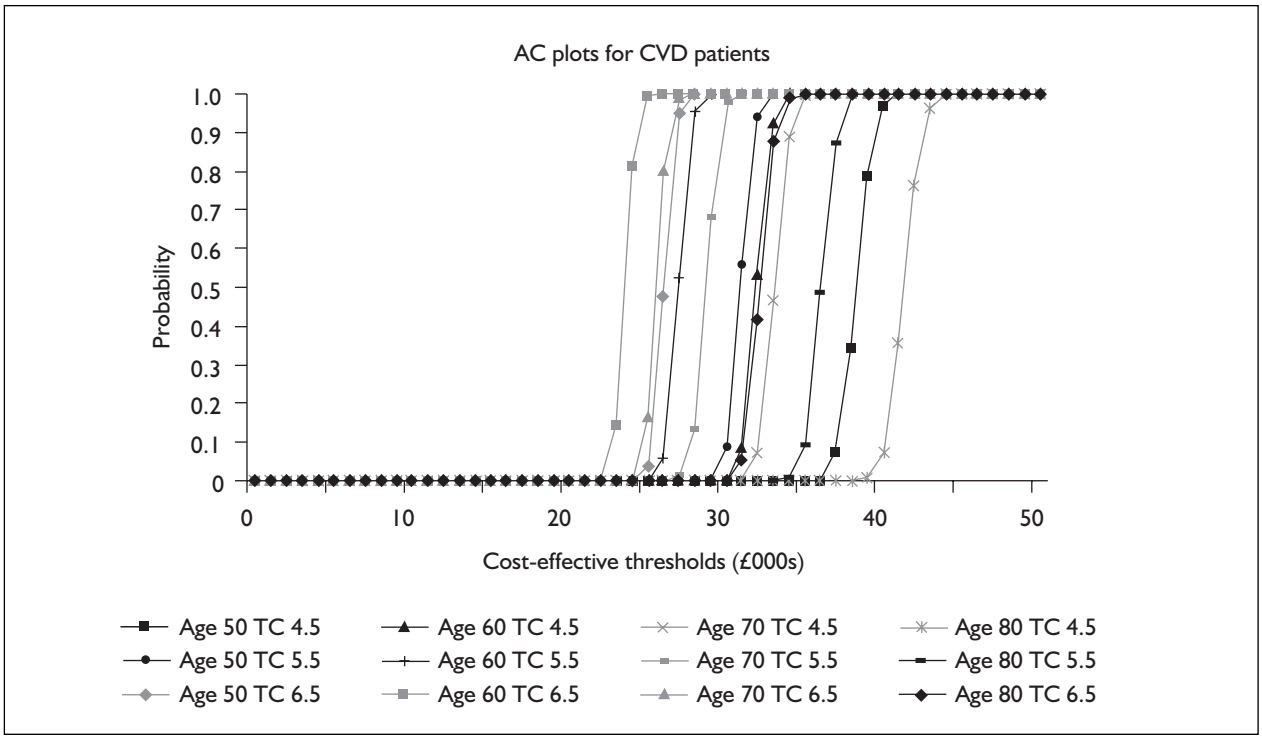


FIGURE 1.1 *Ezetimibe co-administration with statin vs statin titration in females with clinical evidence of CVD – probability of cost-effectiveness by threshold*

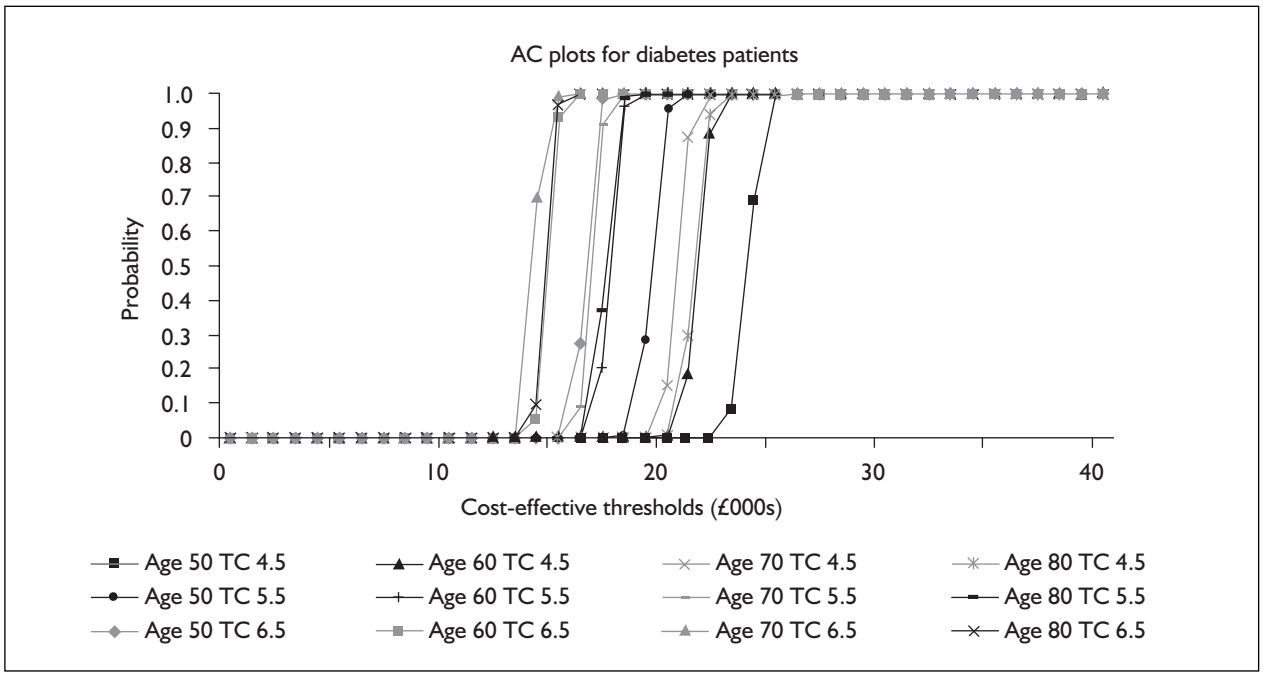


FIGURE 1.2 *Ezetimibe co-administration with statin vs statin titration in females with diabetes but no CVD – probability of cost-effectiveness by threshold*

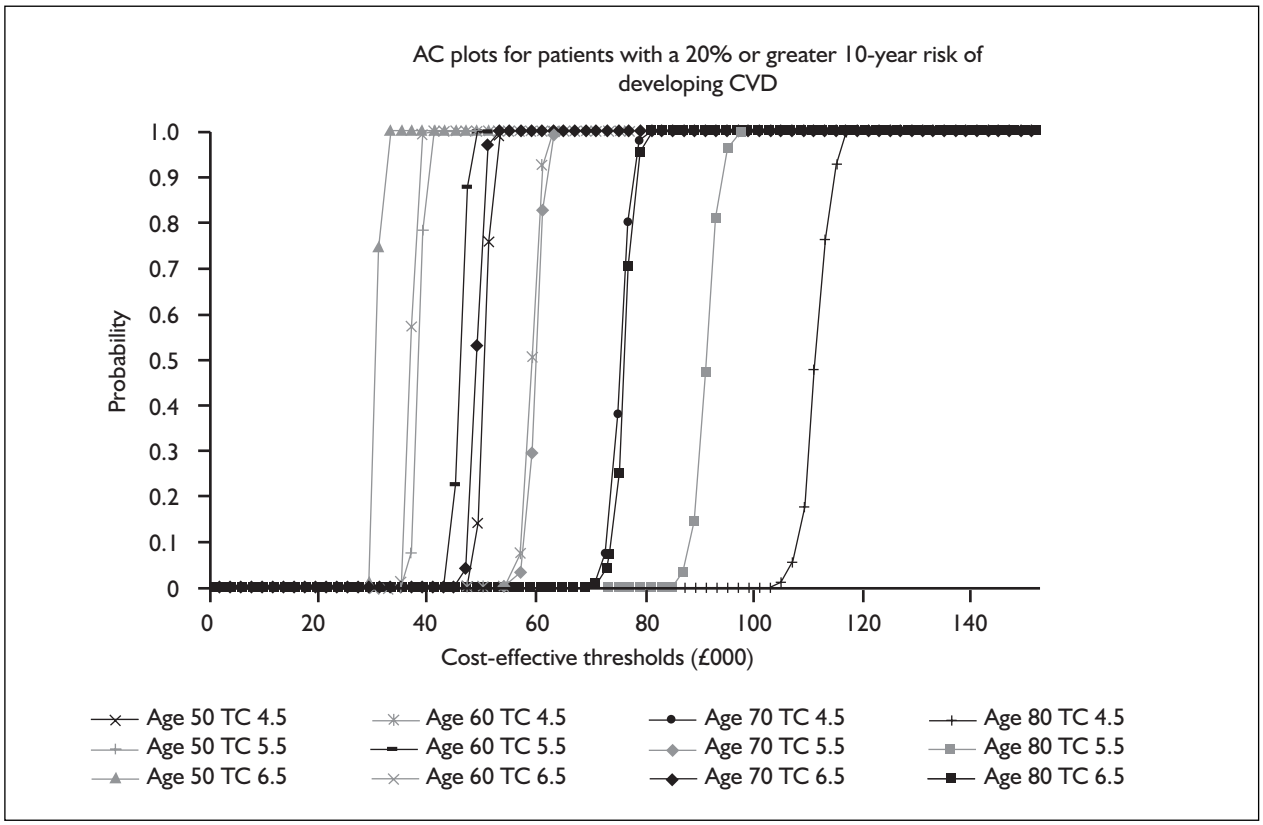


FIGURE 1.3 *Ezetimibe co-administration with statin vs statin titration in females who have a 20% or greater 10-year risk of developing CVD – probability of cost-effectiveness by threshold*

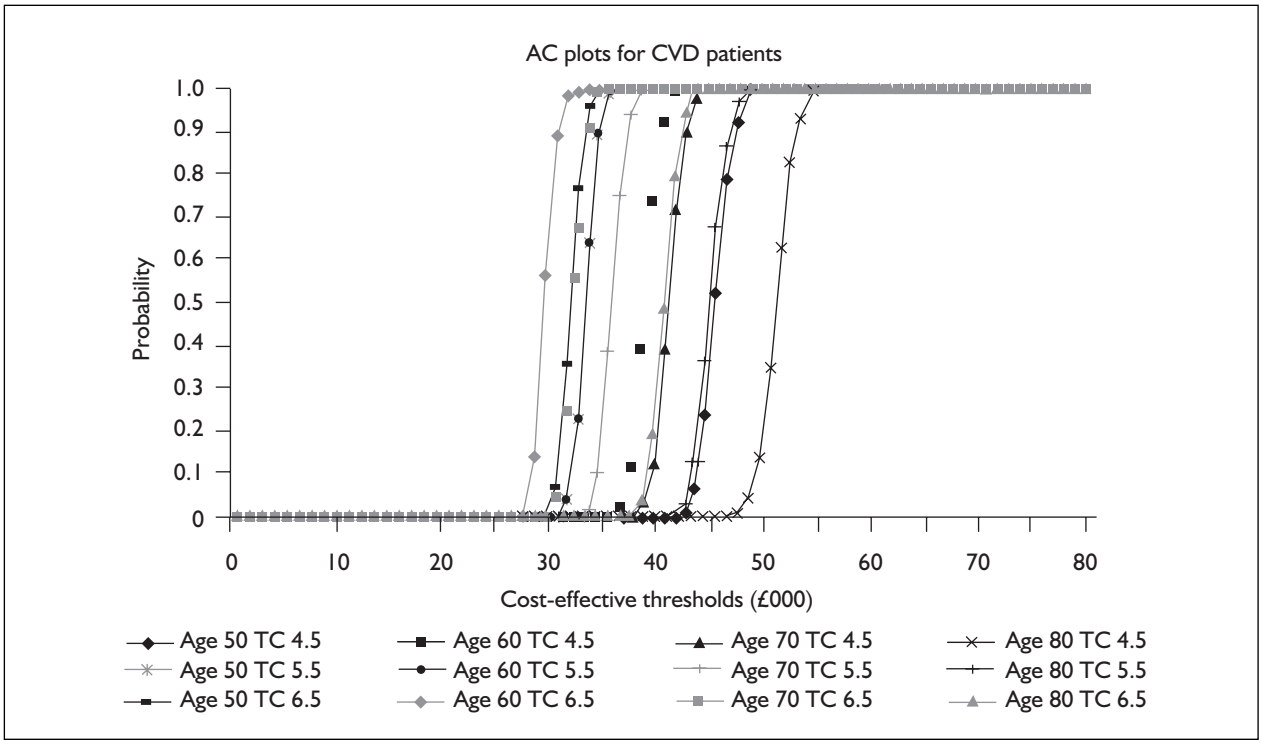


FIGURE 1.4 *Ezetimibe monotherapy in females with clinical evidence of CVD – probability of cost-effectiveness by threshold*

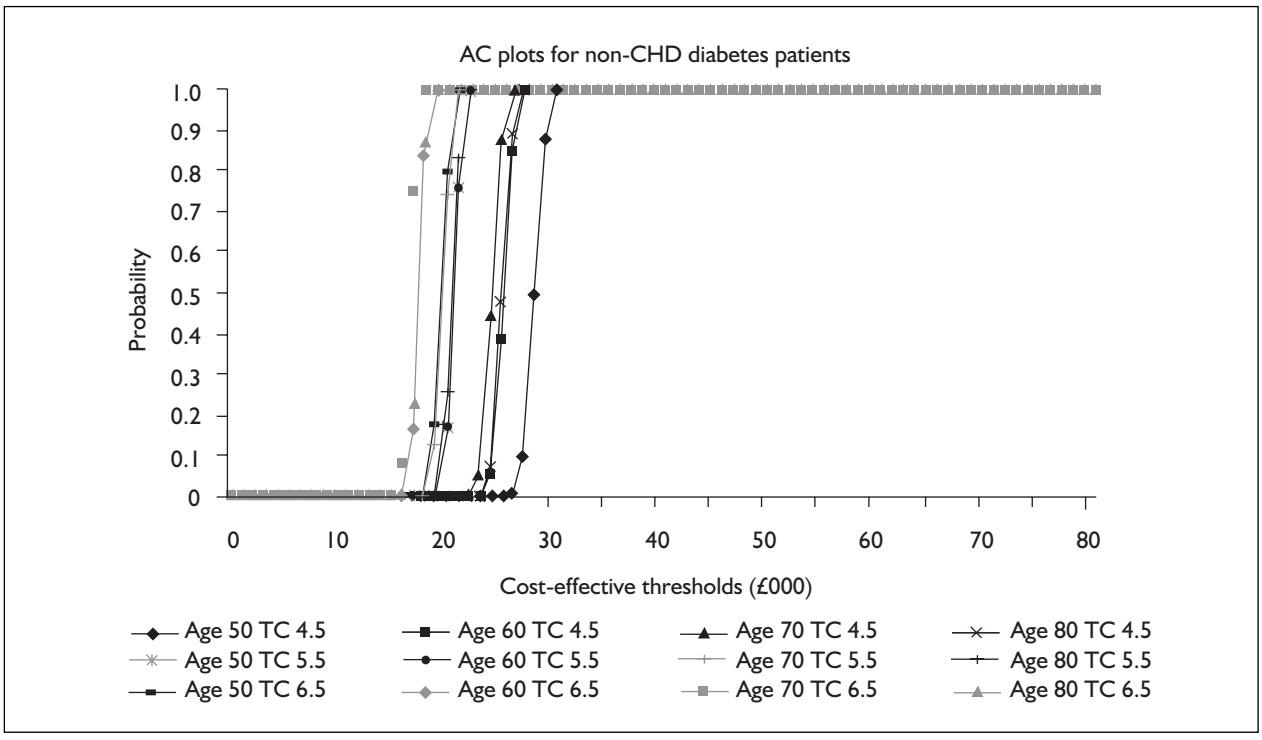


FIGURE 1.5 *Ezetimibe monotherapy in females with diabetes but no CVD – probability of cost-effectiveness by threshold*

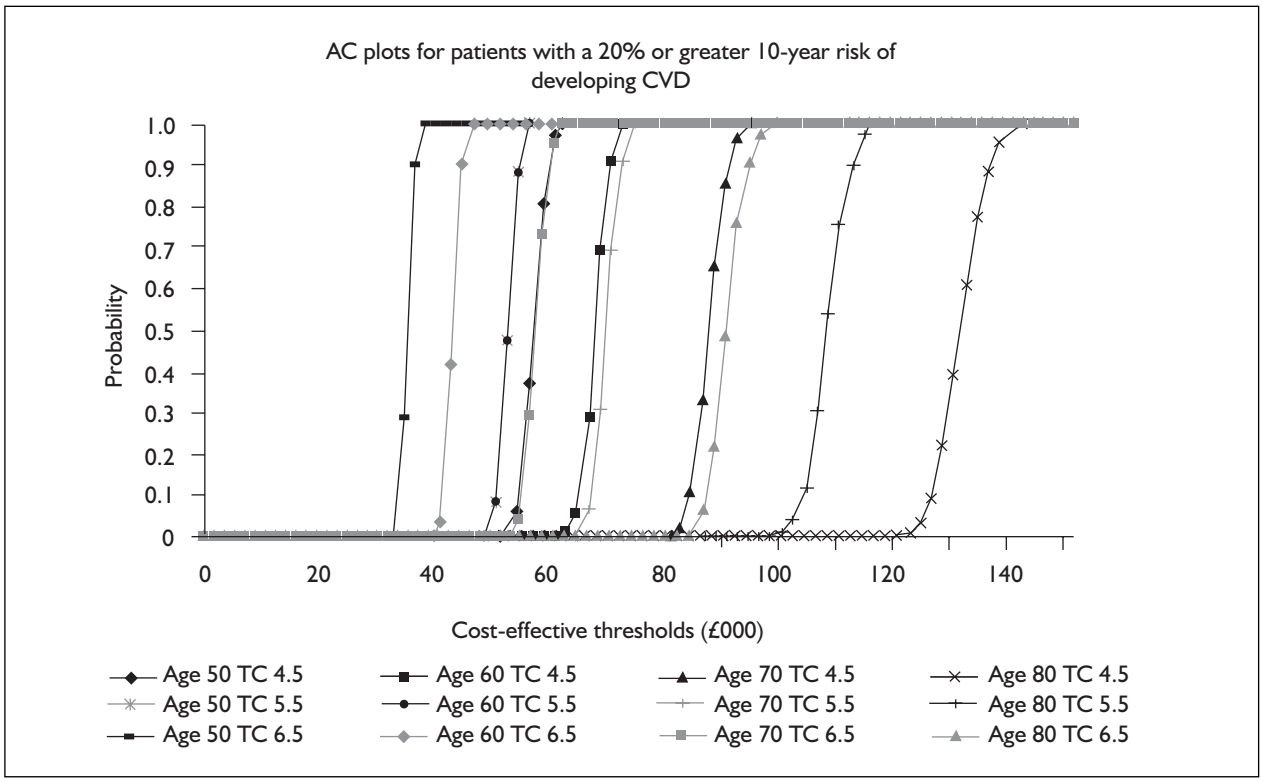


FIGURE 1.6 *Ezetimibe monotherapy in females who have a 20% or greater 10-year risk of developing CVD – probability of cost-effectiveness by threshold*

Appendix 21

Detailed discussion of the critical review of the MSD/SP models

Validity of using risk engines to predict changes in risk based on chemically induced changes in lipids

With the exception of the primary diabetic analyses, the Framingham risk engines are used to predict baseline risks and to model the effect of the different treatment regimens modelled. The authors defend the use of the Framingham equations using arguments such as the following:

- The Framingham equations have been accepted by influential clinical guidelines such as the US NCEP ATP III and the Second European Joint Task Force guidelines.
- The authors of a review on methods for predicting future events in economic models concluded that the algorithms from the Framingham study were the most appropriate methodology.

It is acknowledged that the US NCEP ATP III[258] recommend that the CHD risk charts (which are based on the Framingham algorithms) are used to calculate an individual's CHD risk to determine if treatments are applicable. However, it should be noted that predicting an individual's risk based on a natural risk profile at one point in time is very different from using the algorithms to predict changes in risk on an annual basis due to chemically induced changes in cholesterol levels. To the Assessment Group's knowledge, the organisations quoted above have not suggested that it is correct to use the Framingham equations to model reductions in risks due to lipid-lowering treatments.

The review by Grieve and colleagues[90] presents a systematic and robust process for choosing a method of predicting events in economic models concentrating on the CV field. The research is thorough and the conclusions drawn by the authors were justified based on the evidence available at the time. However, evidence has since emerged which offers an alternative methodology to link changes in cholesterol levels to reductions in CV events.[79] This evidence was utilised in the alternative Basic model presented by MSD/SP demonstrating that the MSD/SP analysts consider the methodology to be appropriate. The authors of the MSD/SP economic evaluation state that results generated by the alternative model are "consistent to those of the more sophisticated model" (p. 43, main report).

Reported and modelled CHD risks

Ten-year CHD risks, calculated using the Anderson primary CHD algorithms and the primary CVD patient profiles (Tables 3.13 and 26.7 of the MSD/SP report), are reported. As the D'Agostino algorithms are used to predict annual risks in the model, it is unclear why the Anderson risks are reported. Presumably they are to demonstrate that the 10-year baseline CVD risk modelled was greater than the 20% recommended for lipid-lowering treatment.[39]

The analysts have assumed that a 15% 10-year CHD risk is equivalent to a 20% 10-year CVD risk across age and gender (MSD/SP report). This is a crude assumption as the ratio for CHD and CVD events differs by age and gender.[77,259] More importantly, the risks reported in Tables 3.13 and 26.7 of the MSD/SP report, which were calculated using the lower bounds of the Total-c bands, are not consistent with the modelled risks, which were calculated using the mid-points of the lipid categories.

Male primary risks

The reported Anderson 10-year CHD risks (column 2 in *Table 73*) increase with age, as would be expected. The modelled risk for males (column 6) also increases with age. The male reported (column 2) and modelled (column 6) risks are comparable for ages 50 and 60 years. For ages 70 and 80 years, the modelled risks are substantially higher than the annual rate (column 4) corresponding to the reported 10-year risks (column 2). The difference in the risks calculated using the different Framingham equations becomes more marked as age increases.

Using a baseline Total-c of 4.5 mmol/l (mid-point 4.625 mmol/l) at the age of 90 years, the Anderson 10-year risk is 42.6% whereas the D'Agostino 1-year risk is 10.99%, and at the age of 99 years (the limit in the model) the Anderson 10-year risk is 47.4% whereas the D'Agostino 1-year risk is 16.99%. When using the baseline Total-c of 6.5 mmol/l (mid-point 6.625 mmol/l), the differences in the calculated risks are even larger: at the age of 99 years the Anderson 10-year risk is 56.1% whereas the D'Agostino 1-year risk is 25.10%.

Presumably this anomaly is because the Framingham equations are valid up to the age of 74 years only.[87] To our knowledge, there is no published methodology which can be used to validate the risks derived by extrapolating beyond the evidence base. It is therefore not possible to determine which, if any, of the two estimates most accurately reflects the true risk for individuals over the age of 74 years.

Female primary risks

With the exception of age 80 years, the reported Anderson 10-year CHD risks (column 3) increase with age, as would be expected. The modelled risk for females (column 7) decreases with age. All the modelled risks (column 7) are substantially lower than the annual rate (column 5) corresponding to the reported 10-year risks (column 3). The modelled risks decrease by age due to an error in the Visual Basic code for the female D'Agostino algorithm. The term which represents females who are menopausal has been incorrectly coded.

As the Framingham equations are also used to determine subsequent risks and the risks for the secondary cohorts, the uncertainty in the predicted risks impacts on all the results presented. It is not possible to estimate the magnitude or direction of the errors in the ICERs generated.

Distribution of predicted risk across event type

The total primary D'Agostino CHD risk (defined as non-fatal MI, CHD death, angina pectoris and coronary insufficiency) is apportioned to event type using predicted risks from the Anderson equations for non-fatal MI and fatal CHD.[87] The probability of angina is estimated by subtracting

TABLE 73 *Comparison of reported and modelled first-year CHD risk used in the MSD/SP economic evaluation*

	Reported[a] 10-year risk (%)		Annual rate[b] (%) (estimated)		First-year risk[c] (%) (modelled)	
Age (years)	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**
Total-c = 4.5 mmol/l (HDL = 1 mmol/l, SBP = 16 mgHg; alcohol = 5.67 fl.oz)						
50	15.8	11.2	1.71	1.18	1.44	0.81
60	23.0	15.5	2.58	1.67	2.40	0.71
70	30.1	17.4	3.52	1.89	4.00	0.63
80	36.7	17.2	4.46	1.87	6.68	0.55
Total-c = 5.5 mmol/l (HDL = 1 mmol/l, SBP = 16 mgHg; alcohol = 5.67 fl.oz)						
50	19.5	14.2	2.15	1.52	1.82	1.03
60	27.4	19.2	3.15	2.11	3.05	0.90
70	34.9	21.2	4.2	2.35	5.10	0.79
80	41.6	21.1	5.24	2.34	8.40	0.70
Total-c = 6.5 mmol/l (HDL = 1 mmol/l, SBP = 16 mgHg, alcohol = 5.67 fl.oz)						
50	22.9	17.0	2.57	1.85	2.22	1.25
60	31.3	22.5	3.68	2.52	3.71	1.10
70	38.9	24.7	4.81	2.80	6.17	0.97
80	45.7	24.6	5.92	2.78	10.20	0.85

SBP, systolic blood pressure.

[a] 10-year CHD risks reported in Table 3.13 (p. 46 of the MSD/SP report) and Table 26.7 (p. 229) which are calculated using Anderson *et al.*[77]

[b] Annual CHD rate estimated using the equation annual rate $= 1 - [1 - p(10\text{-yr})] \times (1/10)$.

[c] Actual annual CHD risk modelled in each MSD/SP analysis using the sum of the first-year primary non-fatal angina and MI and fatal CHD events in the no treatment Markov traces.

the probabilities for non-fatal MI and fatal CHD from the total risk.

When the summed probabilities for non-fatal MI and coronary death are larger than the predicted total CHD risk, a mechanism is employed to set the risk of angina to zero and the total risk is allocated to just non-fatal MI and fatal CHD. The consequence of this is that individuals receiving statin monotherapy have more angina events than those receiving no treatment whereas those receiving ezetimibe plus statin treatment have more angina events than those receiving statin monotherapy or those receiving no treatment. In reality, this means that (1) the treatment regimens increase the number of cases of angina and (2) the number of 'serious' events prevented is overestimated. The impact on the ICERs is unknown, but could be substantial.

Costs and HRQoL utilities used in the MSD/SP models

The MSD/SP analysts relied heavily on the NICE statin HTA report[39,184] to populate the model. There is no evidence to suggest that independent searches were conducted to identify any new evidence for the health states costs, utilities, compliance or monitoring requirements. A number of minor inconsistencies were found:

1. The health state costs were inflated using an incorrect unreferenced inflation rate and are too low, hence the cost offsets due to events avoided are underestimated and the ongoing costs for the secondary analyses are underestimated.
2. The monitoring costs taken from the NICE HTA report[39] were not updated and have been applied incorrectly with 'start-up' costs for initiation of treatment applied to patients who enter the model on ongoing treatment. Although the monitoring costs applied in the MSD/SP evaluation are too high, as they are applied in both arms for the majority of the analyses the impact on the ICERs should be minimal.
3. Drugs tariffs which report rates applicable to hospitals were used for the majority of treatment costs. As the target population is predominantly based in general clinical practice, the correct treatment costs are those reported in the BNF.[188] Although treatment costs are underestimated in all the evaluations, this is unlikely to have a large impact on the results.
4. HRQoL utility values for the health states are reported as being 0.79 for angina and 0.760 for MI (Table 3.9 of the MSD/SP report). No value is reported for the secondary no event health state. In the Cook Excel model, utility values are labelled as 0.75 for angina, 0.79 for MI and a mid-point of 0.875 (range 0.75–1) for prior CHD. Whereas the values of 0.79 for angina, 0.76 for MI and 0.775 for the secondary no event health state are used in the univariate analyses, probabilistic analyses read utility values from the incorrect values in the spreadsheet. As the angina HRQoL value (0.79) is higher than the secondary no event health state (0.775), it would seem that an angina event can increase HRQoL in some analyses. It is unlikely that these inconsistencies will have a large impact on the results.

Appendix 22

Identification of studies for the review of cost-effectiveness

This appendix contains information on the sources searched (*Table 74*) and keyword strategies for the systematic review of cost-effectiveness.

Sources consulted via the Internet

See *Table 52*, Appendix 2.

Database keyword strategies

CINAHL

1982–2006
OVID Online
Search undertaken between April and June 2006

1 Ezetimibe/ (48)
2 ezetimibe.tw. (66)
3 ezetrol.tw. (0)
4 zetia.tw. (3)
5 vytorin.tw. (4)
6 inegy.tw. (2)
7 1 or 2 or 4 or 5 or 6 (87)
8 Hypercholesterolemia/ (2016)
9 hypercholesterolemia.af. (2741)
10 hypercholesterolaemia.af. (258)
11 8 or 9 or 10 (2872)
12 7 and 11 (61)
13 exp economics/ (181163)
14 exp "financial management"/ (11930)
15 exp "financial support"/ (119056)
16 exp "financing organized"/ (37494)
17 exp "business"/ (12404)
18 or/14-17 (171524)
19 18 not 13 (7368)
20 Health resource allocation.sh. (2638)
21 Health resource utilization.sh. (3650)
22 20 or 21 (6205)
23 19 or 22 (13570)
24 (cost or costs or economic$ or pharmacoeconomic$ or price$ or pricing$).tw. (35173)
25 23 or 24 (47353)
26 Editorial.pt. (65097)
27 Letter.pt. (33989)
28 News.pt. (0)
29 or/26-28 (99047)
30 25 not 29 (45615)
31 "Animal studies"/ (3715)
32 30 not 31 (45575)
33 Cochrane library.so. (2540)
34 Anonymous.au. (0)
35 32 not (33 or 34) (45234)
36 12 and 35 (0)
37 fibrate$.tw. (76)
38 Resins/ (60)
39 resin$.tw. (335)
40 Niacin/ (292)
41 nicotinic acid.tw. (38)
42 Statins/ (1533)
43 statin$.tw. (1300)
44 Fatty Acids, Omega 3/ (751)
45 omega 3.tw. (266)
46 1 or 2 or 4 or 5 or 6 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 (3465)
47 11 and 46 (610)
48 35 and 47 (32)
49 Hyperlipidemia/ (1711)
50 hyperlipid$.af. (2713)
51 hypertriglycerid$.af. (497)
52 8 or 9 or 10 or 49 or 50 or 51 (5331)
53 Antilipemic Agents/ (841)
54 lipid lowering.tw. (564)
55 cholesterol lowering.tw. (358)
56 46 or 53 or 54 or 55 (4477)
57 52 and 56 (1528)
58 35 and 57 (76)
59 58 not 48 (44)
60 from 59 keep 1-43 (43)
61 8 or 9 or 10 or 49 or 50 or 51 (5331)
62 35 and 61 (219)
63 62 not 58 (143)

TABLE 74 *Electronic databases searched for the review of cost-effectiveness*

CINAHL
Cochrane Library
DARE-NHS EED-HTA
EMBASE
MEDLINE
OHE HEED
Web of Science

Cochrane Library (CDSR, CENTRAL, DARE, HTA)

Issue 2, 2006
Wiley version
Search undertaken between April and June 2006

9 ezetimibe in All Fields in all products
10 ezetrol in All Fields in all products
11 zetia in All Fields in all products
12 vytorin in All Fields in all products
13 inegy in All Fields in all products
14 #1 OR #2 OR #3 OR #4 OR #5
15 hypercholesterolaemia or hypercholesterolemia in All Fields in all products
16 #6 AND #7

DARE-NHS EED-HTA

Data coverage not known (approximately 1994–2006)
CRD website version
Search undertaken between April and June 2006

((ezetimibe OR ezetrol OR zetia OR vytorin OR inegy) AND (hypercholesterolemia OR hypercholesterolaemia))

EMBASE

1980–2006
Ovid Online version
Search undertaken between April and June 2006

1 ezetimibe.tw.
2 ezetrol.tw.
3 zetia.tw.
4 vytorin.tw.
5 inegy.tw.
6 "163222-33-1.".rn.
7 Ezetimibe/
8 or/1-7
9 hypercholesterolaemia.mp. or hypercholesterolemia.af. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
10 socioeconomics/
11 "Cost Benefit Analysis"/
12 "Cost Effectiveness Analysis"/
13 "Cost of Illness"/
14 "Cost Control"/
15 Economic Aspect/
16 Financial Management/
17 "Health Care Cost"/
18 Health Care Financing/
19 Health Economics/
20 "Hospital Cost"/
21 (fiscal or financial or finance or funding).tw.
22 Cost minimization analysis/
23 (cost adj estimate$).mp.
24 (cost adj variable$).mp.
25 (unit adj cost$).mp.
26 "Quality of Life"/ or Quality Adjusted Life Year/
27 quality adjusted life.tw.
28 (qaly$ or qald$ or qale$ or qtime$).tw.
29 disability adjusted life.tw.
30 daly$.tw.
31 health status indicators/
32 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (5199)
33 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
34 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
35 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
36 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
37 (euroqol or euro qol or eq5d or eq 5d).tw.
38 (hql or hqol or h qol or hrqol or hr qol).tw.
39 (hye or hyes).tw.
40 health$ year$ equivalent$.tw.
41 health utilit$.tw.
42 (hui or hui1 or hui2 or hui3).tw.
43 disutili$.tw.
44 rosser.tw.
45 quality of wellbeing.tw.
46 qwb.tw.
47 willingness to pay.tw.
48 standard gamble$.tw.
49 time trade off.tw.
50 time tradeoff.tw.
51 tto.tw.
52 exp models, economic/
53 *models, theoretical/
54 *models, organizational/
55 economic model$.tw.
56 markov chains/
57 markov$.tw.
58 monte carlo method/
59 monte carlo.tw.
60 exp decision theory/
61 (decision$ adj2 (tree$ or analy$ or model$)).tw.
62 letter.pt.
63 editorial.pt.
64 comment.pt.
65 or/62-64
66 or/10-61
67 66 not 65
68 8 and 9 and 67

MEDLINE

1966–2006
Ovid Online
Search undertaken between April and June 2006

1 ezetimibe.tw.
2 ezetrol.tw.
3 zetia.tw.
4 vytorin.tw.
5 inegy.tw.
6 "163222-33-1.".rn.
7 or/1-6
8 hypercholesterolemia.af.
9 hypercholesterolaemia.af.
10 8 or 9
11 Economics/
12 exp "Costs and Cost Analysis"/
13 economic value of life/
14 exp economics hospital/
15 exp economics medical/
16 economics nursing/
17 exp models economic/
18 Economics, Pharmaceutical/
19 exp "Fees and Charges"/
20 exp budgets/
21 ec.fs.
22 (cost or costs or costed or costly or costing$).tw.
23 (economic$ or pharmacoecomomic$ or price$ or pricing$).tw.
24 quality adjusted life years/
25 (qaly or qaly$).af.
26 or/11-25
27 7 and 10 and 26

OHE HEED

Web version
Search undertaken April–June 2006
Ezetimibe

Web of Science

1900–2006
Web of Knowledge version
Search undertaken between April and June 2006

#1 TS=(hypercholesterolemia OR hypercholesterolaeima) DocType=All document types; Language=All languages; Databases=SCI-EXPANDED, SSCI; Timespan=1900-2006
#2 TS=(ezetimibe OR ezetrol OR zetia OR vytorin OR inegy) DocType=All document types; Language=All languages; Databases=SCI-EXPANDED, SSCI; Timespan=1900-2006
#3 #1 AND #2 DocType=All document types; Language=All languages; Databases=SCI-EXPANDED, SSCI; Timespan=1900-2006

Appendix 23

Searches undertaken to inform model development

This appendix maps out the evidence base used to inform the development of the independent economic model and provides an overview of the methods used to identify the evidence. A description of the categories of evidence used is presented first. Next, each individual source is listed together with details of how the source was identified and how it was used in the model. Lastly, the keyword strategies of searches undertaken to inform the model and a brief description of the scope of search are provided.

Key sources of evidence

The source of the evidence base used to inform the development of the model can be classified into the key categories listed in *Table 75*. Individual sources identified within these key categories are listed in *Table 76*.

Individual sources of evidence

The individual sources which make up the key categories of evidence are listed in *Table 76* with details of how each source was identified and how each source was used in the model.

TABLE 75 *Key sources of evidence used to inform the model*

Review of clinical effectiveness	Assessment of clinical effectiveness of ezetimibe presented in earlier section of the present report
Economic analysis previously undertaken by authors	Assessment of statin treatment undertaken to inform NICE statin guidance[39]
Searches undertaken to inform model development	See below
Searches undertaken to inform the review of cost-effectiveness	See Appendix 22
Searches undertaken to inform the review of clinical effectiveness	See Appendix 2
Ad hoc searches	
Evidence known to authors	
Expert opinion	
Reference sources (e.g. BNF)	

TABLE 76 *Individual sources of evidence used to inform model development*

Source	Use(s) in the model	Process of identification (originating key source)
Anderson *et al.*, 1991[77]	Informing the approach to modelling surrogate to clinical end-points Support assumptions relating to HeFH population Support assumptions relating to baseline CVD risk	Searches undertaken to inform model development
Baigent *et al.*, 2005[79]	Informing the approach to modelling surrogate to clinical end-points Translate changes in LDL-c (surrogate end-point) to reductions in CVD events (clinical end-point) Support assumption relating to no impact of treatment on fatal Str	Searches undertaken to inform model development
Bamford *et al.*, 1988[177]	Support assumptions relating to baseline CVD risk distribution	Economic analysis previously undertaken by authors[39]
BARI, 1991[194]	Provide stable angina HRQoL utility estimate	Economic analysis previously undertaken by authors[39]

continued

TABLE 76 *Individual sources of evidence used to inform model development (cont'd)*

Source	Use(s) in the model	Process of identification (originating key source)
Bates, 1989[167]	Support modelling search methods	Evidence known to authors
BNF, 2006[38]	Provide medication cost estimates	Reference source
Bots and Kastelein 2005[179]	Inform baseline secondary event risks	Searches undertaken to inform model development
Brindle *et al.*, 2003[93]	Informing the approach to modelling surrogate to clinical end-points	Searches undertaken to inform model development
Brindle *et al.*, 2005[98]	Informing the approach to modelling surrogate to clinical end-points	Searches undertaken to inform model development
Brindle *et al.*, 2006[92]	Informing the approach to modelling surrogate to clinical end-points	Searches undertaken to inform model development
British Heart Foundation Database[178]	Inform baseline secondary event risks	Expert advice
Chen *et al.*, 1991[81]	Informing the approach to modelling surrogate to clinical end-points	?
Clarke *et al.*, 2003[155]	Provide fatal MI cost estimate	Economic analysis previously undertaken by authors[39]
Colhoun *et al.*, 2004[103]	Informing the approach to modelling surrogate to clinical end-points	Searches undertaken to inform model development
Cooper *et al.*, 2005[88]	Informing the approach to modelling surrogate to clinical end-points	Searches undertaken to inform model development
Curtis and Netten, 2005[189]	Provide GP contact cost estimates Provide Practice Nurse cost estimates	Reference source
Curtis and Netten, 2006[154]	Adjust cost estimates to 2006	Reference source
D'Agostino *et al.*, 2000[87]	Informing the approach to modelling surrogate to clinical end-points Support assumptions relating to baseline CVD risk	Economic analysis previously undertaken by authors[39]
De Sauvage Nolting, 2003[260]	Support assumptions relating to HeFH population	Searches undertaken to inform model development
Dennis *et al.*, 1993[261]	Support assumptions relating to baseline CVD risk distribution	Economic analysis previously undertaken by authors[39]
Department of Health, 2003[262]	Support assumptions relating to HeFH population	Expert advice
Empana *et al.*, 2003[94]	Informing the approach to modelling surrogate to clinical end-points	Searches undertaken to inform model development
Expert advice (various sources)	Provide references to other sources of evidence used to support model Support assumptions relating to HeFH population Support assumptions relating to non-European groups Inform choice of treatment comparators Inform treatment regimen scenarios Support assumptions relating to baseline secondary event risk Inform TIA HRQoL utility estimate Inform second and third event HRQoL utility estimate	Advisers to current analysis
German, 2006[89]	Informing the approach to modelling surrogate to clinical end-points	Undertaken as part of current analysis
Glick and Kinosian, 1995[264]	Informing the approach to modelling surrogate to clinical end-points	Economic analysis previously undertaken by authors[39]

continued

TABLE 76 *Individual sources of evidence used to inform model development (cont'd)*

Source	Use(s) in the model	Process of identification (originating key source)
Goodacre *et al.*, 2004[195]	Provide unstable angina HRQoL utility estimate Provide MI HRQoL utility estimate	Economic analysis previously undertaken by authors[39]
Gould, 1998[84]	Informing the approach to modelling surrogate to clinical end-points	Searches undertaken to inform model development
Government Actuary Life Tables[205]	Inform assumptions relating to non-vascular mortality	Reference source
Gray and Hapton, 1993[180]	Support assumptions relating to baseline secondary event risk	Expert advice
Grieve *et al.*, 2003[90]	Informing the approach to modelling surrogate to clinical end-points	Searches undertaken to inform model development
Grundy *et al.*, 2004[82]	Informing the approach to modelling surrogate to clinical end-points	Searches undertaken to inform model development
Haacke *et al.*., 2006[198]	Inform TIA HRQoL utility estimate	Searches undertaken to inform model development
Health Survey for England 2003[265]	Support assumptions relating to baseline CVD risk Support assumptions relating to baseline CVD risk distribution	Reference source
Hense *et al.*, 2003[95]	Informing the approach to modelling surrogate to clinical end-points	Searches undertaken to inform model development
Hobbs, 2006[204]	Inform assumptions relating to compliance	Searches undertaken to inform model development
Jurgensen, 2006[97]	Informing the approach to modelling surrogate to clinical end-points	?
Juul-Moller, 1992[183]	Support assumptions relating to baseline secondary event risk	Expert advice
Kim *et al.*, 2007[196]	Inform unstable angina HRQoL utility estimate	Searches undertaken to inform model development
Kind *et al.*, 1998[199]	Provide TIA HRQoL utility estimate Inform HRQoL utility by age	Reference source
Kirby *et al.*, 2006[45]	Inform choice of treatment comparators Inform assumptions relating to compliance	Searches undertaken for review of cost-effectiveness
Knopp, 1999[67]	Inform choice of treatment comparators Provide evidence of clinical effectiveness of statin titration	Searches undertaken for review of clinical effectiveness
Lacey and Walters, 2003[197]	Inform MI HRQoL utility estimate	Searches undertaken to inform model development
Law *et al.*, 2003[83]	Informing the approach to modelling surrogate to clinical end-points	Searches undertaken to inform model development
Law and Singh, 2006[105]	Informing the approach to modelling surrogate to clinical end-points	Searches undertaken to inform model development
Leeds *et al.*, 2004[202]	Inform Str HRQoL utility estimate	Searches undertaken to inform model development
Lenzen *et al.*, 2006[193]	Inform stable angina HRQoL utility estimate	Searches undertaken to inform model development
Leren, 2004[266]	Support assumptions relating to HeFH population	Search undertaken to inform review of cost-effectiveness
SIGN Lipid Guidelines[29]	Inform treatment regimen scenarios	Searches undertaken to inform review of clinical effectiveness
LRCCPPT, 1984[168]	Inform choice of treatment comparators	Searches undertaken to inform model development

continued

TABLE 76 *Individual sources of evidence used to inform model development (cont'd)*

Source	Use(s) in the model	Process of identification (originating key source)
Marang-van de Mheen *et al.*, 2002[271]	Support assumptions relating to HeFH population	Searches undertaken to inform model development
Marks *et al.*, 2003[19]	Support assumptions relating to HeFH population	*Ad hoc* searches
Marks *et al.*, 2000[268]	Support assumptions relating to HeFH population	Expert advice
Marks *et al.*, 2002[267]	Support assumptions relating to HeFH population	Expert advice
Morris, 1997[269]	Support Markov modelling approach	Searches undertaken to inform model development
Mortalilty Statistics, 2001[205]	To inform estimate relating to non-vascular mortality	Reference source
Mueck and Seeger, 2002[171]	Support Markov modelling approach	Evidence known to authors
Neaton *et al.*, 1992[78]	Informing the approach to modelling surrogate to clinical end-points	Economic analysis previously undertaken by authors[39]
Newson and Humphries, 2005[270]	Support assumptions relating to HeFH population	Expert advice
NHS Reference Costs, 2005[192]	Provide monitoring test cost estimates	Reference source
NICE[172]	Support model perspective Support assumptions relating to baseline CVD risk distribution	Reference source
NICE[39]	Support assumption relating to event rates for diabetes population Support assumption in modelling link between surrogate and clinical end-points Support assumption relating to no impact of treatment on fatal Str Support model perspective Inform treatment scenarios Provide references to sources of cost estimates Provide cost estimates (stable angina, unstable angina, TIA) Provide references to sources of HRQoL utilities for health states	Economic analysis previously undertaken by authors[39]
NICE[39]	Inform choice of treatment comparators Inform treatment regimen scenarios Evidence known to authors	Economic analysis previously undertaken by authors[39]
Palmer *et al.*, 2002[190]	Provide non-fatal MI cost estimate	
Pearson *et al.*, 2000[165]	Inform choice of treatment comparators	Review of clinical effectiveness
Pedersen *et al.*, 2004[185]	Support assumption relating to no benefits from treatment in first year	Searches undertaken to inform model development
Pickard *et al*, 2005[203]	Inform Str HRQoL utility estimate	Searches undertaken to inform model development
Prescription Cost Analysis 2005, 2006[43]	Inform choice of treatment comparators Inform treatment regimen scenarios Provide estimated weighted cost of statin treatment	Reference source
Prescription Rates (Wales), 2005[44]	Inform treatment regimen scenarios	Reference source
Review of clinical effectiveness	Support assumptions relating to baseline LDL-c levels Provide clinical effectiveness evidence to populate model Provide references to sources of background evidence	Undertaken as part of current analysis

continued

TABLE 76 *Individual sources of evidence used to inform model development (cont'd)*

Source	Use(s) in the model	Process of identification (originating key source)
Robinson *et al.*, 2005[85]	Informing the approach to modelling surrogate to clinical end-points	*Ad hoc* searches
Rothwell *et al.*, 2004[182]	Support assumptions relating to baseline CVD risk distribution	Economic analysis previously undertaken by authors[39]
Sacks *et al.*, 1996[186]	Support assumption relating to no benefits from treatment in first year	Economic analysis previously undertaken by authors[39]
Schwartz *et al.*, 2001[187]	Support assumption relating to no benefits from treatment in first year	Economic analysis previously undertaken by authors[39]
Sever *et al.*, 2003[272]	Informing the approach to modelling surrogate to clinical end-points	Searches undertaken to inform model development
Simon Broome Register, 1991[273]	Support assumptions relating to HeFH population	Expert advice
Sonnenberg and Beck, 1993[170]	Support Markov modelling approach	Evidence known to authors
Stamler *et al.*, 1993[80]	Informing the approach to modelling surrogate to clinical end-points	Searches undertaken to inform model development
Stein *et al.*, 2004[118]	Support assumptions relating to HeFH population	Review of clinical effectiveness
Stevens *et al.*, 2001[86]	Informing the approach to modelling surrogate to clinical end-points	Searches undertaken to inform model development
Sutcliffe *et al.*, 2003[175]	Support assumptions relating to baseline CVD risk distribution	Economic analysis previously undertaken by authors[39]
Tengs and Lin, 2003[200]	Inform Str HRQoL utility estimate	Economic analysis previously undertaken by authors[39]
Thomsen *et al.*, 2002[96]	Informing the approach to modelling surrogate to clinical end-points	Searches undertaken to inform model development
Van Exel *et al.*, 2004[201]	Inform Str HRQoL utility estimate	Economic analysis previously undertaken by authors[39]
Williams and Stevens, 2003[42]	Inform choice of treatment comparators	Searches undertaken to inform review of cost-effectiveness
Wolfe *et al.*, 2002[181]	Support assumptions relating to baseline secondary event risk	Searches undertaken to inform model development
WOSCOPS, 1997[104]	Informing the approach to modelling surrogate to clinical end-points	Economic analysis previously undertaken by authors[39]
Youman *et al.*, 2003[191]	Provide Str cost estimates Inform Str HRQoL utility estimate	Economic analysis previously undertaken by authors[39]

Searches undertaken to inform the model

Cholesterol models search

Scope	Existing HTA cholesterol-lowering models
Purpose	To update awareness of existing models
Sources searched	DARE MEDLINE
Type of search	Berrypicking search (keyword combinations)[167]
Results	56 references selected from search 14 full papers consulted

DARE
Hypercholesterolaemia or hypercholesterolemia/All fields AND model/All fields (73 hits)
Cholesterol/All fields AND model/All fields ANDNOT Hypercholesterolaemia or hypercholesterolemia/All fields (121 hits)

MEDLINE
1 (hypercholesterol?emia and model).tw. (1014)
2 limit 1 to yr="2004 - 2006" (190)
3 from 2 keep 5-6,20,43,107,115,118,138,156 (9)
4 (hypercholesterol?emia and markov).tw. (7)
5 from 3 keep 1-9 (9)

Cholesterol level as a predictor of coronary/cardiovascular events

Scope	Cholesterol level as a predictor of coronary/CV events
Purpose	To explore the evidence on the link between cholesterol and clinical events
Sources searched	MEDLINE
Type of search	Berrypicking search (keyword combinations)[167]
Results	281 references selected from search 26 full papers consulted

MEDLINE
1 hypercholesterol?emia.ti. (5483)
2 markov.ti. (914)
3 1 and 2 (0)
4 bayes$.ti. (2521)
5 1 and 4 (0)
6 decision$.ti. (21608)
7 1 and 6 (3)
8 from 7 keep 1-3 (3)
9 regression analysis.ti. (1016)
10 1 and 9 (0)
11 algorithm$.ti. (7701)
12 1 and 11 (0)
13 artificial intelligence.ti. (336)
14 1 and 13 (0)
15 computer simulation.ti. (1745)
16 1 and 15 (0)
17 expert systems.ti. (328)
18 1 and 17 (0)
19 forecast$.ti. (1492)
20 1 and 19 (0)
21 model$.ti. (187322)
22 1 and 21 (76)
23 22 not 7 (76)
24 limit 23 to humans [Limit not valid in: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations; records were retained] (28)
25 from 24 keep 5,12,15,20,24 (5)
26 associat$.ti. (282207)
27 1 and 26 (171)
28 from 27 keep 4,6,10,12,21,24,31,35-36,42-43,52,60,62,64,70,74,83,93,110,131,151 (22)
29 correlat$.ti. (87892)
30 1 and 29 (18)
31 surrogate.ti. (1923)
32 1 and 31 (0)
33 predict$.ti. (79627)
34 1 and 33 (23)
35 from 34 keep 2-8,10,13,18,22 (11)
36 univariate analysis.ti. (21)
37 1 and 36 (0)
38 multivariate analysis.ti. (2077)
39 1 and 38 (0)
40 cardio$.ti. (113859)
41 1 and 40 (96)
42 from 41 keep 1-4,6,11-12,14,16-18,20-25,30-31,45-46,48,55-56,64,66-67,70,78-79,82-83,89,91-92 (35)
43 coronary.ti. (101071)
44 1 and 43 (346)
45 7 or 22 or 27 or 30 or 34 or 41 (369)
46 44 not 45 (307)
47 from 46 keep 6,11,14,17,19-20,27,39,45-46,48,64-65,67-68,86,97,100,118,123,126,138,156,161,171-173,175,180,203-204,209-210,221-223,227,229,234-237,239-241,249,252,268,278-279,288,306 (52)
48 8 or 25 or 28 or 35 or 42 or 47 (126)
49 (cholesterol$ and surrogate).tw. (248)
50 (cholesterol$ and surrogate).ti. (0)
51 cholesterol.ti. and surrogate.ab. (33)
52 from 51 keep 20,26,29-30 (4)
53 48 or 52 (130)

1 (hypercholesterol$ or cholesterol).tw. (119937)
2 model$.tw. (816826)
3 1 and 2 (11115)
4 ((hypercholesterol$ or cholesterol) and model$).ti. (525)
5 limit 4 to humans [Limit not valid in: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations; records were retained] (186)
6 from 5 keep 5,19,26,29,36,47,57,72,77,83,104,113,116-117,120,138,141,144,149,177-178 (21)
7 ((hypercholesterol$ or cholesterol) and model$).tw. (11115)
8 (coronary or cardio$ or risk$).tw. (963900)
9 7 and 8 (3582)
10 (coronary or cardio).tw. (199012)
11 7 and 10 (1632)
12 limit 11 to humans [Limit not valid in: Ovid MEDLINE(R) In-Process & Other Non-

Indexed Citations; records were retained] (1351)
13 12 not 4 (1330)
14 from 13 keep 3,5,8,17-19,22-23,28,31-34 (13)
15 risk.tw. (585614)
16 (correlat$ or associat$ or forecast$ or surrogat$ or predict$).tw. (2353947)
17 (cardio$ or coronary or cardiac$).tw. (604311)
18 7 and 15 and 16 and 17 (1475)
19 ((correlat$ or associat$ or forecast$ or surrogat$ or predict$) adj6 (cardio$ or coronary or cardiac$)).tw. (50770)
20 7 and 15 and 18 (1475)
21 ((correlat$ or associat$ or forecast$ or surrogat$ or predict$) adj3 (cardio$ or coronary or cardiac$)).tw. (27951)
22 7 and 15 and 21 (421)
23 from 22 keep 6,8,13,15-16,26-27,29,34-35,42,45,47,56-57,80,86,91,93-94,96,99,101,104,111-113,115,118,126,128,132,138-140,149-150,152-153,155-156,165-166,177,189,195,197,200,203,205,210,218,223-224,226,233,235,238,244,246-247,250,255,257,259,263-264,266,269-270,275-276,278-280,285,287-288,291,296-297,301,309,315-316,318,321,332,335,342-345,347,351,358-359,361,363,365,367-368,370-373,376,379,383,385-387,389-390,394,396,398,400-401,404,406-407,411,413-415,417-421 (131)
24 6 or 23 (151)

Quantitative links between cholesterol lowering and clinical events

Scope	Specified quantitative links between cholesterol lowering and clinical events
Purpose	To explore the link used by CTTCs
Sources searched	MEDLINE Web of Science Google
Type of search	Berrypicking search (keyword combinations, chaining)[167]
Results	28 references selected from search 9 full papers consulted

Chaining search

Starting reference

Baignet C and colleagues. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005;**366**: 1267–78.

MEDLINE

1 law m$.au. (741)
2 limit 1 to yr="2003" (65)
3 "12829526".ui. (1)
4 1 mmol.ti. (1)
5 mmol.ti. (83)
6 1mmol.tw. (22)
7 1 mmol.tw. (3102)
8 >1 mmol.tw. (3102)
9 (1 mmol or 1mmol).tw. (3121)
10 (cholesterol or ldl).tw. (125031)
11 (reduc$ or chang$).tw. (2351251)
12 ((1 mmol or 1mmol) adj6 (cholesterol or ldl) adj6 (reduc$ or chang$)).tw. (8)
13 baigent c$.au. (44)
14 limit 13 to yr="2005" (6)
15 (mmol adj6 (cholesterol or ldl) adj6 (reduc$ or chang$)).tw. (298)
16 (mmol adj6 (cholesterol or ldl) adj6 (reduc$ or chang$)).tw. (298)
17 ((1 mmol or 1mmol or "1 0 mmol") adj6 (cholesterol or ldl) adj6 (reduc$ or chang$)).tw. (8)
18 ((1 mmol or 1mmol or "1?0 mmol") adj6 (cholesterol or ldl) adj6 (reduc$ or chang$)).tw. (8)
19 from 18 keep 4,6-7 (3)
20 from 16 keep 9,40,43,46-47,55,64,73,76,79,83,102,106,132,152,164,196,218-219,221,224,283 (22)

Framingham search

Scope	Evaluation of Framingham risk equation
Purpose	To explore the uncertainties associated with the use of Framingham as a predictor of clinical events
Sources searched	MEDLINE Web of Science Google
Type of search	Berrypicking search (keyword combinations, chaining)[167]
Results	55 references selected from search 25 full papers consulted

Chaining search

Starting references

Brindle P. What are your chances of having a heart attack? *University of Bristol Research News*. March 2004; 19. (http://www.bris.ac.uk/researchreview/2004/1113903134; accessed 7 November 2006).

MEDLINE

1 framingham.af. (3298)

2 framingham.ti. (1086)
3 risk.af. (794057)
4 1 and 3 (1993)
5 2 and 3 (756)
6 cholesterol.af. (148539)
7 5 and 6 (281)
8 1 and 3 and 6 (789)
9 framingham.ti. (1086)
10 risk.ti. (131788)
11 cholesterol (32949)
12 9 and 10 and 11 (10)
13 10 and 11 and 1 (35)
14 from 13 keep 1,5,7,9,11,17… (10)
15 (critic$ and framingham).ti. (0)
16 (critic$ and framingham).tw. (37)
17 from 16 keep 14,24-25 (3)
18 14 or 17 (12)
19 (critic$ adj6 framingham).tw. (0)

1 framingham risk score.ti. (17)
2 from 1 keep 3,9-10,15 (4)
3 framingham risk score.tw. (132)
4 from 3 keep 10,17,33,63,77,86,89,98,110,116,130 (11)
5 ((accurac$ or predictive or valid$) adj6 framingham).ti. (8)
6 from 5 keep 1-3,5-7 (6)
7 ((accurac$ or predictive or valid$) adj6 framingham).tw. (38)
8 from 7 keep 1,5,7-8,11-12,17-20,23,26,29-32,34 (17)
9 2 or 4 or 6 or 8 (28)

Modelling 'biomarkers with time lag'

Scope	Methods papers on modelling the time lag between biomarker and event
Purpose	To explore methods for modelling surrogate outcomes where there is a time lag between the surrogate and the event
Sources searched	MEDLINE
Type of search	Berrypicking search (keyword combinations)[167]
Results	26 references selected from search 5 full papers consulted

MEDLINE
1 (marker$ and future).mp. and model$.ti. [mp=ti, ot, ab, nm, hw] (109)
2 (marker$ and future and model$).ti. (1)
3 (marker$ adj3 future adj3 model$).tw. (3)
4 (risk$ adj3 future adj3 model).ti. (1)
5 (risk$ adj3 future adj3 model).tw. (8)
6 from 5 keep 5 (1)
7 (time lag and model$).ti. (7)
8 (time lag and model$).tw. (316)
9 timelag.tw. (10)
10 from 8 keep 61,127,157,162,245,249,252,257,297,316 (10)

1 ((marker$ or biomarker$ or surrogate$ or prox$) and event$).ti. (173)
2 model$.ti. (189407)
3 1 and 2 (6)
4 from 3 keep 1-2,4-5 (4)
5 ((marker$ or biomarker$ or surrogate$ or prox$) and event$ and model$).tw. (2696)
6 risk.tw. (590491)
7 5 and 6 (494)
8 ((marker$ or biomarker$ or surrogate$ or prox$) adj6 event$ adj6 model$).tw. (14)
9 (((marker$ or biomarker$ or surrogate$ or prox$) adj6 event$) and model$).tw. (239)
10 (((marker$ or biomarker$ or surrogate$ or prox$) adj6 event$) and model$).ti. (6)
11 from 9 keep 15,38,47,102,114,176,188 (7)
12 7 not 9 (439)
13 4 or 11 (11)

1 (risk$ adj3 future adj3 model$).tw. (20)
2 from 1 keep 5,10 (2)

1 (endpoint$ and event$).ti. (15)
2 from 1 keep 11 (1)
3 (endpoint$ and event$).tw. (3127)
4 (endpoint$ and event$ and model$).tw. (374)
5 ((endpoint$ adj6 event$) and model$).tw. (58)
6 from 5 keep 52-53,58 (3)

Indirect comparators

Scope	Comparator treatments other than statins
Purpose	To provide an overview of comparator treatments in the absence of head-to-head comparisons (with a view to undertaking indirect comparisons in the model)
Sources searched	MEDLINE
Type of search	Berrypicking search (keyword combinations)[167]
Results	94 references selected from search 30 full papers consulted

MEDLINE
1 hypercholesterol?emia.ti. (5468)
2 resin$.ti. (11561)

3 1 and 2 (15)
4 colestyramine.ti. (8)
5 1 and 4 (3)
6 colestipol.ti. (166)
7 1 and 6 (41)
8 fibrate$.ti. (304)
9 1 and 8 (5)
10 bezafibrate.ti. (473)
11 1 and 10 (35)
12 ciprofibrate.ti. (186)
13 1 and 12 (3)
14 fenofibrate.ti. (518)
15 1 and 14 (24)
16 nicotinic.ti. (6639)
17 1 and 16 (10)
18 nicotinic acid.ti. (1390)
19 1 and 18 (10)
20 acipimox.ti. (124)
21 1 and 20 (3)
22 omega 3.ti. (1311)
23 1 and 22 (3)
24 cholestyramine.ti. (806)
25 1 and 24 (84)
26 clofibrate.ti. (1471)
27 1 and 26 (18)
28 gemfibrozil.ti. (546)
29 1 and 28 (29)
30 3 or 5 or 7 or 9 or 11 or 13 or 15 or 19 or 21 or 23 or 25 or 27 or 29 (240)
31 ezetimibe.ti. (186)
32 30 and 31 (1)
33 randomized controlled trial.pt. (225361)
34 30 and 33 (93)
35 32 or 34 (94)

Indirect comparators – nicotinic acid

Scope	Trials of nicotinic acid vs placebo
Purpose	To identify trials of nicotinic acid vs placebo (with a view to making an indirect comparison in the model)
Sources searched	MEDLINE
Type of search	Berrypicking search (keyword combinations)[167]
Results	73 references selected from search 23 full papers consulted

MEDLINE
1 nicotinic acid.ti. (1434)
2 hypercholesterol?emia.ti. (5483)
3 1 and 2 (10)
4 limit 3 to randomized controlled trial (1)
5 placebo.tw. (98789)
6 1 and 5 (19)
7 6 not 3 (18)
8 from 7 keep 1-2,5,9 (4)
9 nicotinic acid.ab. (2094)
10 9 not 1 (1557)
11 5 and 10 (51)
12 from 11 keep 1-2,13,16-17,19,26,38,48 (9)
13 nicotinic acid.af. (3022)
14 placebo.af. (111331)
15 13 and 14 (99)
16 4 or 7 or 11 (70)
17 15 not 16 (29)
18 from 17 keep 1,12 (2)
19 niaspan.ti. (12)
20 4 or 7 or 11 or 15 (99)
21 19 not 20 (11)
22 placebo.tw. (98789)
23 21 and 22 (4)
24 from 23 keep 2-4 (3)
25 niaspan.tw. (24)
26 placebo.tw. (98789)
27 25 and 26 (7)
28 4 or 7 or 11 or 15 or 23 (103)
29 27 not 28 (1)
30 from 29 keep 1 (1)
31 niaspan.af. (24)
32 placebo.af. (111331)
33 31 and 32 (7)
34 4 or 7 or 11 or 15 or 23 or 29 (104)
35 33 not 34 (0)
36 niacin.ti. (817)
37 placebo.tw. (98789)
38 36 and 37 (56)
39 4 or 7 or 11 or 15 or 23 or 29 (104)
40 38 not 39 (43)
41 from 40 keep 1,6,8-9,11,13,15,17-18,25,28-31,35-38,41-42 (20)
42 niacin.tw. (1942)
43 placebo.tw. (98789)
44 42 and 43 (105)
45 4 or 7 or 11 or 15 or 23 or 29 or 40 (147)
46 44 not 45 (48)
47 from 46 keep 1,3,5,7,12-13,16,24-25,27-29,31-34,39-42,44-45 (22)
48 niacin.af. (3135)
49 placebo.af. (111331)
50 48 and 49 (137)
51 4 or 7 or 11 or 15 or 23 or 29 or 40 or 46 (195)
52 50 not 51 (15)
53 from 52 keep 1,4-5,10,13 (5)
54 acipimox.ti. (124)
55 placebo.tw. (98789)
56 54 and 55 (39)
57 4 or 7 or 11 or 15 or 23 or 29 or 40 or 46 or 52 (210)
58 56 not 57 (24)
59 from 58 keep 18-24 (7)
60 acipimox.af. (233)

61 placebo.af. (111331)
62 60 and 61 (70)

Indirect comparators – resins

Scope	Trials of resins vs placebo
Purpose	To identify trials of resins vs placebo (with a view to making an indirect comparison in the model)
Sources searched	MEDLINE
Type of search	Berrypicking search (keyword combinations)[167]
Results	67 references selected from search 14 full papers consulted

63 4 or 7 or 11 or 15 or 23 or 29 or 40 or 46 or 52 or 58 (234)
64 62 not 63 (24)
65 8 or 12 or 18 or 24 or 30 or 41 or 47 or 53 or 59 (73)

MEDLINE
1 hypercholesterol?emia.ti. (5496)
2 resin$.ti. (11627)
3 1 and 2 (15)
4 cholestyramine.ti. (810)
5 1 and 4 (84)
6 colestipol.ti. (166)
7 1 and 6 (41)
8 3 or 5 or 7 (137)
9 limit 8 to randomized controlled trial (48)
10 placebo.tw. (99126)
11 8 and 10 (25)
12 11 not 9 (8)
13 from 12 keep 1-4 (4)
14 resin$.tw. (29523)
15 cholestyramine.tw. (1940)
16 colestipol.tw. (338)
17 or/14-16 (31388)
18 hypercholesterol?emia.tw. (15081)
19 placebo.tw. (99126)
20 17 and 18 and 19 (65)
21 20 not (9 or 12) (40)
22 from 21 keep 3-4,7-10,13-15,17-18,20-26,29-30,32,34-36,38 (25)
23 (resin$ or cholestyramine or colestipol).af. (54020)
24 hypercholesterol?emia.af. (26072)
25 placebo.af. (111683)
26 23 and 24 and 25 (123)
27 26 not (9 or 12 or 21) (58)
28 from 27 keep 1-5,7-8,12,14,16-17,20,22-26,28-29,31,35,38-40,42,44-47,49,51-58 (38)
29 13 or 22 or 28 (67)

Triglycerides search

Scope	TG as a predictor of coronary or CV events
Purpose	To inform the decision as to whether to include fibrates as a comparator treatment
Sources searched	MEDLINE
Type of search	Berrypicking search (keyword combinations)[167]
Results	73 references selected from search 43 full papers consulted

MEDLINE
1 (triglycer$ and risk and (cardio$ or coronary or cardiac$) and (correlat$ or associat$ or forecast$ or surrogat$ or predict$)).tw. (4960)
2 (triglycer$ and risk and ((cardio$ or coronary or cardiac$) adj3 (correlat$ or associat$ or forecast$ or surrogat$ or predict$))).tw. (1039)
3 model$.tw. (828366)
4 2 and 3 (165)
5 from 4 keep 3,10,20,29,39-40,46,48,54,59-60,64,66,71-72,81,84,88,94,96,99,103,106,128,141,143,146,149-150,153-157,159-161,165 (38)
6 (triglycer$ adj3 risk adj3 (cardio$ or coronary or cardiac$) adj3 (correlat$ or associat$ or forecast$ or surrogat$ or predict$)).tw. (4)
7 6 not 4 (3)
8 from 7 keep 2 (1)
9 (triglycer$ adj6 risk adj6 (cardio$ or coronary or cardiac$) adj6 (correlat$ or associat$ or forecast$ or surrogat$ or predict$)).tw. (43)
10 9 not (7 or 4) (38)
11 from 10 keep 7,12,14,19-20,22,27,29,31,34,38 (11)
12 2 not (4 or 7 or 10) (853)
13 from 12 keep 14,23,26,29,38,48,51-52,71,80,83-84,90,99,106,127,173,181,189,260,263,275,341 (23)
14 5 or 8 or 11 or 13 (73)

Health state utilities search

Scope	Utility and health states
Purpose	To inform health state utility estimates
Sources searched	Biosis, Cochrane, CINAHL, DARE-NHS EDD-HTA, HEED, EMBASE, MEDLINE, Web of knowledge
Type of search	Keyword searches
Results	3372 references

BIOSIS Previews
1986–2006
WebSPIRS version
Searches undertaken between December 2006 and January 2007

#1 STABLE-ANGINA
#2 stable angina in ti
#3 UNSTABLE-ANGINA
#4 unstable angina in ti
#5 MYOCARDIAL-INFARCTION
#6 HEART-ATTACK
#7 myocardial infarct* in ti
#8 MI in ti
#9 heart attack* in ti
#10 TRANSIENT-ISCHEMIC-ATTACK
#11 transient ischemic attack* in ti
#12 transient ischaemic attack* in ti
#13 TIA in ti
#14 ISCHAEMIC-STROKE
#15 ISCHEMIC-STROKE
#16 ischaemic stroke* in ti
#17 ischemic stroke* in ti
#18 HAEMORRHAGIC-STROKE
#19 HEMORRHAGIC-STROKE
#20 haemorrhagic stroke* in ti
#21 hemorrhagic stroke* in ti
#22 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21
#23 QUALITY-OF-LIFE
#24 quality of life in ti, ab
#25 life quality in ti, ab
#26 hql in ti, ab
#27 (sf 36 or sf36 or sf thirtysix or sf thirty six or short form 36 or short form thirty six or short form thirtysix or shortform 36) in ti, ab
#28 qol in ti, ab
#29 (euroqol or eq5d or eq 5d) in ti, ab
#30 qaly* in ti, ab
#31 quality adjusted life year* in ti, ab
#32 hye* in ti, ab
#33 health* year* equivalent* in ti, ab
#34 health utilit* in ti, ab
#35 hui in ti, ab
#36 quality of wellbeing* in ti, ab
#37 quality of well being in ti, ab
#38 qwb in ti, ab
#39 #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38
#40 #22 and #39

Cochrane Library (CDSR, CENTRAL)
Issue 4, 2006
Wiley version
Searches undertaken between December 2006 and January 2007

#1 MeSH descriptor Angina Pectoris, this term only
#2 (stable angina):ti
#3 MeSH descriptor Angina, Unstable, this term only
#4 (unstable angina):ti
#5 MeSH descriptor Myocardial Infarction, this term only
#6 (myocardial infarct*):ti
#7 (MI):ti
#8 (heart attack*):ti
#9 MeSH descriptor Ischemic Attack, Transient, this term only
#10 (transient ischaemic attack*):ti
#11 (transient ischemic attack*):ti
#12 (TIA):ti
#13 MeSH descriptor Cerebrovascular Accident, this term only
#14 (ischaemic stroke*):ti
#15 (ischemic stroke*):ti
#16 (haemorrhagic stroke*):ti
#17 (hemorrhagic stroke*):ti
#18 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17)
#19 MeSH descriptor Quality of Life explode all trees
#20 (quality of life):ti or (quality of life):ab
#21 (life quality):ti or (life quality):ab
#22 (hql):ti or (hql):ab
#23 (sf 36 or sf36 or sf thirtysix or sf thirty six or short form 36 or short form thirty six or short form thirtysix or shortform 36):ti or (sf 36 or sf36 or sf thirtysix or sf thirty six or short form 36 or short form thirty six or short form thirtysix or shortform 36):ab
#24 (qol):ti or (qol):ab
#25 (euroqol or eq5d or eq 5d):ti or (euroqol or eq5d or eq 5d):ab
#26 (qaly*):ti or (qaly*):ab
#27 (quality adjusted life year*):ti or (quality adjusted life year*):ab
#28 (hye*):ti or (hye*):ab
#29 (health* year* equivalent*):ti or (health* year* equivalent*):ab
#30 (health utilit*):ti or (health utilit*):ab
#31 (hui):ti or (hui):ab
#32 (quality of wellbeing*):ti or (quality of wellbeing*):ab
#33 (quality of well being):ti or (quality of well being):ab

#34 (qwb):ti or (qwb):ab
#35 (qald* or qale* or qtime*):ti or (qald* or qale* or qtime*):ab
#36 (#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35)
#37 (#18 AND #36)
#38 (letter):pt
#39 (editorial):pt
#40 (comment):pt
#41 (#38 OR #39 OR #40)
#42 (#37 AND NOT #41)

CINAHL
1982–2006
Ovid Online version
Searches undertaken between December 2006 and January 2007
1 *Angina Pectoris/
2 stable angina.ti.
3 *Angina, Unstable/
4 unstable angina.ti.
5 *Myocardial Infarction/
6 myocardial infarct$.ti.
7 MI.ti.
8 heart attack$.ti.
9 *Ischemic Attack, Transient/
10 transient ischaemic attack$.ti.
11 TIA.ti.
12 *Cerebrovascular Accident/
13 ischaemic stroke$.ti.
14 haemorrhagic stroke$.ti.
15 hemorrhagic stroke$.ti.
16 1 or 2 or 3 or 4 or 5 or 6 or 8 or 9 or 10 or 12 or 13 or 14 or 15
17 exp quality of life/
18 quality of life.tw.
19 life quality.tw.
20 hql.tw.
21 (sf 36 or sf36 or sf thirtysix or sf thirty six or short form 36 or short form thirty six or short form thirtysix or shortform 36).tw.
22 qol.tw.
23 (euroqol or eq5d or eq 5d).tw.
24 qaly$.tw.
25 quality adjusted life year$.tw.
26 hye$.tw.
27 health$ year$ equivalent$.tw.
28 health utilit$.tw.
29 hui.tw.
30 quality of wellbeing$.tw.
31 quality of well being.tw.
32 qwb.tw.
33 (qald$ or qale$ or qtime$).tw.
34 or/17-33
35 16 and 34
36 letter.pt.
37 editorial.pt.
38 comment.pt.
39 36 or 37 or 38
40 35 not 39

DARE-NHS EED-HTA
Data coverage not known (approximately 1994–2006)
CRD website version
Searches undertaken between December 2006 and January 2007
#1 MeSH Angina Pectoris
#2 stable AND angina:ti
#3 MeSH Angina, Unstable
#4 unstable AND angina:ti
#5 MeSH Myocardial Infarction
#6 myocardial AND infarct*:ti
#7 MI:ti
#8 heart AND attack*:ti
#9 MeSH Ischemic Attack, Transient
#10 transient AND ischaemic AND attack*:ti
#11 transient AND ischemic AND attack*:ti
#12 TIA:ti
#13 MeSH Cerebrovascular Accident
#14 ischaemic AND stroke*:ti
#15 ischemic AND stroke*:ti
#16 haemorrhagic AND stroke*:ti
#17 hemorrhagic AND stroke*:ti
#18 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17
#19 MeSH Quality of Life EXPLODE 1 2
#20 quality AND of AND life
#21 life AND quality
#22 hql
#23 (sf AND 36 OR sf36 OR sf AND thirtysix OR sf AND thirty AND six OR short AND form AND 36 OR short AND form AND thirty AND six OR short AND form AND thirtysix OR shortform AND 36)
#24 qol
#25 (euroqol OR eq5d OR eq AND 5d)
#26 qaly*
#27 quality AND adjusted AND life AND year*
#28 hye*
#29 health* AND year* AND equivalent*
#30 health AND utilit*
#31 hui
#32 quality AND of AND wellbeing*
#33 quality AND of AND well AND being
#34 qwb
#35 (qald* OR qale* OR qtime*)
#36 #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35
#37 #18 and #36

HEED
1967–2006
Wiley online version
Searches undertaken between December 2006 and January 2007
(stable angina or unstable angina or myocardial infarction or MI or heart attack or transient ischaemic attack or transient ischemic attack or TIA or ischaemic stroke or ischemic stroke or haemorrhagic stroke or hemorrhagic stroke) in title
AND
(quality of life or life quality or hql or sf 36 or sf36 or sf thirtysix or sf thirty six or short form 36 or short form thirty six or short form thirtysix or shortform 36 or qol or euroqol or eq5d or eq 5d or qaly or quality adjusted life year or hye or health year equivalent or health utility or health utilities or hui or quality of wellbeing or quality of well being or qwb or qald or qale or qtime) all data

EMBASE
1980–2006
Ovid Online version
Searches undertaken between December 2006 and January 2007
1 *Angina Pectoris/
2 stable angina.ti.
3 *Unstable Angina Pectoris/
4 unstable angina.ti.
5 *Heart Infarction/
6 myocardial infarct$.ti.
7 MI.ti.
8 heart attack$.ti.
9 *Transient Ischemic Attack/
10 transient ischaemic attack$.ti.
11 transient ischemic attack$.ti.
12 TIA.ti.
13 *Cerebrovascular Accident/
14 ischaemic stroke$.ti.
15 ischemic stroke$.ti.
16 haemorrhagic stroke$.ti.
17 hemorrhagic stroke$.ti.
18 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19 exp "Quality of Life"/
20 quality of life.tw.
21 life quality.tw.
22 hql.tw.
23 (sf 36 or sf36 or sf thirtysix or sf thirty six or short form 36 or short form thirty six or short form thirtysix or shortform 36).tw.
24 qol.tw.
25 (euroqol or eq5d or eq 5d).tw.
26 qalyS.tw.
27 quality adjusted life year$.tw.
28 hye$.tw.
29 health$ year$ equivalent$.tw.
30 health utilit$.tw.
31 hui.tw.
32 quality of wellbeing$.tw.
33 quality of well being.tw.
34 qwb.tw.
35 (qald$ or qale$ or qtime$).tw.
36 or/19-35
37 18 and 36
38 letter.pt.
39 editorial.pt.
40 comment.pt.
41 38 or 39
42 37 not 41

MEDLINE
1966–2006
Ovid Online
Searches undertaken between December 2006 and January 2007
1 *Angina Pectoris/
2 stable angina.ti.
3 *Angina, Unstable/
4 unstable angina.ti.
5 *Myocardial Infarction/
6 myocardial infarct$.ti.
7 MI.ti.
8 heart attack$.ti.
9 *Ischemic Attack, Transient/
10 transient ischaemic attack$.ti.
11 TIA.ti.
12 *Cerebrovascular Accident/
13 ischaemic stroke$.ti.
14 haemorrhagic stroke$.ti.
15 hemorrhagic stroke$.ti.
16 1 or 2 or 3 or 4 or 5 or 6 or 8 or 9 or 10 or 12 or 13 or 14 or 15
17 exp quality of life/
18 quality of life.tw.
19 life quality.tw.
20 hql.tw.
21 (sf 36 or sf36 or sf thirtysix or sf thirty six or short form 36 or short form thirty six or short form thirtysix or shortform 36).tw.
22 qol.tw.
23 (euroqol or eq5d or eq 5d).tw.
24 qaly$.tw.
25 quality adjusted life year$.tw.
26 hye$.tw.
27 health$ year$ equivalent$.tw.
28 health utilit$.tw.
29 hui.tw.
30 quality of wellbeing$.tw.
31 quality of well being.tw.
32 qwb.tw.
33 (qald$ or qale$ or qtime$).tw.

34 or/17-33
35 16 and 34
36 letter.pt.
37 editorial.pt.
38 comment.pt.
39 36 or 37 or 38
40 35 not 39

SCI and SSCI
1900–2006
Web of Knowledge version
Searches undertaken between December 2006 and January 2007

#1 TI=(stable angina)
#2 TI=(unstable angina)
#3 TI=(myocardial infarct*)
#4 TI=(MI)
#5 TI=(heart attack*)
#6 TI=(transient ischaemic attack*)
#7 TI=(TIA)
#8 TI=(ischaemic stroke*)
#9 TI=(haemorrhagic stroke*)
#10 TI=(hemorrhagic stroke*)
#11 #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
#12 TS=(quality of life)
#13 TS=(life quality)
#14 TS=(hql)
#15 TS=(sf 36 or sf36 or sf thirtysix or sf thirty six or short form 36 or short form thirty six or short form thirtysix or shortform 36)
#16 TS=(qol)
#17 TS=(euroqol or eq5d or eq 5d)
#18 TS=(qaly*)
#19 TS=(quality adjusted life year*)
#20 TS=(hye)
#21 TS=(health* year* equivalent*)
#22 TS=(health utilit*)
#23 TS=(hui)
#24 TS=(quality of wellbeing*)
#25 TS=(quality of well being)
#26 TS=(qwb)
#27 TS=(qald* or qale* or qtime*)
#28 #27 OR #26 OR #25 OR #24 OR #23 OR #22 OR #21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12
#29 #28 AND #11

Appendix 24

Data used in secondary transitions

Data are presented in *Tables 77* and *78*.

TABLE 77 *Regressions used for subsequent events (Nottingham Heart Attack data)*

Logistic regression coefficients – probability of event type given event

eventype	Coeff.	SE	z	p > z	95% CI
2 age	0.077705	0.034652	2.242	0.025	0.009789 to 0.145622
_cons	–7.17201	2.523846	–2.842	0.004	–12.1187 to –2.22536
3 age	0.047496	0.017134	2.772	0.006	0.013914 to 0.081079
_cons	–3.24095	1.176916	–2.754	0.006	–5.54767 to –0.93424

	age	_cons	age	_cons
2 age	0.001201			
_cons	–0.08667	6.3698		
3 age	0.000165	–0.01093	0.000294	
_cons	–0.01085	0.733099	–0.01993	1.38513

Any event assuming exponential, given survived to end of year 1

_t	Coeff.	SE	z	p > z	95% CI
age	0.025344	0.013465	1.882	0.06	–0.00105 to 0.051735
_cons	–4.95663	0.912665	–5.431	0	–6.74542 to 3.16784

	age	_cons
age	0.000181	
_cons	–0.01213	0.832958

ACS year 1 mlogit

eventype	Coeff.	SE	z	p > z	95% CI
age	0.003234	0.012312	0.263	0.793	–0.0209 to 0.027366
_cons	–3.05907	0.80604	–3.795	0	–4.63888 to –1.47926
age	0.05624	0.009014	6.239	0	0.038572 to 0.073907
_cons	–5.71398	0.648273	–8.814	0	–6.98457 to –4.44338

	01:00		02:00	
	age	_cons	age	_cons
1 age	0.000152			
_cons	–0.00974	0.649701		
2 age	8.50×10^{-6}	–0.00054	0.000081	
_cons	–0.00054	0.035984	–0.00577	0.420258

continued

TABLE 77 *Regressions used for subsequent events (Nottingham Heart Attack data) (cont'd)*

ACS exponential post year 1

_t	Coeff.	SE	z	p > z	95% CI
age	0.051546	0.006256	8.24	0	0.039285 to 0.063807
_cons	–5.93184	0.45102	–13.152	0	–6.81582 to 5.04785

	_t	age	_cons
age		0.000039	
_cons		–0.00279	0.203419

ACS post year 1 mlogit

	Coeff.	SE	z	p > z	95% CI
age	–0.04179	0.017595	–2.375	0.018	–0.07627 to –0.0073
_cons	1.089838	1.205898	0.904	0.366	–1.27368 to 3.453354

	age	_cons
age	0.00031	
_cons	–0.0209	1.45419

SE, standard error.

TABLE 78 *Regressions used for subsequent events (South London Stroke data)*

Year 1: mlogit all events

	eventype	Coeff.	SE	z	p > z	95% CI
1	age	0.008007	0.009213	0.869	0.385	–0.01005 to 0.026063
	_cons	–3.45027	0.651183	–5.298	0	–4.72657 to –2.17398
2	age	0.08874	0.009097	9.755	0	0.070911 to 0.106569
	_cons	–8.61813	0.717794	–12.006	0	–10.025 to –7.21128

(Outcome eventype = 0 is the comparison group)

		age	_cons	age	_cons
1	age	0.000085			
	_cons	–0.00589	0.424039		
2	age	4.90E-06	–0.00033	0.000083	
	_cons	–0.00034	0.02368	–0.00648	0.515229

Year 2: exponential any event

	eventype	Coeff.	SE	z	p > z	95% CI
	age2	0.04211	0.00684	6.157	0	0.028705 to 0.055515
	_cons	–5.88035	0.503282	–11.684	0	–6.86676 to 4.89393

	age2	_cons
age2	0.000047	
_cons	–0.0034	0.253293

Mlogit event1–2

	evtypey2	Coeff.	SE	z	p > z	95% CI
	age2	–0.05784	0.016193	–3.572	0	–0.08958 to –0.0261
	_cons	3.825288	1.177901	3.248	0.001	1.516645 to 6.133931

(Outcome evtypey2 = 2 is the comparison group)

	age2	_cons
age2	0.000262	
_cons	–0.01888	1.38745

SE, standard error.

Appendix 25

Utility by age

Data are given in *Table 79*.

TABLE 79 *Utility by age*[199]

Summary output for linear regression

Regression statistics	
Multiple *R*	0.2005
R^2	0.0402
Adjusted R^2	0.0397
Standard error	0.2576
Observations	1979

ANOVA

	df	*SS*	*MS*	*F*	Significance *F*
Regression	1	5.50	5.497	82.822	2.1×10^{-19}
Residual	1977	131.21	0.066		
Total	1978	136.71			

	Coefficients	Standard error	t-statistic	*p*-Value	Lower 95%	Upper 95%	Lower 95.0%	Upper 95.0%
Intercept	1.060	0.029	36.605	2×10^{-224}	1.003	1.117	1.003	1.118
x	–0.004	0.000	–9.1007	2.13×10^{-19}	–0.005	–0.003	–0.005	–0.003

Appendix 26

Natural increase in risk by age

Regressions used to model the natural increase by age in the ScHARR model:

	Male	Female
Beta0	–0.0459	–0.0163
Beta1	0.0001	–0.0014
Beta2	0.0001	0.000075

Appendix 27

Diabetes data used in the ScHARR cost-effectiveness model

Data are given in *Tables 80* and *81*.

TABLE 80 *Health state utilities used in the diabetic analysis of the ScHARR cost-effectiveness model*

	1st year	Subsequent years
Stable angina	0.768[a]	0.90
Unstable angina	0.732[a]	0.80
1st year MI	0.722	0.80
TIA	1	1
Str	0.598	0.629

[a] Adjusted using 1st-year diabetic MI utility and base-case utilities for stable and unstable angina, respectively.

TABLE 81 *Health state costs (£) used in the diabetic analysis of the ScHARR cost-effectiveness model*[155]

	Base case	Diabetic
Stable angina	201	492[a]
Post-stable angina	201	492[a]
Unstable angina	477	492[a]
Post-unstable angina	201	492[a]
1st-year costs MI	4,867	5,414
Ongoing costs MI	201	492
Fatal MI	1,242	1,662
TIA	1,110	1,612[b]
Post-TIA (ongoing costs)	276	401[b]
1st year costs Str	8,070	11,722[b]
Ongoing costs Str	2,169	3,151
Fatal Str	7,407	10,759[b]

[a] Assumed equal to ongoing costs for MI.
[b] Costs adjusted using ongoing costs for Str and base-case costs.

Appendix 28

List of the key modelling assumptions used in the ScHARR model

The assumptions are listed in *Table 82*.

TABLE 82 *List of assumptions used to build and populate the ScHARR model*

Section	Assumption	Source
Comparator	Assume relevant comparators for target population are statins or no treatment	Literature searches and clinical advice
Population	Assume primary event rate for diabetic is two times norm by age	Clinical opinion
Population	Assume primary event rate for FeFH is two times norm by age	Clinical opinion
Effectiveness data	*Conservative* Assume the results of the meta-analysis of 12-week RCT data (which are derived from cohorts who had a wash-out prior to baseline of studies) are representative for the target population, i.e. patients not at goal on statin treatment	
Effectiveness data	Assume the results of the meta-analysis of 12-week RCT data are valid irrespective of the dose or potency of the statin modelled	
Effectiveness data	Assume observed short-term lipid changes will be maintained over a lifetime Report results using shorter time horizons	
Effectiveness data	Assume ezetimibe-induced changes in lipids translate to reductions in CVD events	
Effectiveness data	*Conservative* Assume a delay of 1 year for changes in LDL-c to translate to reductions in events Perform sensitivity analyses using no delay and a 2-year delay	
Effectiveness data	Assume switch to more potent statin of same dose provides an additional 6% reduction in LDL-c irrespective of statin	Published data[123]
Relationship LDL-c and CVD events	Assume the results of the meta-analysis which provides a relationship between reductions in LDL-c and RR of events (derived from statin RCT data) are generalisable to ezetimibe monotherapy and ezetimibe co-administered with a statin	
	Assume the RR for angina = RR for non-fatal MI Assume the RR for TIA = RR for non-fatal Str	
	Assume the RR for fatal CVD = 1	Based on meta-analyses of statin RCTs and discussions in literature
	Perform sensitivity analyses using the RR for TIA/non-fatal Str/fatal Str = 1	
Time horizon	Report results for several time horizons	
CVD definition	CVD event is defined as stable angina, unstable angina, non-fatal MI, CHD death, TIA, non-fatal Str, death from TIA/CVD-related causes This is based on evidence available for CVD health states	

continued

TABLE 82 *List of assumptions used to build and populate the ScHARR model (cont'd)*

Section	Assumption	Source
Events	Assume a maximum of two events for individuals with a history of CVD Assume an additional primary event for individuals with no history of CVD	
Secondary risks	Assume secondary risk is at least as large as primary risk modelled	
Costs	Assume patients are already on treatment on entering model, hence 1st year monitoring costs apply to the ezetimibe monotherapy regimen only	
Utility	*Conservative* Assume age adjusted utility in the base case Sensitivity analyses performed using constant utility of 1 across all ages Assume post-health state utility values increase Assume 2nd and 3rd events incur an additional disutility Assume no disutility for TIA Assume no disutility associated with treatments modelled	
Compliance	Assume full compliance with treatment	

Appendix 29

Additional results tables for the ScHARR economic evaluation

Data are given in *Tables 83–102*.

TABLE 83 *Scenario 2: discounted incremental costs (£000) on varying the baseline LDL-c value*

Age (years)	Primary			Secondary		
	Baseline LDL-c (mmol/l)					
	3	3.5	4	3	3.5	4
20-year horizon						
Male						
45	4540	4501	4462	4678	4654	4630
55	4211	4169	4127	4203	4184	4164
65	3591	3550	3509	3507	3492	3477
75	2741	2713	2684	2598	2590	2582
Female						
45	4585	4542	4500	4755	4732	4709
55	4300	4251	4201	4378	4356	4335
65	3665	3619	3573	3647	3635	3622
75	2711	2679	2648	2620	2611	2601
Lifetime horizon						
Male						
45	6000	5948	5893	6065	6053	6040
55	4993	4946	4898	4882	4874	4866
65	3852	3810	3769	3709	3700	3689
75	2770	2742	2713	2616	2609	2601
Female						
45	6154	6088	6024	6295	6286	6276
55	5140	5084	5026	5147	5138	5129
65	3935	3888	3841	3865	3858	3851
75	2738	2707	2675	2640	2631	2622

TABLE 84 *Scenario 2: discounted incremental QALYs on varying the baseline LDL-c value*

Age (years)	Primary			Secondary		
	Baseline LDL-c (mmol/l)					
	3	3.5	4	3	3.5	4
20-year horizon						
Male						
45	79.9	93.1	106.3	78.1	91.2	104.3
55	88.2	102.8	117.4	97.4	113.8	130.3
65	90.1	105.1	120.0	94.0	109.9	125.8
75	57.4	66.9	76.3	64.3	75.1	86.0
Female						
45	65.1	75.9	86.7	71.7	83.6	95.6
55	82.6	96.3	109.9	97.0	113.3	129.7
65	85.4	99.6	113.8	94.4	110.3	126.3
75	52.6	61.3	70.0	66.2	77.3	88.5
Lifetime horizon						
Male						
45	211.4	246.9	282.5	181.3	212.4	243.7
55	164.2	191.6	219.1	158.7	185.8	213.0
65	115.5	134.7	154.0	111.5	130.4	149.4
75	59.7	69.6	79.4	65.8	76.8	87.9
Female						
45	188.0	219.4	250.9	177.9	208.3	238.9
55	156.8	182.9	209.1	162.1	189.7	217.5
65	109.2	127.3	145.5	112.6	131.7	150.8
75	54.7	63.7	72.7	67.7	79.1	90.5

TABLE 85 *Scenario 2: univariate lifetime ICERs (£000) for females with baseline LDL-c of 3.5 mmol/l*

Value	Primary prevention				Secondary prevention			
Age (years)	45	55	65	75	45	55	65	75
Scenario 2	**27.7**	**27.8**	**30.5**	**42.5**	**30.2**	**27.1**	**29.3**	**33.3**
Discount rates for costs and utilities								
0%	19.2	20.8	24.7	36.2	21.8	21.1	24.4	29.2
Time lag for effectiveness of treatment								
0	26.4	26.1	27.6	36.0	28.8	25.4	26.3	27.9
2 years	29.2	29.7	34.0	50.8	31.8	29.0	32.9	40.5
Health state costs								
Plus 20%	27.3	27.3	30.0	41.7	30.0	26.9	29.1	33.0
Minus 20%	28.2	28.3	31.1	43.2	30.3	27.2	29.5	33.5
HRQoL utilities								
Plus 10%	30.9	30.5	32.9	45.4	27.6	24.9	26.8	30.5
Minus 10%	25.2	25.5	28.5	39.9	33.3	29.7	32.3	36.5
Constant utility by age	21.2	20.7	22.1	29.6	23.3	20.3	21.3	23.4
Constant utility by age plus 10% on health state utilities	23.5	22.6	23.7	31.6	21.3	18.6	19.5	21.4
Constant utility by age minus 10% on health state utilities	19.3	19.0	20.6	27.9	25.6	22.3	23.5	25.7
RR on events corresponding to reduction in LDL-c								
LCI	22.0	21.9	23.9	33.2	24.3	21.8	23.6	26.8
UCI	37.0	37.2	41.2	57.9	38.7	34.7	37.5	42.8
Effectiveness of ezetimibe treatment								
LCI	26.0	26.1	28.7	39.9	28.4	25.5	27.6	31.3
UCI	29.7	29.7	32.7	45.4	32.2	28.9	31.2	35.5
No RR on Str or TIA								
	45.3	47.9	57.5	96.5	34.1	31.0	33.2	39.1
Baseline LDL-c (mmol/l)								
3.0	32.7	32.8	36.1	50.1	35.4	31.8	34.3	39.0
4.0	24.0	24.0	26.4	36.8	26.3	23.6	25.5	29.0

TABLE 86 *Scenario 2: univariate 20-year ICERs (£000) for females with baseline LDL-c of 3.5 mmol/l*

Value	Primary prevention				Secondary prevention			
Age (years)	45	55	65	75	45	55	65	75
Scenario 2	**59.8**	**44.1**	**36.3**	**43.7**	**56.6**	**38.4**	**32.9**	**33.8**
Discount rates for costs and utilities								
0%	51.2	37.4	31.0	37.6	48.9	32.8	28.5	29.8
Time lag for effectiveness of treatment								
0	54.2	40.1	32.3	36.9	51.6	35.0	29.2	28.3
2 years	66.5	48.9	41.3	52.5	63.0	42.6	37.7	41.3
Health state costs								
Plus 20%	59.0	43.4	35.6	43.0	56.1	38.1	32.7	33.5
Minus 20%	60.6	44.9	37.0	44.5	57.0	38.8	33.2	34.0
HRQoL utilities								
Plus 10%	74.5	51.5	39.8	46.8	51.9	35.4	30.2	31.0
Minus 10%	50.0	38.6	33.4	41.0	62.2	42.1	36.2	37.1
Constant utility by age	48.8	34.1	26.7	30.6	46.2	29.7	24.3	23.8
Constant utility by age plus 10% on health state utilities	60.6	39.7	29.2	32.7	42.3	27.4	22.2	21.8
Constant utility by age minus 10% on health state utilities	40.8	29.9	24.6	28.7	50.7	32.5	26.7	26.1
RR on events corresponding to reduction in LDL-c								
LCI	48.1	35.1	28.5	34.1	45.7	30.9	26.5	27.2
UCI	79.0	58.8	49.0	59.6	72.6	49.4	42.2	43.4
Effectiveness of ezetimibe treatment								
LCI	56.2	41.4	34.1	41.0	53.2	36.2	31.0	31.8
UCI	63.9	47.2	38.9	46.7	60.4	41.0	35.1	36.0
No RR on Str or TIA								
	94.2	74.0	67.3	99.2	64.7	44.0	37.3	39.7
Baseline LDL-c (mmol/l)								
3.0	70.4	52.0	42.9	51.6	66.4	45.1	38.6	39.6
4.0	51.9	38.2	31.4	37.8	49.2	33.4	28.7	29.4

TABLE 87 *Scenario 2: discounted incremental costs (£000) using different time horizons and a baseline LDL-c of 3.5 mmol/l*

Age (years)	Primary			Secondary		
	5-year	20-year	Life	5-year	20-year	Life
Male						
45	1482	4334	5747	1545	4471	5805
55	1469	4025	4784	1516	4022	4677
65	1427	3439	3692	1458	3359	3554
75	1353	2624	2651	1362	2488	2506
Female						
45	1489	4376	5894	1552	4543	6022
55	1472	4112	4929	1528	4188	4928
65	1434	3511	3773	1476	3492	3702
75	1345	2595	2622	1360	2510	2529

TABLE 88 *Scenario 2: discounted incremental QALYs using different time horizons and a baseline LDL-c of 3.5 mmol/l*

Age (years)	Primary			Secondary		
	5-year	20-year	Life	5-year	20-year	Life
Male						
45	4.2	70.0	185.1	4.4	68.4	158.4
55	4.6	77.4	143.8	5.9	85.3	138.7
65	6.0	79.0	101.2	8.4	82.3	97.5
75	6.5	50.3	52.4	10.1	56.3	57.6
Female						
45	3.3	57.1	164.6	4.0	62.8	155.5
55	4.1	72.5	137.4	5.4	85.0	141.7
65	5.7	74.9	95.7	8.1	82.6	98.5
75	5.9	46.1	47.9	10.4	57.9	59.2

TABLE 89 *Scenario 2: discounted incremental costs (£000) on varying the baseline LDL-c value*

Age (years)	Primary			Secondary		
	Baseline LDL-c (mmol/l)					
	3	3.5	4	3	3.5	4
20-year horizon						
Male						
45	4362	4334	4305	4488	4471	4455
55	4055	4025	3995	4034	4022	4010
65	3468	3439	3410	3367	3359	3350
75	2643	2624	2604	2492	2488	2484
Female						
45	4407	4376	4344	4558	4543	4527
55	4148	4112	4076	4202	4188	4174
65	3544	3511	3478	3498	3492	3485
75	2617	2595	2573	2515	2510	2505
Lifetime horizon						
Male						
45	5781	5747	5712	5809	5805	5801
55	4816	4784	4752	4678	4677	4675
65	3722	3692	3664	3558	3554	3550
75	2671	2651	2632	2509	2506	2502
Female						
45	5937	5894	5850	6024	6022	6020
55	4967	4929	4887	4930	4928	4926
65	3805	3773	3740	3703	3702	3700
75	2644	2622	2600	2533	2529	2524

TABLE 90 *Scenario 2: discounted incremental QALYs on varying the baseline LDL-c value*

Age (years)	Primary			Secondary		
	Baseline LDL-c (mmol/l)					
	3	3.5	4	3	3.5	4
20-year horizon						
Male						
45	60.0	70.0	80.0	58.6	68.4	78.2
55	66.3	77.4	88.4	73.0	85.3	97.6
65	67.8	79.0	90.3	70.4	82.3	94.1
75	43.2	50.3	57.5	48.2	56.3	64.4
Female						
45	49.0	57.1	65.2	53.8	62.8	71.8
55	62.1	72.5	82.7	72.8	85.0	97.2
65	64.2	74.9	85.6	70.8	82.6	94.6
75	39.6	46.1	52.7	49.6	57.9	66.3
Lifetime horizon						
Male						
45	158.5	185.1	211.7	135.4	158.4	181.6
55	123.2	143.8	164.4	118.6	138.7	158.9
65	86.7	101.2	115.6	83.4	97.5	111.6
75	44.9	52.4	59.8	49.3	57.6	65.8
Female						
45	141.0	164.6	188.2	132.9	155.5	178.2
55	117.7	137.4	157.0	121.2	141.7	162.3
65	82.0	95.7	109.3	84.3	98.5	112.7
75	41.1	47.9	54.7	50.7	59.2	67.8

TABLE 91 *Scenario 1: discounted incremental costs (£000) on varying the baseline LDL-c value*

Age (years)	Primary			Secondary		
	Baseline LDL-c (mmol/l)					
	3	3.5	4	3	3.5	4
20-year horizon						
Male						
45	3361	3335	3309	3505	3490	3475
55	3129	3103	3075	3160	3151	3142
65	2683	2659	2633	2652	2649	2646
75	2048	2032	2015	1973	1975	1976
Female						
45	3395	3366	3337	3561	3548	3534
55	3201	3169	3136	3294	3285	3275
65	2743	2714	2685	2761	2761	2760
75	2029	2011	1992	1993	1994	1995
Lifetime horizon						
Male						
45	4481	4453	4423	4573	4577	4581
55	3737	3711	3684	3690	3696	3702
65	2886	2863	2839	2812	2815	2818
75	2071	2054	2038	1988	1990	1992
Female						
45	4606	4567	4529	4751	4759	4766
55	3854	3821	3788	3897	3904	3912
65	2955	2928	2900	2933	2940	2947
75	2051	2033	2014	2008	2011	2012

TABLE 92 *Scenario 1: discounted incremental QALYs on varying the baseline LDL-c value*

Age (years)	Primary			Secondary		
	Baseline LDL-c (mmol/l)					
	2.5	3	3.5	2.5	3	3.5
20-year horizon						
Male						
45	47.0	56.3	65.6	50.6	60.8	71.0
55	52.4	62.8	73.1	64.4	77.4	90.4
65	54.1	64.8	75.5	64.3	77.3	90.4
75	34.6	41.4	48.2	46.3	55.6	64.9
Female						
45	38.4	46.0	53.6	47.3	56.7	66.2
55	49.4	59.2	68.9	65.6	78.8	92.0
65	51.6	61.8	72.0	65.8	79.1	92.4
75	32.0	38.3	44.6	48.1	57.8	67.6
Lifetime horizon						
Male						
45	129.1	155.1	181.2	124.9	150.7	176.7
55	99.8	119.8	139.8	108.2	130.4	152.8
65	69.9	83.9	97.8	77.1	92.7	108.5
75	36.1	43.2	50.3	47.3	56.9	66.5
Female						
45	115.8	139.0	162.2	125.1	150.7	176.6
55	96.3	115.5	134.7	112.9	136.0	159.3
65	66.6	79.8	93.1	79.2	95.3	111.4
75	33.3	39.9	46.4	49.3	59.2	69.2

TABLE 93 *Scenario 3: discounted incremental costs (£000) on varying the baseline LDL-c value*

Age (years)	Primary			Secondary		
	Baseline LDL-c (mmol/l)					
	2.5	3	3.5	2.5	3	3.5
20-year horizon						
Male						
45	236	209	181	470	453	436
55	210	181	152	438	426	413
65	174	147	119	385	379	372
75	144	125	106	304	303	302
Female						
45	229	199	169	486	471	455
55	197	163	129	458	445	432
65	165	134	103	414	411	407
75	133	113	92	305	304	302
Lifetime horizon						
Male						
45	357	322	287	697	695	692
55	286	255	223	571	571	571
65	203	176	148	432	431	429
75	147	129	110	309	308	308
Female						
45	345	301	258	743	744	746
55	275	238	200	612	614	616
65	197	166	135	466	468	470
75	137	116	96	311	310	309

TABLE 94 *Scenario 3: discounted incremental QALYs on varying the baseline LDL-c value*

Age (years)	Primary			Secondary		
	Baseline LDL-c (mmol/l)					
	2.5	3	3.5	2.5	3	3.5
20-year horizon						
Male						
45	47.0	56.3	65.6	50.6	60.8	71.0
55	52.4	62.8	73.1	64.4	77.4	90.4
65	54.1	64.8	75.5	64.3	77.3	90.4
75	34.6	41.4	48.2	46.3	55.6	64.9
Female						
45	38.4	46.0	53.6	47.3	56.7	66.2
55	49.4	59.2	68.9	65.6	78.8	92.0
65	51.6	61.8	72.0	65.8	79.1	92.4
75	32.0	38.3	44.6	48.1	57.8	67.6
Lifetime horizon						
Male						
45	129.1	155.1	181.2	124.9	150.7	176.7
55	99.8	119.8	139.8	108.2	130.4	152.8
65	69.9	83.9	97.8	77.1	92.7	108.5
75	36.1	43.2	50.3	47.3	56.9	66.5
Female						
45	115.8	139.0	162.2	125.1	150.7	176.6
55	96.3	115.5	134.7	112.9	136.0	159.3
65	66.6	79.8	93.1	79.2	95.3	111.4
75	33.3	39.9	46.4	49.3	59.2	69.2

TABLE 95 *Scenario 4: discounted incremental costs (£000) on varying the baseline LDL-c value*

Age (years)	Primary			Secondary		
	Baseline LDL-c (mmol/l)					
	2.5	3	3.5	2.5	3	3.5
20-year horizon						
Male						
45	4305	4259	4213	4454	4427	4400
55	3994	3946	3897	4009	3989	3969
65	3409	3363	3316	3350	3336	3322
75	2603	2571	2538	2484	2477	2470
Female						
45	4343	4293	4242	4526	4501	4475
55	4075	4017	3959	4174	4151	4128
65	3477	3424	3369	3485	3474	3462
75	2572	2536	2499	2505	2497	2488
Lifetime horizon						
Male						
45	5711	5654	5593	5800	5793	5785
55	4751	4699	4646	4675	4672	4668
65	3663	3617	3570	3550	3543	3535
75	2631	2599	2567	2502	2496	2490
Female						
45	5848	5775	5701	6020	6015	6010
55	4886	4822	4756	4926	4922	4918
65	3739	3685	3631	3700	3696	3692
75	2599	2563	2527	2524	2517	2509

TABLE 96 *Scenario 4: discounted incremental QALYs on varying the baseline LDL-c value*

Age (years)	Primary			Secondary		
	Baseline LDL-c (mmol/l)					
	2.5	3	3.5	2.5	3	3.5
20-year horizon						
Male						
45	80.3	96.3	112.3	78.6	94.4	110.2
55	88.7	106.4	124.0	98.0	117.8	137.6
65	90.7	108.7	126.7	94.6	113.7	132.9
75	57.7	69.2	80.6	64.7	77.8	90.9
Female						
45	65.5	78.5	91.5	72.1	86.5	101.0
55	83.1	99.6	116.0	97.6	117.3	137.0
65	85.9	103.0	120.1	95.0	114.2	133.5
75	52.9	63.4	73.8	66.5	80.0	93.5
Lifetime horizon						
Male						
45	212.6	255.5	298.5	182.4	219.9	257.8
55	165.1	198.2	231.4	159.6	192.3	225.3
65	116.1	139.4	162.6	112.1	134.9	157.9
75	60.1	72.0	83.8	66.1	79.5	92.9
Female						
45	189.1	227.0	265.0	178.9	215.7	252.7
55	157.7	189.3	220.8	163.0	196.4	230.0
65	109.8	131.7	153.7	113.2	136.3	159.5
75	55.0	65.9	76.8	68.1	81.8	95.7

TABLE 97 *Scenario 5: discounted incremental costs (£000) on varying the baseline LDL-c value*

Age (years)	Primary			Secondary		
	Baseline LDL-c (mmol/l)					
	2.5	3	3.5	2.5	3	3.5
20-year horizon						
Male						
45	4315	4271	4227	4471	4447	4423
55	4010	3965	3919	4035	4020	4004
65	3430	3387	3344	3379	3371	3362
75	2618	2589	2560	2507	2505	2502
Female						
45	4351	4301	4252	4541	4519	4496
55	4088	4033	3977	4198	4180	4162
65	3496	3446	3395	3514	3509	3503
75	2586	2552	2518	2528	2525	2521
Lifetime horizon						
Male						
45	5757	5710	5658	5854	5857	5860
55	4791	4746	4701	4725	4732	4739
65	3693	3652	3611	3587	3587	3587
75	2647	2619	2590	2526	2525	2524
Female						
45	5887	5821	5756	6072	6078	6084
55	4922	4865	4806	4976	4982	4988
65	3766	3718	3669	3738	3742	3745
75	2614	2581	2547	2549	2546	2543

TABLE 98 *Scenario 5: discounted incremental QALYs on varying the baseline LDL-c value*

Age (years)	Primary			Secondary		
	Baseline LDL-c (mmol/l)					
	2.5	3	3.5	2.5	3	3.5
20-year horizon						
Male						
45	80.3	96.3	112.3	78.6	94.4	110.2
55	88.7	106.4	124.0	98.0	117.8	137.6
65	90.7	108.7	126.7	94.6	113.7	132.9
75	57.7	69.2	80.6	64.7	77.8	90.9
Female						
45	65.5	78.5	91.5	72.1	86.5	101.0
55	83.1	99.6	116.0	97.6	117.3	137.0
65	85.9	103.0	120.1	95.0	114.2	133.5
75	52.9	63.4	73.8	66.5	80.0	93.5
Lifetime horizon						
Male						
45	212.6	255.5	298.5	182.4	219.9	257.8
55	165.1	198.2	231.4	159.6	192.3	225.3
65	116.1	139.4	162.6	112.1	134.9	157.9
75	60.1	72.0	83.8	66.1	79.5	92.9
Female						
45	189.1	227.0	265.0	178.9	215.7	252.7
55	157.7	189.3	220.8	163.0	196.4	230.0
65	109.8	131.7	153.7	113.2	136.3	159.5
75	55.0	65.9	76.8	68.1	81.8	95.7

TABLE 99 *Scenario 6, regimen 1: discounted incremental costs (£000) on varying the baseline LDL-c value*

Age (years)	Primary			Secondary		
	Baseline LDL-c (mmol/l)					
	2.5	3	3.5	2.5	3	3.5
20-year horizon						
Male						
45	4421	4394	4368	4530	4514	4498
55	4117	4089	4062	4075	4064	4054
65	3529	3503	3477	3410	3405	3400
75	2690	2673	2655	2529	2529	2530
Female						
45	4470	4440	4411	4601	4587	4573
55	4218	4185	4152	4248	4237	4226
65	3612	3583	3553	3545	3543	3541
75	2669	2650	2630	2555	2555	2554
Lifetime horizon						
Male						
45	5865	5834	5803	5866	5867	5867
55	4895	4867	4839	4727	4730	4733
65	3787	3762	3737	3604	3605	3606
75	2719	2701	2684	2547	2548	2549
Female						
45	6039	5998	5958	6088	6093	6097
55	5056	5022	4987	4989	4994	4998
65	3882	3854	3825	3754	3759	3763
75	2696	2677	2658	2574	2574	2574

TABLE 100 *Scenario 5: discounted incremental QALYs on varying the baseline LDL-c value*

Age (years)	Primary			Secondary		
	Baseline LDL-c (mmol/l)					
	2.5	3	3.5	2.5	3	3.5
20-year horizon						
Male						
45	47.0	56.3	65.6	50.6	60.8	71.0
55	52.4	62.8	73.1	64.4	77.4	90.4
65	54.1	64.8	75.5	64.3	77.3	90.4
75	34.6	41.4	48.2	46.3	55.6	64.9
Female						
45	38.4	46.0	53.6	47.3	56.7	66.2
55	49.4	59.2	68.9	65.6	78.8	92.0
65	51.6	61.8	72.0	65.8	79.1	92.4
75	32.0	38.3	44.6	48.1	57.8	67.6
Lifetime horizon						
Male						
45	129.1	155.1	181.2	124.9	150.7	176.7
55	99.8	119.8	139.8	108.2	130.4	152.8
65	69.9	83.9	97.8	77.1	92.7	108.5
75	36.1	43.2	50.3	47.3	56.9	66.5
Female						
45	115.8	139.0	162.2	125.1	150.7	176.6
55	96.3	115.5	134.7	112.9	136.0	159.3
65	66.6	79.8	93.1	79.2	95.3	111.4
75	33.3	39.9	46.4	49.3	59.2	69.2

TABLE 101 *Scenario 6, regimen 10: discounted incremental costs (£000) on varying the baseline LDL-c value*

Age (years)	Primary			Secondary		
	Baseline LDL-c (mmol/l)					
	2.5	3	3.5	2.5	3	3.5
20-year horizon						
Male						
45	85	58	30	324	307	290
55	70	41	12	307	295	283
65	54	26	–1	277	270	264
75	52	33	15	224	224	223
Female						
45	76	46	16	338	322	307
55	52	18	c/s	322	309	297
65	41	11	c/s	302	299	295
75	42	22	1	225	224	222
Lifetime horizon						
Male						
45	160	125	90	512	510	508
55	121	90	58	423	423	423
65	74	47	20	318	317	316
75	55	36	18	229	229	228
Female						
45	140	97	54	551	553	555
55	104	67	29	456	458	460
65	64	34	3	348	351	353
75	45	24	4	230	229	228

TABLE 102 *Scenario 5: discounted incremental QALYs on varying the baseline LDL-c value*

Age (years)	Primary			Secondary		
	Baseline LDL-c (mmol/l)					
	2.5	3	3.5	2.5	3	3.5
20-year horizon						
Male						
45	47.0	56.3	65.6	50.6	60.8	71.0
55	52.4	62.8	73.1	64.4	77.4	90.4
65	54.1	64.8	75.5	64.3	77.3	90.4
75	34.6	41.4	48.2	46.3	55.6	64.9
Female						
45	38.4	46.0	53.6	47.3	56.7	66.2
55	49.4	59.2	68.9	65.6	78.8	92.0
65	51.6	61.8	72.0	65.8	79.1	92.4
75	32.0	38.3	44.6	48.1	57.8	67.6
Lifetime horizon						
Male						
45	129.1	155.1	181.2	124.9	150.7	176.7
55	99.8	119.8	139.8	108.2	130.4	152.8
65	69.9	83.9	97.8	77.1	92.7	108.5
75	36.1	43.2	50.3	47.3	56.9	66.5
Female						
45	115.8	139.0	162.2	125.1	150.7	176.6
55	96.3	115.5	134.7	112.9	136.0	159.3
65	66.6	79.8	93.1	79.2	95.3	111.4
75	33.3	39.9	46.4	49.3	59.2	69.2

Appendix 30

Detailed discussion of primary and secondary results

For the majority of the analyses, the results for the secondary cohorts are more cost-effective than the results for the primary cohorts of the same age. There are two exceptions to this: (1) the results for cohorts aged 45 years and (2) the results for the analyses which are comparing treatment regimens with similar annual treatment costs. As it is reasonable to assume that providing treatment to a secondary cohort would be more cost-effective than providing treatment to a primary cohort, these results may seem counter-intuitive. A detailed discussion of the results is provided below.

Describing why the primary ICERS are lower than the secondary ICERs for cohorts aged 45 years

The life-years and QALYs accumulated for primary and secondary cohorts aged 45 and 75 years (using Scenario 2) are used to illustrate why the primary results can be lower than the secondary results for cohorts aged 45 years.

Looking at life-years accumulated by the primary and secondary cohorts aged 45 and 75 years (*Table 103*):

- The number of life-years for each cohort increases as the time horizon increases, as would be expected.
- The primary cohorts accrue more life-years than the secondary cohorts of the same age. This is to be expected as the CVD mortality risk is higher in the secondary cohort.
- The incremental number of life-years gained increases as the time horizon increases; again, this is to be expected.
- On comparing the primary and secondary results for cohorts of the same age, the difference in the number of life-years gained also increases as the time horizon increases.

Looking at the QALYs accumulated by the primary and secondary cohorts aged 45 and 75 years (*Table 103*):

- The number of QALYs for each cohort increases, as the time horizon increases, as would be expected
- The incremental number of QALYs gained increases as the time horizon increases.
- The primary cohorts accrue more QALYs than the secondary cohorts of the same age due to the baseline QoL of the secondary cohort.
- For cohorts aged 75 years, the secondary

TABLE 103 *Life-years and QALYs for primary and secondary cohorts aged 45 and 75 years when using Scenario 2*

			Undiscounted life-years				Discounted QALYs			
Age (years)	**CVD**	**Arm**	**5 years**	**10 years**	**20 years**	**Lifetime**	**5 years**	**10 years**	**20 years**	**Lifetime**
45	P	T	4,938	9,719	18,465	29,729	3,939	7,017	11,121	13,979
45	P	C	4,936	9,706	18,378	29,130	3,933	6,992	11,027	13,732
Incremental		*2.2*	*13.6*	*87.2*	*598.5*	*5.6*	*25.3*	*93.1*	*246.9*	
45	S	T	4,896	9,549	17,746	26,942	3,189	5,644	8,824	10,828
45	S	C	4,891	9,520	17,598	26,284	3,183	5,618	8,733	10,616
Incremental			*5.4*	*28.9*	*148.5*	*657.9*	*5.9*	*25.8*	*91.2*	*212.4*
75	P	T	4,361	7,311	9,456	9,580	2,952	4,544	5,424	5,459
75	P	C	4,354	7,272	9,352	9,467	2,944	4,510	5,358	5,390
Incremental			*6.7*	*38.1*	*104.4*	*112.8*	*8.6*	*33.5*	*66.9*	*69.6*
75	S	T	4,095	6,490	7,926	7,991	2,226	3,272	3,759	3,775
75	S	C	4,075	6,408	7,762	7,820	2,212	3,228	3,684	3,698
Incremental			*20.1*	*82.2*	*164.3*	*170.9*	*13.4*	*44.9*	*75.1*	*76.8*

C, control; P, primary; S, secondary; T, treatment.

cohorts continue to gain more QALYs than the primary cohorts over the full lifetime horizon.
- For cohorts aged 45 years, the secondary cohorts gain slightly more QALYs than the primary cohorts when accruing benefits over shorter horizons (5.9 versus 5.6 at 5 years and 25.8 versus 25.3 at 10 years).
- For cohorts aged 45 years, when accruing benefits over longer horizons, the primary cohorts gain more QALYs than the secondary cohorts (93.1 versus 91.2 at 20 years and 246.9 versus 212.4 at lifetime).

All individuals with a history of CVD commence the model with a disutility associated with the disease, hence preventing an event in a secondary cohort is worth less in terms of QALY gain than preventing an event in a primary cohort (*Table 103*).

The cumulative QALY gain from preventing one non-fatal MI in a primary cohort is 8.33. To obtain the same QALY gain in a secondary cohort, an intervention would need to prevent 2.5 MIs if the individual had experienced a previous MI and over 3 MIs if the individual had experienced a previous Str.

The cumulative QALY gain from preventing one non-fatal Str in a primary cohort is 15.39. To obtain the same QALY gain in a secondary cohort, an intervention would need to prevent 1.6 Str if the individual had experienced a previous MI, and almost 6 Str if the individual had experienced a previous Str.

An approximation of the number of QALYs accumulated by an individual in the secondary cohort who remains event free over the duration of the model is calculated by weighting the number of QALYs for each of the starting health states (post: angina, unstable angina, MI, TIA and Str) by the starting distribution (*Table 104*). An intervention would need to prevent 1.2 fatal events in the secondary cohort to obtain the QALY gain accumulated through preventing one in the primary cohort.

At younger ages (i.e. 45 years), the ratio of fatal to non-fatal events means that the majority of risk is attributed to the non-fatal events and therefore the majority of benefits are accrued through non-fatal events. The number of fatal secondary events increases more rapidly than the number of fatal primary events as age increases, hence the cumulative impact of saving more fatal events in the secondary cohorts outweighs the differential gain of saving non-fatal events in the primary cohorts for the older age groups.

Describing why the primary ICERs are lower than the secondary ICERs for treatment scenarios with relatively small incremental annual treatment costs

There are analyses where all the primary results are lower than the secondary results for cohorts of the same age. These analyses use treatment

TABLE 104 *Number of undiscounted QALYs accumulated by an individual aged 45 years*

	No event	Fatal event	Saving	No. of events
Primary	41.48		41.48	1
Secondary weighted by distribution across the post-primary health states	33.76		33.76	1.2
	No event	**Non-fatal MI**	**Saving**	
Primary	41.48	33.15	8.33	1.0
Secondary stable angina	37.33	29.83	7.50	1.1
Secondary MI	33.18	29.83	3.35	2.5
Secondary Str	26.09	23.48	2.61	3.2
	No event	**Non-fatal Str**	**Saving**	
Primary	41.48	26.09	15.391	1
Secondary stable angina	37.33	23.48	13.85	1.1
Secondary MI	33.18	23.48	9.70	1.6
Secondary Str	26.09	23.48	2.61	5.9

regimens which have a relatively small difference in the annual cost of treatments; namely ezetimibe co-administered with generic simvastatin versus the same dose of atorvastatin. The results for Scenario 6, treatment regimen 10 (ezetimibe co-administered with simvastatin 40 mg versus atorvastatin 40 mg), and the results for Scenario 6, treatment regimen 1 (ezetimibe co-administered with pravastatin 10 mg versus generic simvastatin 10 mg), are used to illustrate why the primary ICERs are lower than the secondary ICERs. These two treatment regimens were selected as regimen 1 has the smallest difference in annual treatment costs (£30.37) and regimen 10 has the largest difference in annual treatment costs (£344.40).

Table 105 provides the discounted therapy costs for each arm, the incremental therapy costs, the incremental total costs and the ICERs for male cohorts aged 65 years using treatment regimens 1 and 10. The incremental QALYs and the cumulative health state costs are the same for both analyses as the only difference is the cost associated with the therapies being compared. For treatment regimen 1, all ICERs for the secondary cohorts are lower than the ICERs for the primary cohorts. Conversely, for treatment regimen 10, all ICERs for the secondary cohorts are higher than the ICERs for the primary cohorts.

The incremental costs associated with the therapies are much smaller for treatment regimen

TABLE 105 *Comparing the results for primary and secondary cohorts aged 65 years*[a]

Cohort	Treatment regimen 10 (E10 + S10 vs A40)				Treatment regimen 1 (E10 + P10 vs S10)			
	5 years	10 years	20 years	Lifetime	5 years	10 years	20 years	Lifetime
Treatment arm therapy costs (£000)								
P65	1793	3093	4425	4734	1658	2859	4090	4376
S65	1757	2936	4004	4207	1624	2714	3701	3888
Comparator arm therapy costs (£000)								
P65	1656	2853	4070	4348	106	183	261	279
S65	1622	2704	3670	3850	104	173	235	247
Incremental therapy costs (£000)								
P65	137	240	355	386	1552	2676	3829	4097
S65	135	232	333	357	1520	2540	3465	3641
Treatment arm health state costs (£000)								
P65	627	1558	3132	3599	627	1558	3132	3599
S65	3351	5837	8216	8650	3351	5837	8216	8650
Comparator arm health state costs (£000)								
P65	726	1748	3414	3893	726	1748	3414	3893
S65	3385	5897	8268	8688	3385	5897	8268	8688
Incremental health state costs (£000)								
P65	–99	–190	–282	–293	–99	–190	–282	–293
S65	–34	–60	–52	–38	–34	–60	–52	–38
Total incremental costs (£000)								
P65	39	50	73	93	1453	2486	3547	3804
S65	102	173	281	319	1487	2481	3413	3604
Total incremental QALYs								
P65	3.4	15.5	46.7	60.4	3.4	15.5	46.7	60.4
S65	5.4	21.8	55.6	66.5	5.4	21.8	55.6	66.5
Discounted ICER (£000)								
P65	11.3	3.2	1.6	1.5	423.3	160.2	76.0	63.0
S65	18.9	7.9	5.1	4.8	276.8	113.8	61.4	54.2

A40, atorvastatin 40 mg; E10, ezetimibe 10 mg; P10, pravastatin 10 mg; P65, primary cohort aged 65 years; S10; simvastatin 10 mg; S65, secondary cohort aged 65 years.

[a] When using Scenario 6, treatment regimen 10 (ezetimibe co-administered with generic simvastatin 40 mg compared with atorvastatin 40 mg) and treatment regimen 1 (ezetimibe co-administered with generic pravastatin 10 mg versus generic simvastatin 10 mg).

10 than for treatment regimen 1, as would be expected as the difference in the annual costs of the treatments being compared is much smaller. On comparing the lifetime results, the incremental therapy costs are similar at £386,000 versus £357,000 for regimen 10 and £4,097,000 versus £3,641,000 for regimen 1 for the primary and secondary cohorts, respectively.

The health state costs associated with primary cohorts are much smaller than those accrued by the secondary cohorts, as would be expected. However, the cost offsets due to events avoided are much larger for the primary cohorts.

All individuals in the secondary cohorts commence the analyses with an ongoing cost associated with the disease whereas those in the primary cohorts commence the analyses with no health state costs other than monitoring. Consequently, saving a subsequent event in a secondary cohort accrues less cost savings than saving the same event in a primary cohort.

If an MI was prevented in a primary cohort, the cost savings would include the first-year costs (£4934) plus subsequent-year costs (£201) until death. Preventing the same event in a secondary population, if the individual had already had one MI, then the total cost savings attributable to the prevented event would be the first-year costs minus the ongoing costs (£4934–201). For an individual aged 45 years, the maximum total savings associated with a primary non-fatal MI are £4934 + (£201 × 44) = £13,778, whereas the maximum total savings associated with a secondary non-fatal MI are £4934 – £201 = £4733. Looking at non-fatal Str, the maximum total savings associated with a primary non-fatal Str are £8070 + (£2169 × 44) = £103,506. For a secondary non-fatal Str, the maximum total savings are (£8070 – £201) + (£2169 – £201) × 44 = £94,461 for an individual with a history of angina or a previous MI, and £8070 – £2169 = £5901 for an individual with a previous Str.

The impact of this is that when looking at the total incremental costs, the cost savings due to events avoided by the primary cohort when using the treatment regimen 1 are absorbed by the difference in the therapy costs, resulting in a total incremental cost which is similar to that accrued by the secondary cohort. Conversely, as the incremental therapy costs are much smaller for treatment regimen 10, the total incremental costs are also much smaller and the total cost associated with the primary cohort is smaller that that accrued by the secondary cohort, giving primary ICERs which are smaller than the secondary ICERs.

Health Technology Assessment reports published to date

Volume 1, 1997

No. 1
Home parenteral nutrition: a systematic review.
By Richards DM, Deeks JJ, Sheldon TA, Shaffer JL.

No. 2
Diagnosis, management and screening of early localised prostate cancer.
A review by Selley S, Donovan J, Faulkner A, Coast J, Gillatt D.

No. 3
The diagnosis, management, treatment and costs of prostate cancer in England and Wales.
A review by Chamberlain J, Melia J, Moss S, Brown J.

No. 4
Screening for fragile X syndrome.
A review by Murray J, Cuckle H, Taylor G, Hewison J.

No. 5
A review of near patient testing in primary care.
By Hobbs FDR, Delaney BC, Fitzmaurice DA, Wilson S, Hyde CJ, Thorpe GH, *et al*.

No. 6
Systematic review of outpatient services for chronic pain control.
By McQuay HJ, Moore RA, Eccleston C, Morley S, de C Williams AC.

No. 7
Neonatal screening for inborn errors of metabolism: cost, yield and outcome.
A review by Pollitt RJ, Green A, McCabe CJ, Booth A, Cooper NJ, Leonard JV, *et al*.

No. 8
Preschool vision screening.
A review by Snowdon SK, Stewart-Brown SL.

No. 9
Implications of socio-cultural contexts for the ethics of clinical trials.
A review by Ashcroft RE, Chadwick DW, Clark SRL, Edwards RHT, Frith L, Hutton JL.

No. 10
A critical review of the role of neonatal hearing screening in the detection of congenital hearing impairment.
By Davis A, Bamford J, Wilson I, Ramkalawan T, Forshaw M, Wright S.

No. 11
Newborn screening for inborn errors of metabolism: a systematic review.
By Seymour CA, Thomason MJ, Chalmers RA, Addison GM, Bain MD, Cockburn F, *et al*.

No. 12
Routine preoperative testing: a systematic review of the evidence.
By Munro J, Booth A, Nicholl J.

No. 13
Systematic review of the effectiveness of laxatives in the elderly.
By Petticrew M, Watt I, Sheldon T.

No. 14
When and how to assess fast-changing technologies: a comparative study of medical applications of four generic technologies.
A review by Mowatt G, Bower DJ, Brebner JA, Cairns JA, Grant AM, McKee L.

Volume 2, 1998

No. 1
Antenatal screening for Down's syndrome.
A review by Wald NJ, Kennard A, Hackshaw A, McGuire A.

No. 2
Screening for ovarian cancer: a systematic review.
By Bell R, Petticrew M, Luengo S, Sheldon TA.

No. 3
Consensus development methods, and their use in clinical guideline development.
A review by Murphy MK, Black NA, Lamping DL, McKee CM, Sanderson CFB, Askham J, *et al*.

No. 4
A cost–utility analysis of interferon beta for multiple sclerosis.
By Parkin D, McNamee P, Jacoby A, Miller P, Thomas S, Bates D.

No. 5
Effectiveness and efficiency of methods of dialysis therapy for end-stage renal disease: systematic reviews.
By MacLeod A, Grant A, Donaldson C, Khan I, Campbell M, Daly C, *et al*.

No. 6
Effectiveness of hip prostheses in primary total hip replacement: a critical review of evidence and an economic model.
By Faulkner A, Kennedy LG, Baxter K, Donovan J, Wilkinson M, Bevan G.

No. 7
Antimicrobial prophylaxis in colorectal surgery: a systematic review of randomised controlled trials.
By Song F, Glenny AM.

No. 8
Bone marrow and peripheral blood stem cell transplantation for malignancy.
A review by Johnson PWM, Simnett SJ, Sweetenham JW, Morgan GJ, Stewart LA.

No. 9
Screening for speech and language delay: a systematic review of the literature.
By Law J, Boyle J, Harris F, Harkness A, Nye C.

No. 10
Resource allocation for chronic stable angina: a systematic review of effectiveness, costs and cost-effectiveness of alternative interventions.
By Sculpher MJ, Petticrew M, Kelland JL, Elliott RA, Holdright DR, Buxton MJ.

No. 11
Detection, adherence and control of hypertension for the prevention of stroke: a systematic review.
By Ebrahim S.

No. 12
Postoperative analgesia and vomiting, with special reference to day-case surgery: a systematic review.
By McQuay HJ, Moore RA.

No. 13
Choosing between randomised and nonrandomised studies: a systematic review.
By Britton A, McKee M, Black N, McPherson K, Sanderson C, Bain C.

No. 14
Evaluating patient-based outcome measures for use in clinical trials.
A review by Fitzpatrick R, Davey C, Buxton MJ, Jones DR.

No. 15
Ethical issues in the design and conduct of randomised controlled trials.
A review by Edwards SJL, Lilford RJ, Braunholtz DA, Jackson JC, Hewison J, Thornton J.

No. 16
Qualitative research methods in health technology assessment: a review of the literature.
By Murphy E, Dingwall R, Greatbatch D, Parker S, Watson P.

No. 17
The costs and benefits of paramedic skills in pre-hospital trauma care.
By Nicholl J, Hughes S, Dixon S, Turner J, Yates D.

No. 18
Systematic review of endoscopic ultrasound in gastro-oesophageal cancer.
By Harris KM, Kelly S, Berry E, Hutton J, Roderick P, Cullingworth J, *et al*.

No. 19
Systematic reviews of trials and other studies.
By Sutton AJ, Abrams KR, Jones DR, Sheldon TA, Song F.

No. 20
Primary total hip replacement surgery: a systematic review of outcomes and modelling of cost-effectiveness associated with different prostheses.
A review by Fitzpatrick R, Shortall E, Sculpher M, Murray D, Morris R, Lodge M, *et al*.

Volume 3, 1999

No. 1
Informed decision making: an annotated bibliography and systematic review.
By Bekker H, Thornton JG, Airey CM, Connelly JB, Hewison J, Robinson MB, *et al*.

No. 2
Handling uncertainty when performing economic evaluation of healthcare interventions.
A review by Briggs AH, Gray AM.

No. 3
The role of expectancies in the placebo effect and their use in the delivery of health care: a systematic review.
By Crow R, Gage H, Hampson S, Hart J, Kimber A, Thomas H.

No. 4
A randomised controlled trial of different approaches to universal antenatal HIV testing: uptake and acceptability. Annex: Antenatal HIV testing – assessment of a routine voluntary approach.
By Simpson WM, Johnstone FD, Boyd FM, Goldberg DJ, Hart GJ, Gormley SM, *et al*.

No. 5
Methods for evaluating area-wide and organisation-based interventions in health and health care: a systematic review.
By Ukoumunne OC, Gulliford MC, Chinn S, Sterne JAC, Burney PGJ.

No. 6
Assessing the costs of healthcare technologies in clinical trials.
A review by Johnston K, Buxton MJ, Jones DR, Fitzpatrick R.

No. 7
Cooperatives and their primary care emergency centres: organisation and impact.
By Hallam L, Henthorne K.

No. 8
Screening for cystic fibrosis.
A review by Murray J, Cuckle H, Taylor G, Littlewood J, Hewison J.

No. 9
A review of the use of health status measures in economic evaluation.
By Brazier J, Deverill M, Green C, Harper R, Booth A.

No. 10
Methods for the analysis of quality-of-life and survival data in health technology assessment.
A review by Billingham LJ, Abrams KR, Jones DR.

No. 11
Antenatal and neonatal haemoglobinopathy screening in the UK: review and economic analysis.
By Zeuner D, Ades AE, Karnon J, Brown J, Dezateux C, Anionwu EN.

No. 12
Assessing the quality of reports of randomised trials: implications for the conduct of meta-analyses.
A review by Moher D, Cook DJ, Jadad AR, Tugwell P, Moher M, Jones A, *et al*.

No. 13
'Early warning systems' for identifying new healthcare technologies.
By Robert G, Stevens A, Gabbay J.

No. 14
A systematic review of the role of human papillomavirus testing within a cervical screening programme.
By Cuzick J, Sasieni P, Davies P, Adams J, Normand C, Frater A, *et al*.

No. 15
Near patient testing in diabetes clinics: appraising the costs and outcomes.
By Grieve R, Beech R, Vincent J, Mazurkiewicz J.

No. 16
Positron emission tomography: establishing priorities for health technology assessment.
A review by Robert G, Milne R.

No. 17 (Pt 1)
The debridement of chronic wounds: a systematic review.
By Bradley M, Cullum N, Sheldon T.

No. 17 (Pt 2)
Systematic reviews of wound care management: (2) Dressings and topical agents used in the healing of chronic wounds.
By Bradley M, Cullum N, Nelson EA, Petticrew M, Sheldon T, Torgerson D.

No. 18
A systematic literature review of spiral and electron beam computed tomography: with particular reference to clinical applications in hepatic lesions, pulmonary embolus and coronary artery disease.
By Berry E, Kelly S, Hutton J, Harris KM, Roderick P, Boyce JC, *et al*.

No. 19
What role for statins? A review and economic model.
By Ebrahim S, Davey Smith G, McCabe C, Payne N, Pickin M, Sheldon TA, *et al*.

No. 20
Factors that limit the quality, number and progress of randomised controlled trials.
A review by Prescott RJ, Counsell CE, Gillespie WJ, Grant AM, Russell IT, Kiauka S, *et al*.

No. 21
Antimicrobial prophylaxis in total hip replacement: a systematic review.
By Glenny AM, Song F.

No. 22
Health promoting schools and health promotion in schools: two systematic reviews.
By Lister-Sharp D, Chapman S, Stewart-Brown S, Sowden A.

No. 23
Economic evaluation of a primary care-based education programme for patients with osteoarthritis of the knee.
A review by Lord J, Victor C, Littlejohns P, Ross FM, Axford JS.

Volume 4, 2000

No. 1
The estimation of marginal time preference in a UK-wide sample (TEMPUS) project.
A review by Cairns JA, van der Pol MM.

No. 2
Geriatric rehabilitation following fractures in older people: a systematic review.
By Cameron I, Crotty M, Currie C, Finnegan T, Gillespie L, Gillespie W, *et al*.

No. 3
Screening for sickle cell disease and thalassaemia: a systematic review with supplementary research.
By Davies SC, Cronin E, Gill M, Greengross P, Hickman M, Normand C.

No. 4
Community provision of hearing aids and related audiology services.
A review by Reeves DJ, Alborz A, Hickson FS, Bamford JM.

No. 5
False-negative results in screening programmes: systematic review of impact and implications.
By Petticrew MP, Sowden AJ, Lister-Sharp D, Wright K.

No. 6
Costs and benefits of community postnatal support workers: a randomised controlled trial.
By Morrell CJ, Spiby H, Stewart P, Walters S, Morgan A.

No. 7
Implantable contraceptives (subdermal implants and hormonally impregnated intrauterine systems) versus other forms of reversible contraceptives: two systematic reviews to assess relative effectiveness, acceptability, tolerability and cost-effectiveness.
By French RS, Cowan FM, Mansour DJA, Morris S, Procter T, Hughes D, *et al*.

No. 8
An introduction to statistical methods for health technology assessment.
A review by White SJ, Ashby D, Brown PJ.

No. 9
Disease-modifying drugs for multiple sclerosis: a rapid and systematic review.
By Clegg A, Bryant J, Milne R.

No. 10
Publication and related biases.
A review by Song F, Eastwood AJ, Gilbody S, Duley L, Sutton AJ.

No. 11
Cost and outcome implications of the organisation of vascular services.
By Michaels J, Brazier J, Palfreyman S, Shackley P, Slack R.

No. 12
Monitoring blood glucose control in diabetes mellitus: a systematic review.
By Coster S, Gulliford MC, Seed PT, Powrie JK, Swaminathan R.

No. 13
The effectiveness of domiciliary health visiting: a systematic review of international studies and a selective review of the British literature.
By Elkan R, Kendrick D, Hewitt M, Robinson JJA, Tolley K, Blair M, *et al*.

No. 14
The determinants of screening uptake and interventions for increasing uptake: a systematic review.
By Jepson R, Clegg A, Forbes C, Lewis R, Sowden A, Kleijnen J.

No. 15
The effectiveness and cost-effectiveness of prophylactic removal of wisdom teeth.
A rapid review by Song F, O'Meara S, Wilson P, Golder S, Kleijnen J.

No. 16
Ultrasound screening in pregnancy: a systematic review of the clinical effectiveness, cost-effectiveness and women's views.
By Bricker L, Garcia J, Henderson J, Mugford M, Neilson J, Roberts T, *et al*.

No. 17
A rapid and systematic review of the effectiveness and cost-effectiveness of the taxanes used in the treatment of advanced breast and ovarian cancer.
By Lister-Sharp D, McDonagh MS, Khan KS, Kleijnen J.

No. 18
Liquid-based cytology in cervical screening: a rapid and systematic review.
By Payne N, Chilcott J, McGoogan E.

No. 19
Randomised controlled trial of non-directive counselling, cognitive–behaviour therapy and usual general practitioner care in the management of depression as well as mixed anxiety and depression in primary care.
By King M, Sibbald B, Ward E, Bower P, Lloyd M, Gabbay M, *et al*.

No. 20
Routine referral for radiography of patients presenting with low back pain: is patients' outcome influenced by GPs' referral for plain radiography?
By Kerry S, Hilton S, Patel S, Dundas D, Rink E, Lord J.

No. 21
Systematic reviews of wound care management: (3) antimicrobial agents for chronic wounds; (4) diabetic foot ulceration.
By O'Meara S, Cullum N, Majid M, Sheldon T.

No. 22
Using routine data to complement and enhance the results of randomised controlled trials.
By Lewsey JD, Leyland AH, Murray GD, Boddy FA.

No. 23
Coronary artery stents in the treatment of ischaemic heart disease: a rapid and systematic review.
By Meads C, Cummins C, Jolly K, Stevens A, Burls A, Hyde C.

No. 24
Outcome measures for adult critical care: a systematic review.
By Hayes JA, Black NA, Jenkinson C, Young JD, Rowan KM, Daly K, *et al*.

No. 25
A systematic review to evaluate the effectiveness of interventions to promote the initiation of breastfeeding.
By Fairbank L, O'Meara S, Renfrew MJ, Woolridge M, Sowden AJ, Lister-Sharp D.

No. 26
Implantable cardioverter defibrillators: arrhythmias. A rapid and systematic review.
By Parkes J, Bryant J, Milne R.

No. 27
Treatments for fatigue in multiple sclerosis: a rapid and systematic review.
By Brañas P, Jordan R, Fry-Smith A, Burls A, Hyde C.

No. 28
Early asthma prophylaxis, natural history, skeletal development and economy (EASE): a pilot randomised controlled trial.
By Baxter-Jones ADG, Helms PJ, Russell G, Grant A, Ross S, Cairns JA, *et al*.

No. 29
Screening for hypercholesterolaemia versus case finding for familial hypercholesterolaemia: a systematic review and cost-effectiveness analysis.
By Marks D, Wonderling D, Thorogood M, Lambert H, Humphries SE, Neil HAW.

No. 30
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of glycoprotein IIb/IIIa antagonists in the medical management of unstable angina.
By McDonagh MS, Bachmann LM, Golder S, Kleijnen J, ter Riet G.

No. 31
A randomised controlled trial of prehospital intravenous fluid replacement therapy in serious trauma.
By Turner J, Nicholl J, Webber L, Cox H, Dixon S, Yates D.

No. 32
Intrathecal pumps for giving opioids in chronic pain: a systematic review.
By Williams JE, Louw G, Towlerton G.

No. 33
Combination therapy (interferon alfa and ribavirin) in the treatment of chronic hepatitis C: a rapid and systematic review.
By Shepherd J, Waugh N, Hewitson P.

No. 34
A systematic review of comparisons of effect sizes derived from randomised and non-randomised studies.
By MacLehose RR, Reeves BC, Harvey IM, Sheldon TA, Russell IT, Black AMS.

No. 35
Intravascular ultrasound-guided interventions in coronary artery disease: a systematic literature review, with decision-analytic modelling, of outcomes and cost-effectiveness.
By Berry E, Kelly S, Hutton J, Lindsay HSJ, Blaxill JM, Evans JA, *et al*.

No. 36
A randomised controlled trial to evaluate the effectiveness and cost-effectiveness of counselling patients with chronic depression.
By Simpson S, Corney R, Fitzgerald P, Beecham J.

No. 37
Systematic review of treatments for atopic eczema.
By Hoare C, Li Wan Po A, Williams H.

No. 38
Bayesian methods in health technology assessment: a review.
By Spiegelhalter DJ, Myles JP, Jones DR, Abrams KR.

No. 39
The management of dyspepsia: a systematic review.
By Delaney B, Moayyedi P, Deeks J, Innes M, Soo S, Barton P, *et al*.

No. 40
A systematic review of treatments for severe psoriasis.
By Griffiths CEM, Clark CM, Chalmers RJG, Li Wan Po A, Williams HC.

Volume 5, 2001

No. 1
Clinical and cost-effectiveness of donepezil, rivastigmine and galantamine for Alzheimer's disease: a rapid and systematic review.
By Clegg A, Bryant J, Nicholson T, McIntyre L, De Broe S, Gerard K, *et al*.

No. 2
The clinical effectiveness and cost-effectiveness of riluzole for motor neurone disease: a rapid and systematic review.
By Stewart A, Sandercock J, Bryan S, Hyde C, Barton PM, Fry-Smith A, *et al*.

No. 3
Equity and the economic evaluation of healthcare.
By Sassi F, Archard L, Le Grand J.

No. 4
Quality-of-life measures in chronic diseases of childhood.
By Eiser C, Morse R.

No. 5
Eliciting public preferences for healthcare: a systematic review of techniques.
By Ryan M, Scott DA, Reeves C, Bate A, van Teijlingen ER, Russell EM, *et al*.

No. 6
General health status measures for people with cognitive impairment: learning disability and acquired brain injury.
By Riemsma RP, Forbes CA, Glanville JM, Eastwood AJ, Kleijnen J.

No. 7
An assessment of screening strategies for fragile X syndrome in the UK.
By Pembrey ME, Barnicoat AJ, Carmichael B, Bobrow M, Turner G.

No. 8
Issues in methodological research: perspectives from researchers and commissioners.
By Lilford RJ, Richardson A, Stevens A, Fitzpatrick R, Edwards S, Rock F, *et al*.

No. 9
Systematic reviews of wound care management: (5) beds; (6) compression; (7) laser therapy, therapeutic ultrasound, electrotherapy and electromagnetic therapy.
By Cullum N, Nelson EA, Flemming K, Sheldon T.

No. 10
Effects of educational and psychosocial interventions for adolescents with diabetes mellitus: a systematic review.
By Hampson SE, Skinner TC, Hart J, Storey L, Gage H, Foxcroft D, *et al*.

No. 11
Effectiveness of autologous chondrocyte transplantation for hyaline cartilage defects in knees: a rapid and systematic review.
By Jobanputra P, Parry D, Fry-Smith A, Burls A.

No. 12
Statistical assessment of the learning curves of health technologies.
By Ramsay CR, Grant AM, Wallace SA, Garthwaite PH, Monk AF, Russell IT.

No. 13
The effectiveness and cost-effectiveness of temozolomide for the treatment of recurrent malignant glioma: a rapid and systematic review.
By Dinnes J, Cave C, Huang S, Major K, Milne R.

No. 14
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of debriding agents in treating surgical wounds healing by secondary intention.
By Lewis R, Whiting P, ter Riet G, O'Meara S, Glanville J.

No. 15
Home treatment for mental health problems: a systematic review.
By Burns T, Knapp M, Catty J, Healey A, Henderson J, Watt H, *et al*.

No. 16
How to develop cost-conscious guidelines.
By Eccles M, Mason J.

No. 17
The role of specialist nurses in multiple sclerosis: a rapid and systematic review.
By De Broe S, Christopher F, Waugh N.

No. 18
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of orlistat in the management of obesity.
By O'Meara S, Riemsma R, Shirran L, Mather L, ter Riet G.

No. 19
The clinical effectiveness and cost-effectiveness of pioglitazone for type 2 diabetes mellitus: a rapid and systematic review.
By Chilcott J, Wight J, Lloyd Jones M, Tappenden P.

No. 20
Extended scope of nursing practice: a multicentre randomised controlled trial of appropriately trained nurses and preregistration house officers in pre-operative assessment in elective general surgery.
By Kinley H, Czoski-Murray C, George S, McCabe C, Primrose J, Reilly C, *et al*.

No. 21
Systematic reviews of the effectiveness of day care for people with severe mental disorders: (1) Acute day hospital versus admission; (2) Vocational rehabilitation; (3) Day hospital versus outpatient care.
By Marshall M, Crowther R, Almaraz-Serrano A, Creed F, Sledge W, Kluiter H, *et al*.

No. 22
The measurement and monitoring of surgical adverse events.
By Bruce J, Russell EM, Mollison J, Krukowski ZH.

No. 23
Action research: a systematic review and guidance for assessment.
By Waterman H, Tillen D, Dickson R, de Koning K.

No. 24
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of gemcitabine for the treatment of pancreatic cancer.
By Ward S, Morris E, Bansback N, Calvert N, Crellin A, Forman D, *et al*.

No. 25
A rapid and systematic review of the evidence for the clinical effectiveness and cost-effectiveness of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer.
By Lloyd Jones M, Hummel S, Bansback N, Orr B, Seymour M.

No. 26
Comparison of the effectiveness of inhaler devices in asthma and chronic obstructive airways disease: a systematic review of the literature.
By Brocklebank D, Ram F, Wright J, Barry P, Cates C, Davies L, *et al*.

No. 27
The cost-effectiveness of magnetic resonance imaging for investigation of the knee joint.
By Bryan S, Weatherburn G, Bungay H, Hatrick C, Salas C, Parry D, *et al*.

No. 28
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of topotecan for ovarian cancer.
By Forbes C, Shirran L, Bagnall A-M, Duffy S, ter Riet G.

No. 29
Superseded by a report published in a later volume.

No. 30
The role of radiography in primary care patients with low back pain of at least 6 weeks duration: a randomised (unblinded) controlled trial.
By Kendrick D, Fielding K, Bentley E, Miller P, Kerslake R, Pringle M.

No. 31
Design and use of questionnaires: a review of best practice applicable to surveys of health service staff and patients.
By McColl E, Jacoby A, Thomas L, Soutter J, Bamford C, Steen N, *et al*.

No. 32
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of paclitaxel, docetaxel, gemcitabine and vinorelbine in non-small-cell lung cancer.
By Clegg A, Scott DA, Sidhu M, Hewitson P, Waugh N.

No. 33
Subgroup analyses in randomised controlled trials: quantifying the risks of false-positives and false-negatives.
By Brookes ST, Whitley E, Peters TJ, Mulheran PA, Egger M, Davey Smith G.

No. 34
Depot antipsychotic medication in the treatment of patients with schizophrenia: (1) Meta-review; (2) Patient and nurse attitudes.
By David AS, Adams C.

No. 35
A systematic review of controlled trials of the effectiveness and cost-effectiveness of brief psychological treatments for depression.
By Churchill R, Hunot V, Corney R, Knapp M, McGuire H, Tylee A, *et al*.

No. 36
Cost analysis of child health surveillance.
By Sanderson D, Wright D, Acton C, Duree D.

Volume 6, 2002

No. 1
A study of the methods used to select review criteria for clinical audit.
By Hearnshaw H, Harker R, Cheater F, Baker R, Grimshaw G.

No. 2
Fludarabine as second-line therapy for B cell chronic lymphocytic leukaemia: a technology assessment.
By Hyde C, Wake B, Bryan S, Barton P, Fry-Smith A, Davenport C, *et al*.

No. 3
Rituximab as third-line treatment for refractory or recurrent Stage III or IV follicular non-Hodgkin's lymphoma: a systematic review and economic evaluation.
By Wake B, Hyde C, Bryan S, Barton P, Song F, Fry-Smith A, *et al*.

No. 4
A systematic review of discharge arrangements for older people.
By Parker SG, Peet SM, McPherson A, Cannaby AM, Baker R, Wilson A, *et al*.

No. 5
The clinical effectiveness and cost-effectiveness of inhaler devices used in the routine management of chronic asthma in older children: a systematic review and economic evaluation.
By Peters J, Stevenson M, Beverley C, Lim J, Smith S.

No. 6
The clinical effectiveness and cost-effectiveness of sibutramine in the management of obesity: a technology assessment.
By O'Meara S, Riemsma R, Shirran L, Mather L, ter Riet G.

No. 7
The cost-effectiveness of magnetic resonance angiography for carotid artery stenosis and peripheral vascular disease: a systematic review.
By Berry E, Kelly S, Westwood ME, Davies LM, Gough MJ, Bamford JM, *et al*.

No. 8
Promoting physical activity in South Asian Muslim women through 'exercise on prescription'.
By Carroll B, Ali N, Azam N.

No. 9
Zanamivir for the treatment of influenza in adults: a systematic review and economic evaluation.
By Burls A, Clark W, Stewart T, Preston C, Bryan S, Jefferson T, *et al*.

No. 10
A review of the natural history and epidemiology of multiple sclerosis: implications for resource allocation and health economic models.
By Richards RG, Sampson FC, Beard SM, Tappenden P.

No. 11
Screening for gestational diabetes: a systematic review and economic evaluation.
By Scott DA, Loveman E, McIntyre L, Waugh N.

No. 12
The clinical effectiveness and cost-effectiveness of surgery for people with morbid obesity: a systematic review and economic evaluation.
By Clegg AJ, Colquitt J, Sidhu MK, Royle P, Loveman E, Walker A.

No. 13
The clinical effectiveness of trastuzumab for breast cancer: a systematic review.
By Lewis R, Bagnall A-M, Forbes C, Shirran E, Duffy S, Kleijnen J, *et al*.

No. 14
The clinical effectiveness and cost-effectiveness of vinorelbine for breast cancer: a systematic review and economic evaluation.
By Lewis R, Bagnall A-M, King S, Woolacott N, Forbes C, Shirran L, *et al*.

No. 15
A systematic review of the effectiveness and cost-effectiveness of metal-on-metal hip resurfacing arthroplasty for treatment of hip disease.
By Vale L, Wyness L, McCormack K, McKenzie L, Brazzelli M, Stearns SC.

No. 16
The clinical effectiveness and cost-effectiveness of bupropion and nicotine replacement therapy for smoking cessation: a systematic review and economic evaluation.
By Woolacott NF, Jones L, Forbes CA, Mather LC, Sowden AJ, Song FJ, *et al*.

No. 17
A systematic review of effectiveness and economic evaluation of new drug treatments for juvenile idiopathic arthritis: etanercept.
By Cummins C, Connock M, Fry-Smith A, Burls A.

No. 18
Clinical effectiveness and cost-effectiveness of growth hormone in children: a systematic review and economic evaluation.
By Bryant J, Cave C, Mihaylova B, Chase D, McIntyre L, Gerard K, *et al*.

No. 19
Clinical effectiveness and cost-effectiveness of growth hormone in adults in relation to impact on quality of life: a systematic review and economic evaluation.
By Bryant J, Loveman E, Chase D, Mihaylova B, Cave C, Gerard K, *et al*.

No. 20
Clinical medication review by a pharmacist of patients on repeat prescriptions in general practice: a randomised controlled trial.
By Zermansky AG, Petty DR, Raynor DK, Lowe CJ, Freementle N, Vail A.

No. 21
The effectiveness of infliximab and etanercept for the treatment of rheumatoid arthritis: a systematic review and economic evaluation.
By Jobanputra P, Barton P, Bryan S, Burls A.

No. 22
A systematic review and economic evaluation of computerised cognitive behaviour therapy for depression and anxiety.
By Kaltenthaler E, Shackley P, Stevens K, Beverley C, Parry G, Chilcott J.

No. 23
A systematic review and economic evaluation of pegylated liposomal doxorubicin hydrochloride for ovarian cancer.
By Forbes C, Wilby J, Richardson G, Sculpher M, Mather L, Reimsma R.

No. 24
A systematic review of the effectiveness of interventions based on a stages-of-change approach to promote individual behaviour change.
By Riemsma RP, Pattenden J, Bridle C, Sowden AJ, Mather L, Watt IS, *et al*.

No. 25
A systematic review update of the clinical effectiveness and cost-effectiveness of glycoprotein IIb/IIIa antagonists.
By Robinson M, Ginnelly L, Sculpher M, Jones L, Riemsma R, Palmer S, *et al*.

No. 26
A systematic review of the effectiveness, cost-effectiveness and barriers to implementation of thrombolytic and neuroprotective therapy for acute ischaemic stroke in the NHS.
By Sandercock P, Berge E, Dennis M, Forbes J, Hand P, Kwan J, *et al*.

No. 27
A randomised controlled crossover trial of nurse practitioner versus doctor-led outpatient care in a bronchiectasis clinic.
By Caine N, Sharples LD, Hollingworth W, French J, Keogan M, Exley A, *et al*.

No. 28
Clinical effectiveness and cost – consequences of selective serotonin reuptake inhibitors in the treatment of sex offenders.
By Adi Y, Ashcroft D, Browne K, Beech A, Fry-Smith A, Hyde C.

No. 29
Treatment of established osteoporosis: a systematic review and cost–utility analysis.
By Kanis JA, Brazier JE, Stevenson M, Calvert NW, Lloyd Jones M.

No. 30
Which anaesthetic agents are cost-effective in day surgery? Literature review, national survey of practice and randomised controlled trial.
By Elliott RA Payne K, Moore JK, Davies LM, Harper NJN, St Leger AS, *et al*.

No. 31
Screening for hepatitis C among injecting drug users and in genitourinary medicine clinics: systematic reviews of effectiveness, modelling study and national survey of current practice.
By Stein K, Dalziel K, Walker A, McIntyre L, Jenkins B, Horne J, *et al*.

No. 32
The measurement of satisfaction with healthcare: implications for practice from a systematic review of the literature.
By Crow R, Gage H, Hampson S, Hart J, Kimber A, Storey L, *et al*.

No. 33
The effectiveness and cost-effectiveness of imatinib in chronic myeloid leukaemia: a systematic review.
By Garside R, Round A, Dalziel K, Stein K, Royle R.

No. 34
A comparative study of hypertonic saline, daily and alternate-day rhDNase in children with cystic fibrosis.
By Suri R, Wallis C, Bush A, Thompson S, Normand C, Flather M, *et al*.

No. 35
A systematic review of the costs and effectiveness of different models of paediatric home care.
By Parker G, Bhakta P, Lovett CA, Paisley S, Olsen R, Turner D, *et al*.

Volume 7, 2003

No. 1
How important are comprehensive literature searches and the assessment of trial quality in systematic reviews? Empirical study.
By Egger M, Jüni P, Bartlett C, Holenstein F, Sterne J.

No. 2
Systematic review of the effectiveness and cost-effectiveness, and economic evaluation, of home versus hospital or satellite unit haemodialysis for people with end-stage renal failure.
By Mowatt G, Vale L, Perez J, Wyness L, Fraser C, MacLeod A, *et al*.

No. 3
Systematic review and economic evaluation of the effectiveness of infliximab for the treatment of Crohn's disease.
By Clark W, Raftery J, Barton P, Song F, Fry-Smith A, Burls A.

No. 4
A review of the clinical effectiveness and cost-effectiveness of routine anti-D prophylaxis for pregnant women who are rhesus negative.
By Chilcott J, Lloyd Jones M, Wight J, Forman K, Wray J, Beverley C, *et al*.

No. 5
Systematic review and evaluation of the use of tumour markers in paediatric oncology: Ewing's sarcoma and neuroblastoma.
By Riley RD, Burchill SA, Abrams KR, Heney D, Lambert PC, Jones DR, *et al*.

No. 6
The cost-effectiveness of screening for *Helicobacter pylori* to reduce mortality and morbidity from gastric cancer and peptic ulcer disease: a discrete-event simulation model.
By Roderick P, Davies R, Raftery J, Crabbe D, Pearce R, Bhandari P, *et al*.

No. 7
The clinical effectiveness and cost-effectiveness of routine dental checks: a systematic review and economic evaluation.
By Davenport C, Elley K, Salas C, Taylor-Weetman CL, Fry-Smith A, Bryan S, *et al*.

No. 8
A multicentre randomised controlled trial assessing the costs and benefits of using structured information and analysis of women's preferences in the management of menorrhagia.
By Kennedy ADM, Sculpher MJ, Coulter A, Dwyer N, Rees M, Horsley S, *et al*.

No. 9
Clinical effectiveness and cost–utility of photodynamic therapy for wet age-related macular degeneration: a systematic review and economic evaluation.
By Meads C, Salas C, Roberts T, Moore D, Fry-Smith A, Hyde C.

No. 10
Evaluation of molecular tests for prenatal diagnosis of chromosome abnormalities.
By Grimshaw GM, Szczepura A, Hultén M, MacDonald F, Nevin NC, Sutton F, *et al*.

No. 11
First and second trimester antenatal screening for Down's syndrome: the results of the Serum, Urine and Ultrasound Screening Study (SURUSS).
By Wald NJ, Rodeck C, Hackshaw AK, Walters J, Chitty L, Mackinson AM.

No. 12
The effectiveness and cost-effectiveness of ultrasound locating devices for central venous access: a systematic review and economic evaluation.
By Calvert N, Hind D, McWilliams RG, Thomas SM, Beverley C, Davidson A.

No. 13
A systematic review of atypical antipsychotics in schizophrenia.
By Bagnall A-M, Jones L, Lewis R, Ginnelly L, Glanville J, Torgerson D, *et al*.

No. 14
Prostate Testing for Cancer and Treatment (ProtecT) feasibility study.
By Donovan J, Hamdy F, Neal D, Peters T, Oliver S, Brindle L, *et al*.

No. 15
Early thrombolysis for the treatment of acute myocardial infarction: a systematic review and economic evaluation.
By Boland A, Dundar Y, Bagust A, Haycox A, Hill R, Mujica Mota R, *et al*.

No. 16
Screening for fragile X syndrome: a literature review and modelling.
By Song FJ, Barton P, Sleightholme V, Yao GL, Fry-Smith A.

No. 17
Systematic review of endoscopic sinus surgery for nasal polyps.
By Dalziel K, Stein K, Round A, Garside R, Royle P.

No. 18
Towards efficient guidelines: how to monitor guideline use in primary care.
By Hutchinson A, McIntosh A, Cox S, Gilbert C.

No. 19
Effectiveness and cost-effectiveness of acute hospital-based spinal cord injuries services: systematic review.
By Bagnall A-M, Jones L, Richardson G, Duffy S, Riemsma R.

No. 20
Prioritisation of health technology assessment. The PATHS model: methods and case studies.
By Townsend J, Buxton M, Harper G.

No. 21
Systematic review of the clinical effectiveness and cost-effectiveness of tension-free vaginal tape for treatment of urinary stress incontinence.
By Cody J, Wyness L, Wallace S, Glazener C, Kilonzo M, Stearns S, *et al*.

No. 22
The clinical and cost-effectiveness of patient education models for diabetes: a systematic review and economic evaluation.
By Loveman E, Cave C, Green C, Royle P, Dunn N, Waugh N.

No. 23
The role of modelling in prioritising and planning clinical trials.
By Chilcott J, Brennan A, Booth A, Karnon J, Tappenden P.

No. 24
Cost–benefit evaluation of routine influenza immunisation in people 65–74 years of age.
By Allsup S, Gosney M, Haycox A, Regan M.

No. 25
The clinical and cost-effectiveness of pulsatile machine perfusion versus cold storage of kidneys for transplantation retrieved from heart-beating and non-heart-beating donors.
By Wight J, Chilcott J, Holmes M, Brewer N.

No. 26
Can randomised trials rely on existing electronic data? A feasibility study to explore the value of routine data in health technology assessment.
By Williams JG, Cheung WY, Cohen DR, Hutchings HA, Longo MF, Russell IT.

No. 27
Evaluating non-randomised intervention studies.
By Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, *et al*.

No. 28
A randomised controlled trial to assess the impact of a package comprising a patient-orientated, evidence-based self-help guidebook and patient-centred consultations on disease management and satisfaction in inflammatory bowel disease.
By Kennedy A, Nelson E, Reeves D, Richardson G, Roberts C, Robinson A, *et al*.

No. 29
The effectiveness of diagnostic tests for the assessment of shoulder pain due to soft tissue disorders: a systematic review.
By Dinnes J, Loveman E, McIntyre L, Waugh N.

No. 30
The value of digital imaging in diabetic retinopathy.
By Sharp PF, Olson J, Strachan F, Hipwell J, Ludbrook A, O'Donnell M, *et al*.

No. 31
Lowering blood pressure to prevent myocardial infarction and stroke: a new preventive strategy.
By Law M, Wald N, Morris J.

No. 32
Clinical and cost-effectiveness of capecitabine and tegafur with uracil for the treatment of metastatic colorectal cancer: systematic review and economic evaluation.
By Ward S, Kaltenthaler E, Cowan J, Brewer N.

No. 33
Clinical and cost-effectiveness of new and emerging technologies for early localised prostate cancer: a systematic review.
By Hummel S, Paisley S, Morgan A, Currie E, Brewer N.

No. 34
Literature searching for clinical and cost-effectiveness studies used in health technology assessment reports carried out for the National Institute for Clinical Excellence appraisal system.
By Royle P, Waugh N.

No. 35
Systematic review and economic decision modelling for the prevention and treatment of influenza A and B.
By Turner D, Wailoo A, Nicholson K, Cooper N, Sutton A, Abrams K.

No. 36
A randomised controlled trial to evaluate the clinical and cost-effectiveness of Hickman line insertions in adult cancer patients by nurses.
By Boland A, Haycox A, Bagust A, Fitzsimmons L.

No. 37
Redesigning postnatal care: a randomised controlled trial of protocol-based midwifery-led care focused on individual women's physical and psychological health needs.
By MacArthur C, Winter HR, Bick DE, Lilford RJ, Lancashire RJ, Knowles H, *et al*.

No. 38
Estimating implied rates of discount in healthcare decision-making.
By West RR, McNabb R, Thompson AGH, Sheldon TA, Grimley Evans J.

No. 39
Systematic review of isolation policies in the hospital management of methicillin-resistant *Staphylococcus aureus*: a review of the literature with epidemiological and economic modelling.
By Cooper BS, Stone SP, Kibbler CC, Cookson BD, Roberts JA, Medley GF, *et al*.

No. 40
Treatments for spasticity and pain in multiple sclerosis: a systematic review.
By Beard S, Hunn A, Wight J.

No. 41
The inclusion of reports of randomised trials published in languages other than English in systematic reviews.
By Moher D, Pham B, Lawson ML, Klassen TP.

No. 42
The impact of screening on future health-promoting behaviours and health beliefs: a systematic review.
By Bankhead CR, Brett J, Bukach C, Webster P, Stewart-Brown S, Munafo M, *et al*.

Volume 8, 2004

No. 1
What is the best imaging strategy for acute stroke?
By Wardlaw JM, Keir SL, Seymour J, Lewis S, Sandercock PAG, Dennis MS, *et al*.

No. 2
Systematic review and modelling of the investigation of acute and chronic chest pain presenting in primary care.
By Mant J, McManus RJ, Oakes RAL, Delaney BC, Barton PM, Deeks JJ, *et al*.

No. 3
The effectiveness and cost-effectiveness of microwave and thermal balloon endometrial ablation for heavy menstrual bleeding: a systematic review and economic modelling.
By Garside R, Stein K, Wyatt K, Round A, Price A.

No. 4
A systematic review of the role of bisphosphonates in metastatic disease.
By Ross JR, Saunders Y, Edmonds PM, Patel S, Wonderling D, Normand C, *et al*.

No. 5
Systematic review of the clinical effectiveness and cost-effectiveness of capecitabine (Xeloda®) for locally advanced and/or metastatic breast cancer.
By Jones L, Hawkins N, Westwood M, Wright K, Richardson G, Riemsma R.

No. 6
Effectiveness and efficiency of guideline dissemination and implementation strategies.
By Grimshaw JM, Thomas RE, MacLennan G, Fraser C, Ramsay CR, Vale L, *et al*.

No. 7
Clinical effectiveness and costs of the Sugarbaker procedure for the treatment of pseudomyxoma peritonei.
By Bryant J, Clegg AJ, Sidhu MK, Brodin H, Royle P, Davidson P.

No. 8
Psychological treatment for insomnia in the regulation of long-term hypnotic drug use.
By Morgan K, Dixon S, Mathers N, Thompson J, Tomeny M.

No. 9
Improving the evaluation of therapeutic interventions in multiple sclerosis: development of a patient-based measure of outcome.
By Hobart JC, Riazi A, Lamping DL, Fitzpatrick R, Thompson AJ.

No. 10
A systematic review and economic evaluation of magnetic resonance cholangiopancreatography compared with diagnostic endoscopic retrograde cholangiopancreatography.
By Kaltenthaler E, Bravo Vergel Y, Chilcott J, Thomas S, Blakeborough T, Walters SJ, *et al*.

No. 11
The use of modelling to evaluate new drugs for patients with a chronic condition: the case of antibodies against tumour necrosis factor in rheumatoid arthritis.
By Barton P, Jobanputra P, Wilson J, Bryan S, Burls A.

No. 12
Clinical effectiveness and cost-effectiveness of neonatal screening for inborn errors of metabolism using tandem mass spectrometry: a systematic review.
By Pandor A, Eastham J, Beverley C, Chilcott J, Paisley S.

No. 13
Clinical effectiveness and cost-effectiveness of pioglitazone and rosiglitazone in the treatment of type 2 diabetes: a systematic review and economic evaluation.
By Czoski-Murray C, Warren E, Chilcott J, Beverley C, Psyllaki MA, Cowan J.

No. 14
Routine examination of the newborn: the EMREN study. Evaluation of an extension of the midwife role including a randomised controlled trial of appropriately trained midwives and paediatric senior house officers.
By Townsend J, Wolke D, Hayes J, Davé S, Rogers C, Bloomfield L, *et al*.

No. 15
Involving consumers in research and development agenda setting for the NHS: developing an evidence-based approach.
By Oliver S, Clarke-Jones L, Rees R, Milne R, Buchanan P, Gabbay J, *et al*.

No. 16
A multi-centre randomised controlled trial of minimally invasive direct coronary bypass grafting versus percutaneous transluminal coronary angioplasty with stenting for proximal stenosis of the left anterior descending coronary artery.
By Reeves BC, Angelini GD, Bryan AJ, Taylor FC, Cripps T, Spyt TJ, *et al*.

No. 17
Does early magnetic resonance imaging influence management or improve outcome in patients referred to secondary care with low back pain? A pragmatic randomised controlled trial.
By Gilbert FJ, Grant AM, Gillan MGC, Vale L, Scott NW, Campbell MK, *et al*.

No. 18
The clinical and cost-effectiveness of anakinra for the treatment of rheumatoid arthritis in adults: a systematic review and economic analysis.
By Clark W, Jobanputra P, Barton P, Burls A.

No. 19
A rapid and systematic review and economic evaluation of the clinical and cost-effectiveness of newer drugs for treatment of mania associated with bipolar affective disorder.
By Bridle C, Palmer S, Bagnall A-M, Darba J, Duffy S, Sculpher M, *et al*.

No. 20
Liquid-based cytology in cervical screening: an updated rapid and systematic review and economic analysis.
By Karnon J, Peters J, Platt J, Chilcott J, McGoogan E, Brewer N.

No. 21
Systematic review of the long-term effects and economic consequences of treatments for obesity and implications for health improvement.
By Avenell A, Broom J, Brown TJ, Poobalan A, Aucott L, Stearns SC, *et al*.

No. 22
Autoantibody testing in children with newly diagnosed type 1 diabetes mellitus.
By Dretzke J, Cummins C, Sandercock J, Fry-Smith A, Barrett T, Burls A.

No. 23
Clinical effectiveness and cost-effectiveness of prehospital intravenous fluids in trauma patients.
By Dretzke J, Sandercock J, Bayliss S, Burls A.

No. 24
Newer hypnotic drugs for the short-term management of insomnia: a systematic review and economic evaluation.
By Dündar Y, Boland A, Strobl J, Dodd S, Haycox A, Bagust A, *et al*.

No. 25
Development and validation of methods for assessing the quality of diagnostic accuracy studies.
By Whiting P, Rutjes AWS, Dinnes J, Reitsma JB, Bossuyt PMM, Kleijnen J.

No. 26
EVALUATE hysterectomy trial: a multicentre randomised trial comparing abdominal, vaginal and laparoscopic methods of hysterectomy.
By Garry R, Fountain J, Brown J, Manca A, Mason S, Sculpher M, *et al*.

No. 27
Methods for expected value of information analysis in complex health economic models: developments on the health economics of interferon-β and glatiramer acetate for multiple sclerosis.
By Tappenden P, Chilcott JB, Eggington S, Oakley J, McCabe C.

No. 28
Effectiveness and cost-effectiveness of imatinib for first-line treatment of chronic myeloid leukaemia in chronic phase: a systematic review and economic analysis.
By Dalziel K, Round A, Stein K, Garside R, Price A.

No. 29
VenUS I: a randomised controlled trial of two types of bandage for treating venous leg ulcers.
By Iglesias C, Nelson EA, Cullum NA, Torgerson DJ on behalf of the VenUS Team.

No. 30
Systematic review of the effectiveness and cost-effectiveness, and economic evaluation, of myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction.
By Mowatt G, Vale L, Brazzelli M, Hernandez R, Murray A, Scott N, *et al*.

No. 31
A pilot study on the use of decision theory and value of information analysis as part of the NHS Health Technology Assessment programme.
By Claxton K, Ginnelly L, Sculpher M, Philips Z, Palmer S.

No. 32
The Social Support and Family Health Study: a randomised controlled trial and economic evaluation of two alternative forms of postnatal support for mothers living in disadvantaged inner-city areas.
By Wiggins M, Oakley A, Roberts I, Turner H, Rajan L, Austerberry H, *et al*.

No. 33
Psychosocial aspects of genetic screening of pregnant women and newborns: a systematic review.
By Green JM, Hewison J, Bekker HL, Bryant, Cuckle HS.

No. 34
Evaluation of abnormal uterine bleeding: comparison of three outpatient procedures within cohorts defined by age and menopausal status.
By Critchley HOD, Warner P, Lee AJ, Brechin S, Guise J, Graham B.

No. 35
Coronary artery stents: a rapid systematic review and economic evaluation.
By Hill R, Bagust A, Bakhai A, Dickson R, Dündar Y, Haycox A, *et al*.

No. 36
Review of guidelines for good practice in decision-analytic modelling in health technology assessment.
By Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, *et al*.

No. 37
Rituximab (MabThera®) for aggressive non-Hodgkin's lymphoma: systematic review and economic evaluation.
By Knight C, Hind D, Brewer N, Abbott V.

No. 38
Clinical effectiveness and cost-effectiveness of clopidogrel and modified-release dipyridamole in the secondary prevention of occlusive vascular events: a systematic review and economic evaluation.
By Jones L, Griffin S, Palmer S, Main C, Orton V, Sculpher M, *et al.*

No. 39
Pegylated interferon α-2a and -2b in combination with ribavirin in the treatment of chronic hepatitis C: a systematic review and economic evaluation.
By Shepherd J, Brodin H, Cave C, Waugh N, Price A, Gabbay J.

No. 40
Clopidogrel used in combination with aspirin compared with aspirin alone in the treatment of non-ST-segment-elevation acute coronary syndromes: a systematic review and economic evaluation.
By Main C, Palmer S, Griffin S, Jones L, Orton V, Sculpher M, *et al.*

No. 41
Provision, uptake and cost of cardiac rehabilitation programmes: improving services to under-represented groups.
By Beswick AD, Rees K, Griebsch I, Taylor FC, Burke M, West RR, *et al.*

No. 42
Involving South Asian patients in clinical trials.
By Hussain-Gambles M, Leese B, Atkin K, Brown J, Mason S, Tovey P.

No. 43
Clinical and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes.
By Colquitt JL, Green C, Sidhu MK, Hartwell D, Waugh N.

No. 44
Identification and assessment of ongoing trials in health technology assessment reviews.
By Song FJ, Fry-Smith A, Davenport C, Bayliss S, Adi Y, Wilson JS, *et al*.

No. 45
Systematic review and economic evaluation of a long-acting insulin analogue, insulin glargine
By Warren E, Weatherley-Jones E, Chilcott J, Beverley C.

No. 46
Supplementation of a home-based exercise programme with a class-based programme for people with osteoarthritis of the knees: a randomised controlled trial and health economic analysis.
By McCarthy CJ, Mills PM, Pullen R, Richardson G, Hawkins N, Roberts CR, *et al*.

No. 47
Clinical and cost-effectiveness of once-daily versus more frequent use of same potency topical corticosteroids for atopic eczema: a systematic review and economic evaluation.
By Green C, Colquitt JL, Kirby J, Davidson P, Payne E.

No. 48
Acupuncture of chronic headache disorders in primary care: randomised controlled trial and economic analysis.
By Vickers AJ, Rees RW, Zollman CE, McCarney R, Smith CM, Ellis N, *et al*.

No. 49
Generalisability in economic evaluation studies in healthcare: a review and case studies.
By Sculpher MJ, Pang FS, Manca A, Drummond MF, Golder S, Urdahl H, *et al*.

No. 50
Virtual outreach: a randomised controlled trial and economic evaluation of joint teleconferenced medical consultations.
By Wallace P, Barber J, Clayton W, Currell R, Fleming K, Garner P, *et al*.

Volume 9, 2005

No. 1
Randomised controlled multiple treatment comparison to provide a cost-effectiveness rationale for the selection of antimicrobial therapy in acne.
By Ozolins M, Eady EA, Avery A, Cunliffe WJ, O'Neill C, Simpson NB, *et al*.

No. 2
Do the findings of case series studies vary significantly according to methodological characteristics?
By Dalziel K, Round A, Stein K, Garside R, Castelnuovo E, Payne L.

No. 3
Improving the referral process for familial breast cancer genetic counselling: findings of three randomised controlled trials of two interventions.
By Wilson BJ, Torrance N, Mollison J, Wordsworth S, Gray JR, Haites NE, *et al*.

No. 4
Randomised evaluation of alternative electrosurgical modalities to treat bladder outflow obstruction in men with benign prostatic hyperplasia.
By Fowler C, McAllister W, Plail R, Karim O, Yang Q.

No. 5
A pragmatic randomised controlled trial of the cost-effectiveness of palliative therapies for patients with inoperable oesophageal cancer.
By Shenfine J, McNamee P, Steen N, Bond J, Griffin SM.

No. 6
Impact of computer-aided detection prompts on the sensitivity and specificity of screening mammography.
By Taylor P, Champness J, Given-Wilson R, Johnston K, Potts H.

No. 7
Issues in data monitoring and interim analysis of trials.
By Grant AM, Altman DG, Babiker AB, Campbell MK, Clemens FJ, Darbyshire JH, *et al*.

No. 8
Lay public's understanding of equipoise and randomisation in randomised controlled trials.
By Robinson EJ, Kerr CEP, Stevens AJ, Lilford RJ, Braunholtz DA, Edwards SJ, *et al*.

No. 9
Clinical and cost-effectiveness of electroconvulsive therapy for depressive illness, schizophrenia, catatonia and mania: systematic reviews and economic modelling studies.
By Greenhalgh J, Knight C, Hind D, Beverley C, Walters S.

No. 10
Measurement of health-related quality of life for people with dementia: development of a new instrument (DEMQOL) and an evaluation of current methodology.
By Smith SC, Lamping DL, Banerjee S, Harwood R, Foley B, Smith P, *et al*.

No. 11
Clinical effectiveness and cost-effectiveness of drotrecogin alfa (activated) (Xigris®) for the treatment of severe sepsis in adults: a systematic review and economic evaluation.
By Green C, Dinnes J, Takeda A, Shepherd J, Hartwell D, Cave C, *et al*.

No. 12
A methodological review of how heterogeneity has been examined in systematic reviews of diagnostic test accuracy.
By Dinnes J, Deeks J, Kirby J, Roderick P.

No. 13
Cervical screening programmes: can automation help? Evidence from systematic reviews, an economic analysis and a simulation modelling exercise applied to the UK.
By Willis BH, Barton P, Pearmain P, Bryan S, Hyde C.

No. 14
Laparoscopic surgery for inguinal hernia repair: systematic review of effectiveness and economic evaluation.
By McCormack K, Wake B, Perez J, Fraser C, Cook J, McIntosh E, *et al*.

No. 15
Clinical effectiveness, tolerability and cost-effectiveness of newer drugs for epilepsy in adults: a systematic review and economic evaluation.
By Wilby J, Kainth A, Hawkins N, Epstein D, McIntosh H, McDaid C, *et al*.

No. 16
A randomised controlled trial to compare the cost-effectiveness of tricyclic antidepressants, selective serotonin reuptake inhibitors and lofepramine.
By Peveler R, Kendrick T, Buxton M, Longworth L, Baldwin D, Moore M, *et al*.

No. 17
Clinical effectiveness and cost-effectiveness of immediate angioplasty for acute myocardial infarction: systematic review and economic evaluation.
By Hartwell D, Colquitt J, Loveman E, Clegg AJ, Brodin H, Waugh N, *et al*.

No. 18
A randomised controlled comparison of alternative strategies in stroke care.
By Kalra L, Evans A, Perez I, Knapp M, Swift C, Donaldson N.

No. 19
The investigation and analysis of critical incidents and adverse events in healthcare.
By Woloshynowych M, Rogers S, Taylor-Adams S, Vincent C.

No. 20
Potential use of routine databases in health technology assessment.
By Raftery J, Roderick P, Stevens A.

No. 21
Clinical and cost-effectiveness of newer immunosuppressive regimens in renal transplantation: a systematic review and modelling study.
By Woodroffe R, Yao GL, Meads C, Bayliss S, Ready A, Raftery J, *et al*.

No. 22
A systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal osteoporosis.
By Stevenson M, Lloyd Jones M, De Nigris E, Brewer N, Davis S, Oakley J.

No. 23
A systematic review to examine the impact of psycho-educational interventions on health outcomes and costs in adults and children with difficult asthma.
By Smith JR, Mugford M, Holland R, Candy B, Noble MJ, Harrison BDW, *et al*.

No. 24
An evaluation of the costs, effectiveness and quality of renal replacement therapy provision in renal satellite units in England and Wales.
By Roderick P, Nicholson T, Armitage A, Mehta R, Mullee M, Gerard K, *et al*.

No. 25
Imatinib for the treatment of patients with unresectable and/or metastatic gastrointestinal stromal tumours: systematic review and economic evaluation.
By Wilson J, Connock M, Song F, Yao G, Fry-Smith A, Raftery J, *et al*.

No. 26
Indirect comparisons of competing interventions.
By Glenny AM, Altman DG, Song F, Sakarovitch C, Deeks JJ, D'Amico R, *et al*.

No. 27
Cost-effectiveness of alternative strategies for the initial medical management of non-ST elevation acute coronary syndrome: systematic review and decision-analytical modelling.
By Robinson M, Palmer S, Sculpher M, Philips Z, Ginnelly L, Bowens A, *et al*.

No. 28
Outcomes of electrically stimulated gracilis neosphincter surgery.
By Tillin T, Chambers M, Feldman R.

No. 29
The effectiveness and cost-effectiveness of pimecrolimus and tacrolimus for atopic eczema: a systematic review and economic evaluation.
By Garside R, Stein K, Castelnuovo E, Pitt M, Ashcroft D, Dimmock P, *et al*.

No. 30
Systematic review on urine albumin testing for early detection of diabetic complications.
By Newman DJ, Mattock MB, Dawnay ABS, Kerry S, McGuire A, Yaqoob M, *et al*.

No. 31
Randomised controlled trial of the cost-effectiveness of water-based therapy for lower limb osteoarthritis.
By Cochrane T, Davey RC, Matthes Edwards SM.

No. 32
Longer term clinical and economic benefits of offering acupuncture care to patients with chronic low back pain.
By Thomas KJ, MacPherson H, Ratcliffe J, Thorpe L, Brazier J, Campbell M, *et al*.

No. 33
Cost-effectiveness and safety of epidural steroids in the management of sciatica.
By Price C, Arden N, Coglan L, Rogers P.

No. 34
The British Rheumatoid Outcome Study Group (BROSG) randomised controlled trial to compare the effectiveness and cost-effectiveness of aggressive versus symptomatic therapy in established rheumatoid arthritis.
By Symmons D, Tricker K, Roberts C, Davies L, Dawes P, Scott DL.

No. 35
Conceptual framework and systematic review of the effects of participants' and professionals' preferences in randomised controlled trials.
By King M, Nazareth I, Lampe F, Bower P, Chandler M, Morou M, *et al*.

No. 36
The clinical and cost-effectiveness of implantable cardioverter defibrillators: a systematic review.
By Bryant J, Brodin H, Loveman E, Payne E, Clegg A.

No. 37
A trial of problem-solving by community mental health nurses for anxiety, depression and life difficulties among general practice patients. The CPN-GP study.
By Kendrick T, Simons L, Mynors-Wallis L, Gray A, Lathlean J, Pickering R, *et al*.

No. 38
The causes and effects of socio-demographic exclusions from clinical trials.
By Bartlett C, Doyal L, Ebrahim S, Davey P, Bachmann M, Egger M, *et al*.

No. 39
Is hydrotherapy cost-effective? A randomised controlled trial of combined hydrotherapy programmes compared with physiotherapy land techniques in children with juvenile idiopathic arthritis.
By Epps H, Ginnelly L, Utley M, Southwood T, Gallivan S, Sculpher M, *et al*.

No. 40
A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study.
By Hobbs FDR, Fitzmaurice DA, Mant J, Murray E, Jowett S, Bryan S, *et al*.

No. 41
Displaced intracapsular hip fractures in fit, older people: a randomised comparison of reduction and fixation, bipolar hemiarthroplasty and total hip arthroplasty.
By Keating JF, Grant A, Masson M, Scott NW, Forbes JF.

No. 42
Long-term outcome of cognitive behaviour therapy clinical trials in central Scotland.
By Durham RC, Chambers JA, Power KG, Sharp DM, Macdonald RR, Major KA, *et al*.

No. 43
The effectiveness and cost-effectiveness of dual-chamber pacemakers compared with single-chamber pacemakers for bradycardia due to atrioventricular block or sick sinus syndrome: systematic review and economic evaluation.
By Castelnuovo E, Stein K, Pitt M, Garside R, Payne E.

No. 44
Newborn screening for congenital heart defects: a systematic review and cost-effectiveness analysis.
By Knowles R, Griebsch I, Dezateux C, Brown J, Bull C, Wren C.

No. 45
The clinical and cost-effectiveness of left ventricular assist devices for end-stage heart failure: a systematic review and economic evaluation.
By Clegg AJ, Scott DA, Loveman E, Colquitt J, Hutchinson J, Royle P, *et al*.

No. 46
The effectiveness of the Heidelberg Retina Tomograph and laser diagnostic glaucoma scanning system (GDx) in detecting and monitoring glaucoma.
By Kwartz AJ, Henson DB, Harper RA, Spencer AF, McLeod D.

No. 47
Clinical and cost-effectiveness of autologous chondrocyte implantation for cartilage defects in knee joints: systematic review and economic evaluation.
By Clar C, Cummins E, McIntyre L, Thomas S, Lamb J, Bain L, *et al*.

No. 48
Systematic review of effectiveness of different treatments for childhood retinoblastoma.
By McDaid C, Hartley S, Bagnall A-M, Ritchie G, Light K, Riemsma R.

No. 49
Towards evidence-based guidelines for the prevention of venous thromboembolism: systematic reviews of mechanical methods, oral anticoagulation, dextran and regional anaesthesia as thromboprophylaxis.
By Roderick P, Ferris G, Wilson K, Halls H, Jackson D, Collins R, *et al*.

No. 50
The effectiveness and cost-effectiveness of parent training/education programmes for the treatment of conduct disorder, including oppositional defiant disorder, in children.
By Dretzke J, Frew E, Davenport C, Barlow J, Stewart-Brown S, Sandercock J, *et al*.

Volume 10, 2006

No. 1
The clinical and cost-effectiveness of donepezil, rivastigmine, galantamine and memantine for Alzheimer's disease.
By Loveman E, Green C, Kirby J, Takeda A, Picot J, Payne E, *et al*.

No. 2
FOOD: a multicentre randomised trial evaluating feeding policies in patients admitted to hospital with a recent stroke.
By Dennis M, Lewis S, Cranswick G, Forbes J.

No. 3
The clinical effectiveness and cost-effectiveness of computed tomography screening for lung cancer: systematic reviews.
By Black C, Bagust A, Boland A, Walker S, McLeod C, De Verteuil R, *et al*.

No. 4
A systematic review of the effectiveness and cost-effectiveness of neuroimaging assessments used to visualise the seizure focus in people with refractory epilepsy being considered for surgery.
By Whiting P, Gupta R, Burch J, Mujica Mota RE, Wright K, Marson A, *et al*.

No. 5
Comparison of conference abstracts and presentations with full-text articles in the health technology assessments of rapidly evolving technologies.
By Dundar Y, Dodd S, Dickson R, Walley T, Haycox A, Williamson PR.

No. 6
Systematic review and evaluation of methods of assessing urinary incontinence.
By Martin JL, Williams KS, Abrams KR, Turner DA, Sutton AJ, Chapple C, *et al*.

No. 7
The clinical effectiveness and cost-effectiveness of newer drugs for children with epilepsy. A systematic review.
By Connock M, Frew E, Evans B-W, Bryan S, Cummins C, Fry-Smith A, *et al*.

No. 8
Surveillance of Barrett's oesophagus: exploring the uncertainty through systematic review, expert workshop and economic modelling.
By Garside R, Pitt M, Somerville M, Stein K, Price A, Gilbert N.

No. 9
Topotecan, pegylated liposomal doxorubicin hydrochloride and paclitaxel for second-line or subsequent treatment of advanced ovarian cancer: a systematic review and economic evaluation.
By Main C, Bojke L, Griffin S, Norman G, Barbieri M, Mather L, *et al*.

No. 10
Evaluation of molecular techniques in prediction and diagnosis of cytomegalovirus disease in immunocompromised patients.
By Szczepura A, Westmoreland D, Vinogradova Y, Fox J, Clark M.

No. 11
Screening for thrombophilia in high-risk situations: systematic review and cost-effectiveness analysis. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) study.
By Wu O, Robertson L, Twaddle S, Lowe GDO, Clark P, Greaves M, *et al*.

No. 12
A series of systematic reviews to inform a decision analysis for sampling and treating infected diabetic foot ulcers.
By Nelson EA, O'Meara S, Craig D, Iglesias C, Golder S, Dalton J, *et al*.

No. 13
Randomised clinical trial, observational study and assessment of cost-effectiveness of the treatment of varicose veins (REACTIV trial).
By Michaels JA, Campbell WB, Brazier JE, MacIntyre JB, Palfreyman SJ, Ratcliffe J, *et al*.

No. 14
The cost-effectiveness of screening for oral cancer in primary care.
By Speight PM, Palmer S, Moles DR, Downer MC, Smith DH, Henriksson M *et al*.

No. 15
Measurement of the clinical and cost-effectiveness of non-invasive diagnostic testing strategies for deep vein thrombosis.
By Goodacre S, Sampson F, Stevenson M, Wailoo A, Sutton A, Thomas S, *et al*.

No. 16
Systematic review of the effectiveness and cost-effectiveness of HealOzone® for the treatment of occlusal pit/fissure caries and root caries.
By Brazzelli M, McKenzie L, Fielding S, Fraser C, Clarkson J, Kilonzo M, *et al*.

No. 17
Randomised controlled trials of conventional antipsychotic versus new atypical drugs, and new atypical drugs versus clozapine, in people with schizophrenia responding poorly to, or intolerant of, current drug treatment.
By Lewis SW, Davies L, Jones PB, Barnes TRE, Murray RM, Kerwin R, *et al*.

No. 18
Diagnostic tests and algorithms used in the investigation of haematuria: systematic reviews and economic evaluation.
By Rodgers M, Nixon J, Hempel S, Aho T, Kelly J, Neal D, *et al*.

No. 19
Cognitive behavioural therapy in addition to antispasmodic therapy for irritable bowel syndrome in primary care: randomised controlled trial.
By Kennedy TM, Chalder T, McCrone P, Darnley S, Knapp M, Jones RH, *et al*.

No. 20
A systematic review of the clinical effectiveness and cost-effectiveness of enzyme replacement therapies for Fabry's disease and mucopolysaccharidosis type 1.
By Connock M, Juarez-Garcia A, Frew E, Mans A, Dretzke J, Fry-Smith A, *et al*.

No. 21
Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation.
By Wright M, Grieve R, Roberts J, Main J, Thomas HC on behalf of the UK Mild Hepatitis C Trial Investigators.

No. 22
Pressure relieving support surfaces: a randomised evaluation.
By Nixon J, Nelson EA, Cranny G, Iglesias CP, Hawkins K, Cullum NA, *et al*.

No. 23
A systematic review and economic model of the effectiveness and cost-effectiveness of methylphenidate, dexamfetamine and atomoxetine for the treatment of attention deficit hyperactivity disorder in children and adolescents.
By King S, Griffin S, Hodges Z, Weatherly H, Asseburg C, Richardson G, *et al*.

No. 24
The clinical effectiveness and cost-effectiveness of enzyme replacement therapy for Gaucher's disease: a systematic review.
By Connock M, Burls A, Frew E, Fry-Smith A, Juarez-Garcia A, McCabe C, *et al*.

No. 25
Effectiveness and cost-effectiveness of salicylic acid and cryotherapy for cutaneous warts. An economic decision model.
By Thomas KS, Keogh-Brown MR, Chalmers JR, Fordham RJ, Holland RC, Armstrong SJ, *et al*.

No. 26
A systematic literature review of the effectiveness of non-pharmacological interventions to prevent wandering in dementia and evaluation of the ethical implications and acceptability of their use.
By Robinson L, Hutchings D, Corner L, Beyer F, Dickinson H, Vanoli A, *et al*.

No. 27
A review of the evidence on the effects and costs of implantable cardioverter defibrillator therapy in different patient groups, and modelling of cost-effectiveness and cost–utility for these groups in a UK context.
By Buxton M, Caine N, Chase D, Connelly D, Grace A, Jackson C, *et al*.

No. 28
Adefovir dipivoxil and pegylated interferon alfa-2a for the treatment of chronic hepatitis B: a systematic review and economic evaluation.
By Shepherd J, Jones J, Takeda A, Davidson P, Price A.

No. 29
An evaluation of the clinical and cost-effectiveness of pulmonary artery catheters in patient management in intensive care: a systematic review and a randomised controlled trial.
By Harvey S, Stevens K, Harrison D, Young D, Brampton W, McCabe C, *et al*.

No. 30
Accurate, practical and cost-effective assessment of carotid stenosis in the UK.
By Wardlaw JM, Chappell FM, Stevenson M, De Nigris E, Thomas S, Gillard J, *et al*.

No. 31
Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review and economic evaluation.
By Woolacott N, Bravo Vergel Y, Hawkins N, Kainth A, Khadjesari Z, Misso K, *et al*.

No. 32
The cost-effectiveness of testing for hepatitis C in former injecting drug users.
By Castelnuovo E, Thompson-Coon J, Pitt M, Cramp M, Siebert U, Price A, *et al*.

No. 33
Computerised cognitive behaviour therapy for depression and anxiety update: a systematic review and economic evaluation.
By Kaltenthaler E, Brazier J, De Nigris E, Tumur I, Ferriter M, Beverley C, *et al*.

No. 34
Cost-effectiveness of using prognostic information to select women with breast cancer for adjuvant systemic therapy.
By Williams C, Brunskill S, Altman D, Briggs A, Campbell H, Clarke M, *et al*.

No. 35
Psychological therapies including dialectical behaviour therapy for borderline personality disorder: a systematic review and preliminary economic evaluation.
By Brazier J, Tumur I, Holmes M, Ferriter M, Parry G, Dent-Brown K, *et al*.

No. 36
Clinical effectiveness and cost-effectiveness of tests for the diagnosis and investigation of urinary tract infection in children: a systematic review and economic model.
By Whiting P, Westwood M, Bojke L, Palmer S, Richardson G, Cooper J, *et al*.

No. 37
Cognitive behavioural therapy in chronic fatigue syndrome: a randomised controlled trial of an outpatient group programme.
By O'Dowd H, Gladwell P, Rogers CA, Hollinghurst S, Gregory A.

No. 38
A comparison of the cost-effectiveness of five strategies for the prevention of non-steroidal anti-inflammatory drug-induced gastrointestinal toxicity: a systematic review with economic modelling.
By Brown TJ, Hooper L, Elliott RA, Payne K, Webb R, Roberts C, *et al*.

No. 39
The effectiveness and cost-effectiveness of computed tomography screening for coronary artery disease: systematic review.
By Waugh N, Black C, Walker S, McIntyre L, Cummins E, Hillis G.

No. 40
What are the clinical outcome and cost-effectiveness of endoscopy undertaken by nurses when compared with doctors? A Multi-Institution Nurse Endoscopy Trial (MINuET).
By Williams J, Russell I, Durai D, Cheung W-Y, Farrin A, Bloor K, *et al*.

No. 41
The clinical and cost-effectiveness of oxaliplatin and capecitabine for the adjuvant treatment of colon cancer: systematic review and economic evaluation.
By Pandor A, Eggington S, Paisley S, Tappenden P, Sutcliffe P.

No. 42
A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness.
By Chen Y-F, Jobanputra P, Barton P, Jowett S, Bryan S, Clark W, *et al*.

No. 43
Telemedicine in dermatology: a randomised controlled trial.
By Bowns IR, Collins K, Walters SJ, McDonagh AJG.

No. 44
Cost-effectiveness of cell salvage and alternative methods of minimising perioperative allogeneic blood transfusion: a systematic review and economic model.
By Davies L, Brown TJ, Haynes S, Payne K, Elliott RA, McCollum C.

No. 45
Clinical effectiveness and cost-effectiveness of laparoscopic surgery for colorectal cancer: systematic reviews and economic evaluation.
By Murray A, Lourenco T, de Verteuil R, Hernandez R, Fraser C, McKinley A, *et al*.

No. 46
Etanercept and efalizumab for the treatment of psoriasis: a systematic review.
By Woolacott N, Hawkins N, Mason A, Kainth A, Khadjesari Z, Bravo Vergel Y, *et al*.

No. 47
Systematic reviews of clinical decision tools for acute abdominal pain.
By Liu JLY, Wyatt JC, Deeks JJ, Clamp S, Keen J, Verde P, *et al*.

No. 48
Evaluation of the ventricular assist device programme in the UK.
By Sharples L, Buxton M, Caine N, Cafferty F, Demiris N, Dyer M, *et al*.

No. 49
A systematic review and economic model of the clinical and cost-effectiveness of immunosuppressive therapy for renal transplantation in children.
By Yao G, Albon E, Adi Y, Milford D, Bayliss S, Ready A, *et al*.

No. 50
Amniocentesis results: investigation of anxiety. The ARIA trial.
By Hewison J, Nixon J, Fountain J, Cocks K, Jones C, Mason G, *et al*.

Volume 11, 2007

No. 1
Pemetrexed disodium for the treatment of malignant pleural mesothelioma: a systematic review and economic evaluation.
By Dundar Y, Bagust A, Dickson R, Dodd S, Green J, Haycox A, *et al*.

No. 2
A systematic review and economic model of the clinical effectiveness and cost-effectiveness of docetaxel in combination with prednisone or prednisolone for the treatment of hormone-refractory metastatic prostate cancer.
By Collins R, Fenwick E, Trowman R, Perard R, Norman G, Light K, *et al*.

No. 3
A systematic review of rapid diagnostic tests for the detection of tuberculosis infection.
By Dinnes J, Deeks J, Kunst H, Gibson A, Cummins E, Waugh N, *et al*.

No. 4
The clinical effectiveness and cost-effectiveness of strontium ranelate for the prevention of osteoporotic fragility fractures in postmenopausal women.
By Stevenson M, Davis S, Lloyd-Jones M, Beverley C.

No. 5
A systematic review of quantitative and qualitative research on the role and effectiveness of written information available to patients about individual medicines.
By Raynor DK, Blenkinsopp A, Knapp P, Grime J, Nicolson DJ, Pollock K, *et al*.

No. 6
Oral naltrexone as a treatment for relapse prevention in formerly opioid-dependent drug users: a systematic review and economic evaluation.
By Adi Y, Juarez-Garcia A, Wang D, Jowett S, Frew E, Day E, *et al*.

No. 7
Glucocorticoid-induced osteoporosis: a systematic review and cost–utility analysis.
By Kanis JA, Stevenson M, McCloskey EV, Davis S, Lloyd-Jones M.

No. 8
Epidemiological, social, diagnostic and economic evaluation of population screening for genital chlamydial infection.
By Low N, McCarthy A, Macleod J, Salisbury C, Campbell R, Roberts TE, *et al*.

No. 9
Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation.
By Connock M, Juarez-Garcia A, Jowett S, Frew E, Liu Z, Taylor RJ, *et al*.

No. 10
Exercise Evaluation Randomised Trial (EXERT): a randomised trial comparing GP referral for leisure centre-based exercise, community-based walking and advice only.
By Isaacs AJ, Critchley JA, See Tai S, Buckingham K, Westley D, Harridge SDR, *et al*.

No. 11
Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation.
By Shepherd J, Jones J, Hartwell D, Davidson P, Price A, Waugh N.

No. 12
Systematic review and economic evaluation of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer.
By Tappenden P, Jones R, Paisley S, Carroll C.

No. 13
A systematic review and economic evaluation of epoetin alfa, epoetin beta and darbepoetin alfa in anaemia associated with cancer, especially that attributable to cancer treatment.
By Wilson J, Yao GL, Raftery J, Bohlius J, Brunskill S, Sandercock J, *et al*.

No. 14
A systematic review and economic evaluation of statins for the prevention of coronary events.
By Ward S, Lloyd Jones M, Pandor A, Holmes M, Ara R, Ryan A, *et al*.

No. 15
A systematic review of the effectiveness and cost-effectiveness of different models of community-based respite care for frail older people and their carers.
By Mason A, Weatherly H, Spilsbury K, Arksey H, Golder S, Adamson J, *et al*.

No. 16
Additional therapy for young children with spastic cerebral palsy: a randomised controlled trial.
By Weindling AM, Cunningham CC, Glenn SM, Edwards RT, Reeves DJ.

No. 17
Screening for type 2 diabetes: literature review and economic modelling.
By Waugh N, Scotland G, McNamee P, Gillett M, Brennan A, Goyder E, *et al*.

No. 18
The effectiveness and cost-effectiveness of cinacalcet for secondary hyperparathyroidism in end-stage renal disease patients on dialysis: a systematic review and economic evaluation.
By Garside R, Pitt M, Anderson R, Mealing S, Roome C, Snaith A, *et al*.

No. 19
The clinical effectiveness and cost-effectiveness of gemcitabine for metastatic breast cancer: a systematic review and economic evaluation.
By Takeda AL, Jones J, Loveman E, Tan SC, Clegg AJ.

No. 20
A systematic review of duplex ultrasound, magnetic resonance angiography and computed tomography angiography for the diagnosis and assessment of symptomatic, lower limb peripheral arterial disease.
By Collins R, Cranny G, Burch J, Aguiar-Ibáñez R, Craig D, Wright K, *et al*.

No. 21
The clinical effectiveness and cost-effectiveness of treatments for children with idiopathic steroid-resistant nephrotic syndrome: a systematic review.
By Colquitt JL, Kirby J, Green C, Cooper K, Trompeter RS.

No. 22
A systematic review of the routine monitoring of growth in children of primary school age to identify growth-related conditions.
By Fayter D, Nixon J, Hartley S, Rithalia A, Butler G, Rudolf M, *et al*.

No. 23
Systematic review of the effectiveness of preventing and treating *Staphylococcus aureus* carriage in reducing peritoneal catheter-related infections.
By McCormack K, Rabindranath K, Kilonzo M, Vale L, Fraser C, McIntyre L, *et al*.

No. 24
The clinical effectiveness and cost of repetitive transcranial magnetic stimulation versus electroconvulsive therapy in severe depression: a multicentre pragmatic randomised controlled trial and economic analysis.
By McLoughlin DM, Mogg A, Eranti S, Pluck G, Purvis R, Edwards D, *et al*.

No. 25
A randomised controlled trial and economic evaluation of direct versus indirect and individual versus group modes of speech and language therapy for children with primary language impairment.
By Boyle J, McCartney E, Forbes J, O'Hare A.

No. 26
Hormonal therapies for early breast cancer: systematic review and economic evaluation.
By Hind D, Ward S, De Nigris E, Simpson E, Carroll C, Wyld L.

No. 27
Cardioprotection against the toxic effects of anthracyclines given to children with cancer: a systematic review.
By Bryant J, Picot J, Levitt G, Sullivan I, Baxter L, Clegg A.

No. 28
Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systematic review and economic evaluation.
By McLeod C, Bagust A, Boland A, Dagenais P, Dickson R, Dundar Y, *et al*.

No. 29
Prenatal screening and treatment strategies to prevent group B streptococcal and other bacterial infections in early infancy: cost-effectiveness and expected value of information analyses.
By Colbourn T, Asseburg C, Bojke L, Philips Z, Claxton K, Ades AE, *et al*.

No. 30
Clinical effectiveness and cost-effectiveness of bone morphogenetic proteins in the non-healing of fractures and spinal fusion: a systematic review.
By Garrison KR, Donell S, Ryder J, Shemilt I, Mugford M, Harvey I, *et al*.

No. 31
A randomised controlled trial of postoperative radiotherapy following breast-conserving surgery in a minimum-risk older population. The PRIME trial.
By Prescott RJ, Kunkler IH, Williams LJ, King CC, Jack W, van der Pol M, *et al*.

No. 32
Current practice, accuracy, effectiveness and cost-effectiveness of the school entry hearing screen.
By Bamford J, Fortnum H, Bristow K, Smith J, Vamvakas G, Davies L, *et al*.

No. 33
The clinical effectiveness and cost-effectiveness of inhaled insulin in diabetes mellitus: a systematic review and economic evaluation.
By Black C, Cummins E, Royle P, Philip S, Waugh N.

No. 34
Surveillance of cirrhosis for hepatocellular carcinoma: systematic review and economic analysis.
By Thompson Coon J, Rogers G, Hewson P, Wright D, Anderson R, Cramp M, *et al*.

No. 35
The Birmingham Rehabilitation Uptake Maximisation Study (BRUM). Home-based compared with hospital-based cardiac rehabilitation in a multi-ethnic population: cost-effectiveness and patient adherence.
By Jolly K, Taylor R, Lip GYH, Greenfield S, Raftery J, Mant J, *et al*.

No. 36
A systematic review of the clinical, public health and cost-effectiveness of rapid diagnostic tests for the detection and identification of bacterial intestinal pathogens in faeces and food.
By Abubakar I, Irvine L, Aldus CF, Wyatt GM, Fordham R, Schelenz S, *et al*.

No. 37
A randomised controlled trial examining the longer-term outcomes of standard versus new antiepileptic drugs. The SANAD trial.
By Marson AG, Appleton R, Baker GA, Chadwick DW, Doughty J, Eaton B, *et al*.

No. 38
Clinical effectiveness and cost-effectiveness of different models of managing long-term oral anticoagulation therapy: a systematic review and economic modelling.
By Connock M, Stevens C, Fry-Smith A, Jowett S, Fitzmaurice D, Moore D, *et al*.

No. 39
A systematic review and economic model of the clinical effectiveness and cost-effectiveness of interventions for preventing relapse in people with bipolar disorder.
By Soares-Weiser K, Bravo Vergel Y, Beynon S, Dunn G, Barbieri M, Duffy S, *et al*.

No. 40
Taxanes for the adjuvant treatment of early breast cancer: systematic review and economic evaluation.
By Ward S, Simpson E, Davis S, Hind D, Rees A, Wilkinson A.

No. 41
The clinical effectiveness and cost-effectiveness of screening for open angle glaucoma: a systematic review and economic evaluation.
By Burr JM, Mowatt G, Hernández R, Siddiqui MAR, Cook J, Lourenco T, *et al*.

No. 42
Acceptability, benefit and costs of early screening for hearing disability: a study of potential screening tests and models.
By Davis A, Smith P, Ferguson M, Stephens D, Gianopoulos I.

No. 43
Contamination in trials of educational interventions.
By Keogh-Brown MR, Bachmann MO, Shepstone L, Hewitt C, Howe A, Ramsay CR, *et al*.

No. 44
Overview of the clinical effectiveness of positron emission tomography imaging in selected cancers.
By Facey K, Bradbury I, Laking G, Payne E.

No. 45
The effectiveness and cost-effectiveness of carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma: a systematic review and economic evaluation.
By Garside R, Pitt M, Anderson R, Rogers G, Dyer M, Mealing S, *et al*.

No. 46
Drug-eluting stents: a systematic review and economic evaluation.
By Hill RA, Boland A, Dickson R, Dündar Y, Haycox A, McLeod C, *et al*.

No. 47
The clinical effectiveness and cost-effectiveness of cardiac resynchronisation (biventricular pacing) for heart failure: systematic review and economic model.
By Fox M, Mealing S, Anderson R, Dean J, Stein K, Price A, *et al*.

No. 48
Recruitment to randomised trials: strategies for trial enrolment and participation study. The STEPS study.
By Campbell MK, Snowdon C, Francis D, Elbourne D, McDonald AM, Knight R, *et al*.

No. 49
Cost-effectiveness of functional cardiac testing in the diagnosis and management of coronary artery disease: a randomised controlled trial. The CECaT trial.
By Sharples L, Hughes V, Crean A, Dyer M, Buxton M, Goldsmith K, *et al*.

No. 50
Evaluation of diagnostic tests when there is no gold standard. A review of methods.
By Rutjes AWS, Reitsma JB, Coomarasamy A, Khan KS, Bossuyt PMM.

No. 51
Systematic reviews of the clinical effectiveness and cost-effectiveness of proton pump inhibitors in acute upper gastrointestinal bleeding.
By Leontiadis GI, Sreedharan A, Dorward S, Barton P, Delaney B, Howden CW, *et al*.

No. 52
A review and critique of modelling in prioritising and designing screening programmes.
By Karnon J, Goyder E, Tappenden P, McPhie S, Towers I, Brazier J, *et al*.

No. 53
An assessment of the impact of the NHS Health Technology Assessment Programme.
By Hanney S, Buxton M, Green C, Coulson D, Raftery J.

Volume 12, 2008

No. 1
A systematic review and economic model of switching from non-glycopeptide to glycopeptide antibiotic prophylaxis for surgery.
By Cranny G, Elliott R, Weatherly H, Chambers D, Hawkins N, Myers L, *et al*.

No. 2
'Cut down to quit' with nicotine replacement therapies in smoking cessation: a systematic review of effectiveness and economic analysis.
By Wang D, Connock M, Barton P, Fry-Smith A, Aveyard P, Moore D.

No. 3
A systematic review of the effectiveness of strategies for reducing fracture risk in children with juvenile idiopathic arthritis with additional data on long-term risk of fracture and cost of disease management.
By Thornton J, Ashcroft D, O'Neill T, Elliott R, Adams J, Roberts C, *et al*.

No. 4
Does befriending by trained lay workers improve psychological well-being and quality of life for carers of people with dementia, and at what cost? A randomised controlled trial.
By Charlesworth G, Shepstone L, Wilson E, Thalanany M, Mugford M, Poland F.

No. 5
A multi-centre retrospective cohort study comparing the efficacy, safety and cost-effectiveness of hysterectomy and uterine artery embolisation for the treatment of symptomatic uterine fibroids. The HOPEFUL study.
By Hirst A, Dutton S, Wu O, Briggs A, Edwards C, Waldenmaier L, *et al*.

No. 6
Methods of prediction and prevention of pre-eclampsia: systematic reviews of accuracy and effectiveness literature with economic modelling.
By Meads CA, Cnossen JS, Meher S, Juarez-Garcia A, ter Riet G, Duley L, *et al*.

No. 7
The use of economic evaluations in NHS decision-making: a review and empirical investigation.
By Williams I, McIver S, Moore D, Bryan S.

No. 8
Stapled haemorrhoidectomy (haemorrhoidopexy) for the treatment of haemorrhoids: a systematic review and economic evaluation.
By Burch J, Epstein D, Baba-Akbari A, Weatherly H, Fox D, Golder S, *et al*.

No. 9
The clinical effectiveness of diabetes education models for Type 2 diabetes: a systematic review.
By Loveman E, Frampton GK, Clegg AJ.

No. 10
Payment to healthcare professionals for patient recruitment to trials: systematic review and qualitative study.
By Raftery J, Bryant J, Powell J, Kerr C, Hawker S.

No. 11
Cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for osteoarthritis and rheumatoid arthritis: a systematic review and economic evaluation.
By Chen Y-F, Jobanputra P, Barton P, Bryan S, Fry-Smith A, Harris G, *et al*.

No. 12
The clinical effectiveness and cost-effectiveness of central venous catheters treated with anti-infective agents in preventing bloodstream infections: a systematic review and economic evaluation.
By Hockenhull JC, Dwan K, Boland A, Smith G, Bagust A, Dündar Y, *et al*.

No. 13
Stepped treatment of older adults on laxatives. The STOOL trial.
By Mihaylov S, Stark C, McColl E, Steen N, Vanoli A, Rubin G, *et al*.

No. 14
A randomised controlled trial of cognitive behaviour therapy in adolescents with major depression treated by selective serotonin reuptake inhibitors. The ADAPT trial.
By Goodyer IM, Dubicka B, Wilkinson P, Kelvin R, Roberts C, Byford S, *et al*.

No. 15
The use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer: systematic review and economic evaluation.
By Hind D, Tappenden P, Tumur I, Eggington E, Sutcliffe P, Ryan A.

No. 16
Ranibizumab and pegaptanib for the treatment of age-related macular degeneration: a systematic review and economic evaluation.
By Colquitt JL, Jones J, Tan SC, Takeda A, Clegg AJ, Price A.

No. 17
Systematic review of the clinical effectiveness and cost-effectiveness of 64-slice or higher computed tomography angiography as an alternative to invasive coronary angiography in the investigation of coronary artery disease.
By Mowatt G, Cummins E, Waugh N, Walker S, Cook J, Jia X, *et al*.

No. 18
Structural neuroimaging in psychosis: a systematic review and economic evaluation.
By Albon E, Tsourapas A, Frew E, Davenport C, Oyebode F, Bayliss S, *et al*.

No. 19
Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta$_2$ agonists for the treatment of chronic asthma in adults and children aged 12 years and over.
By Shepherd J, Rogers G, Anderson R, Main C, Thompson-Coon J, Hartwell D, *et al*.

No. 20
Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta$_2$ agonists for the treatment of chronic asthma in children under the age of 12 years.
By Main C, Shepherd J, Anderson R, Rogers G, Thompson-Coon J, Liu Z, *et al*.

No. 21
Ezetimibe for the treatment of hypercholesterolaemia: a systematic review and economic evaluation.
By Ara R, Tumur I, Pandor A, Duenas A, Williams R, Wilkinson A, *et al*.

Health Technology Assessment Programme

Prioritisation Strategy Group

Members

HTA Commissioning Board

Members

Current and past membership details of all HTA 'committees' are available from the HTA website (www.hta.ac.uk)

Diagnostic Technologies & Screening Panel

Members

Chair,
Dr Ron Zimmern, Director of the Public Health Genetics Unit, Strangeways Research Laboratories, Cambridge

Ms Norma Armston, Freelance Consumer Advocate, Bolton

Professor Max Bachmann, Professor of Health Care Interfaces, Department of Health Policy and Practice, University of East Anglia

Professor Rudy Bilous Professor of Clinical Medicine & Consultant Physician, The Academic Centre, South Tees Hospitals NHS Trust

Ms Dea Birkett, Service User Representative, London

Dr Paul Cockcroft, Consultant Medical Microbiologist and Clinical Director of Pathology, Department of Clinical Microbiology, St Mary's Hospital, Portsmouth

Professor Adrian K Dixon, Professor of Radiology, University Department of Radiology, University of Cambridge Clinical School

Dr David Elliman, Consultant in Community Child Health, Islington PCT & Great Ormond Street Hospital, London

Professor Glyn Elwyn, Research Chair, Centre for Health Sciences Research, Cardiff University, Department of General Practice, Cardiff

Professor Paul Glasziou, Director, Centre for Evidence-Based Practice, University of Oxford

Dr Jennifer J Kurinczuk, Consultant Clinical Epidemiologist, National Perinatal Epidemiology Unit, Oxford

Dr Susanne M Ludgate, Clinical Director, Medicines & Healthcare Products Regulatory Agency, London

Mr Stephen Pilling, Director, Centre for Outcomes, Research & Effectiveness, Joint Director, National Collaborating Centre for Mental Health, University College London

Mrs Una Rennard, Service User Representative, Oxford

Dr Phil Shackley, Senior Lecturer in Health Economics, Academic Vascular Unit, University of Sheffield

Dr Margaret Somerville, Director of Public Health Learning, Peninsula Medical School, University of Plymouth

Dr Graham Taylor, Scientific Director & Senior Lecturer, Regional DNA Laboratory, The Leeds Teaching Hospitals

Professor Lindsay Wilson Turnbull, Scientific Director, Centre for MR Investigations & YCR Professor of Radiology, University of Hull

Professor Martin J Whittle, Clinical Co-director, National Co-ordinating Centre for Women's and Childhealth

Dr Dennis Wright, Consultant Biochemist & Clinical Director, The North West London Hospitals NHS Trust, Middlesex

Pharmaceuticals Panel

Members

Chair,
Professor Robin Ferner, Consultant Physician and Director, West Midlands Centre for Adverse Drug Reactions, City Hospital NHS Trust, Birmingham

Ms Anne Baileff, Consultant Nurse in First Contact Care, Southampton City Primary Care Trust, University of Southampton

Professor Imti Choonara, Professor in Child Health, Academic Division of Child Health, University of Nottingham

Professor John Geddes, Professor of Epidemiological Psychiatry, University of Oxford

Mrs Barbara Greggains, Non-Executive Director, Greggains Management Ltd

Dr Bill Gutteridge, Medical Adviser, National Specialist Commissioning Advisory Group (NSCAG), London

Mrs Sharon Hart, Consultant Pharmaceutical Adviser, Reading

Dr Jonathan Karnon, Senior Research Fellow, Health Economics and Decision Science, University of Sheffield

Dr Yoon Loke, Senior Lecturer in Clinical Pharmacology, University of East Anglia

Ms Barbara Meredith, Lay Member, Epsom

Dr Andrew Prentice, Senior Lecturer and Consultant Obstetrician & Gynaecologist, Department of Obstetrics & Gynaecology, University of Cambridge

Dr Frances Rotblat, CPMP Delegate, Medicines & Healthcare Products Regulatory Agency, London

Dr Martin Shelly, General Practitioner, Leeds

Mrs Katrina Simister, Assistant Director New Medicines, National Prescribing Centre, Liverpool

Dr Richard Tiner, Medical Director, Medical Department, Association of the British Pharmaceutical Industry, London

Therapeutic Procedures Panel

Members

Chair,
Professor Bruce Campbell, Consultant Vascular and General Surgeon, Department of Surgery, Royal Devon & Exeter Hospital

Dr Mahmood Adil, Deputy Regional Director of Public Health, Department of Health, Manchester

Dr Aileen Clarke, Consultant in Public Health, Public Health Resource Unit, Oxford

Professor Matthew Cooke, Professor of Emergency Medicine, Warwick Emergency Care and Rehabilitation, University of Warwick

Mr Mark Emberton, Senior Lecturer in Oncological Urology, Institute of Urology, University College Hospital

Professor Paul Gregg, Professor of Orthopaedic Surgical Science, Department of General Practice and Primary Care, South Tees Hospital NHS Trust, Middlesbrough

Ms Maryann L Hardy, Lecturer, Division of Radiography, University of Bradford

Dr Simon de Lusignan, Senior Lecturer, Primary Care Informatics, Department of Community Health Sciences, St George's Hospital Medical School, London

Dr Peter Martin, Consultant Neurologist, Addenbrooke's Hospital, Cambridge

Professor Neil McIntosh, Edward Clark Professor of Child Life & Health, Department of Child Life & Health, University of Edinburgh

Professor Jim Neilson, Professor of Obstetrics and Gynaecology, Department of Obstetrics and Gynaecology, University of Liverpool

Dr John C Pounsford, Consultant Physician, Directorate of Medical Services, North Bristol NHS Trust

Dr Karen Roberts, Nurse Consultant, Queen Elizabeth Hospital, Gateshead

Dr Vimal Sharma, Consultant Psychiatrist/Hon. Senior Lecturer, Mental Health Resource Centre, Cheshire and Wirral Partnership NHS Trust, Wallasey

Professor Scott Weich, Professor of Psychiatry, Division of Health in the Community, University of Warwick

Disease Prevention Panel

Members

Chair,
Dr Edmund Jessop, Medical Adviser, National Specialist Commissioning Advisory Group (NSCAG), London

Mrs Sheila Clark, Chief Executive, St James's Hospital, Portsmouth

Mr Richard Copeland, Lead Pharmacist: Clinical Economy/Interface, Wansbeck General Hospital, Northumberland

Dr Elizabeth Fellow-Smith, Medical Director, West London Mental Health Trust, Middlesex

Mr Ian Flack, Director PPI Forum Support, Council of Ethnic Minority Voluntary Sector Organisations, Stratford

Dr John Jackson, General Practitioner, Newcastle upon Tyne

Mrs Veronica James, Chief Officer, Horsham District Age Concern, Horsham

Professor Mike Kelly, Director, Centre for Public Health Excellence, National Institute for Health and Clinical Excellence, London

Professor Yi Mien Koh, Director of Public Health and Medical Director, London NHS (North West London Strategic Health Authority), London

Ms Jeanett Martin, Director of Clinical Leadership & Quality, Lewisham PCT, London

Dr Chris McCall, General Practitioner, Dorset

Dr David Pencheon, Director, Eastern Region Public Health Observatory, Cambridge

Dr Ken Stein, Senior Clinical Lecturer in Public Health, Director, Peninsula Technology Assessment Group, University of Exeter, Exeter

Dr Carol Tannahill, Director, Glasgow Centre for Population Health, Glasgow

Professor Margaret Thorogood, Professor of Epidemiology, University of Warwick, Coventry

Dr Ewan Wilkinson, Consultant in Public Health, Royal Liverpool University Hospital, Liverpool

Expert Advisory Network

Members

Professor Douglas Altman, Professor of Statistics in Medicine, Centre for Statistics in Medicine, University of Oxford

Professor John Bond, Director, Centre for Health Services Research, University of Newcastle upon Tyne, School of Population & Health Sciences, Newcastle upon Tyne

Professor Andrew Bradbury, Professor of Vascular Surgery, Solihull Hospital, Birmingham

Mr Shaun Brogan, Chief Executive, Ridgeway Primary Care Group, Aylesbury

Mrs Stella Burnside OBE, Chief Executive, Regulation and Improvement Authority, Belfast

Ms Tracy Bury, Project Manager, World Confederation for Physical Therapy, London

Professor Iain T Cameron, Professor of Obstetrics and Gynaecology and Head of the School of Medicine, University of Southampton

Dr Christine Clark, Medical Writer & Consultant Pharmacist, Rossendale

Professor Collette Clifford, Professor of Nursing & Head of Research, School of Health Sciences, University of Birmingham, Edgbaston, Birmingham

Professor Barry Cookson, Director, Laboratory of Healthcare Associated Infection, Health Protection Agency, London

Dr Carl Counsell, Clinical Senior Lecturer in Neurology, Department of Medicine & Therapeutics, University of Aberdeen

Professor Howard Cuckle, Professor of Reproductive Epidemiology, Department of Paediatrics, Obstetrics & Gynaecology, University of Leeds

Dr Katherine Darton, Information Unit, MIND – The Mental Health Charity, London

Professor Carol Dezateux, Professor of Paediatric Epidemiology, London

Dr Keith Dodd, Consultant Paediatrician, Derby

Mr John Dunning, Consultant Cardiothoracic Surgeon, Cardiothoracic Surgical Unit, Papworth Hospital NHS Trust, Cambridge

Mr Jonothan Earnshaw, Consultant Vascular Surgeon, Gloucestershire Royal Hospital, Gloucester

Professor Martin Eccles, Professor of Clinical Effectiveness, Centre for Health Services Research, University of Newcastle upon Tyne

Professor Pam Enderby, Professor of Community Rehabilitation, Institute of General Practice and Primary Care, University of Sheffield

Professor Gene Feder, Professor of Primary Care Research & Development, Centre for Health Sciences, Barts & The London Queen Mary's School of Medicine & Dentistry, London

Mr Leonard R Fenwick, Chief Executive, Newcastle upon Tyne Hospitals NHS Trust

Mrs Gillian Fletcher, Antenatal Teacher & Tutor and President, National Childbirth Trust, Henfield

Professor Jayne Franklyn, Professor of Medicine, Department of Medicine, University of Birmingham, Queen Elizabeth Hospital, Edgbaston, Birmingham

Dr Neville Goodman, Consultant Anaesthetist, Southmead Hospital, Bristol

Professor Robert E Hawkins, CRC Professor and Director of Medical Oncology, Christie CRC Research Centre, Christie Hospital NHS Trust, Manchester

Professor Allen Hutchinson, Director of Public Health & Deputy Dean of ScHARR, Department of Public Health, University of Sheffield

Professor Peter Jones, Professor of Psychiatry, University of Cambridge, Cambridge

Professor Stan Kaye, Cancer Research UK Professor of Medical Oncology, Section of Medicine, Royal Marsden Hospital & Institute of Cancer Research, Surrey

Dr Duncan Keeley, General Practitioner (Dr Burch & Ptnrs), The Health Centre, Thame

Dr Donna Lamping, Research Degrees Programme Director & Reader in Psychology, Health Services Research Unit, London School of Hygiene and Tropical Medicine, London

Mr George Levvy, Chief Executive, Motor Neurone Disease Association, Northampton

Professor James Lindesay, Professor of Psychiatry for the Elderly, University of Leicester, Leicester General Hospital

Professor Julian Little, Professor of Human Genome Epidemiology, Department of Epidemiology & Community Medicine, University of Ottawa

Professor Rajan Madhok, Consultant in Public Health, South Manchester Primary Care Trust, Manchester

Professor Alexander Markham, Director, Molecular Medicine Unit, St James's University Hospital, Leeds

Professor Alistaire McGuire, Professor of Health Economics, London School of Economics

Dr Peter Moore, Freelance Science Writer, Ashtead

Dr Andrew Mortimore, Public Health Director, Southampton City Primary Care Trust, Southampton

Dr Sue Moss, Associate Director, Cancer Screening Evaluation Unit, Institute of Cancer Research, Sutton

Mrs Julietta Patnick, Director, NHS Cancer Screening Programmes, Sheffield

Professor Robert Peveler, Professor of Liaison Psychiatry, Royal South Hants Hospital, Southampton

Professor Chris Price, Visiting Professor in Clinical Biochemistry, University of Oxford

Professor William Rosenberg, Professor of Hepatology and Consultant Physician, University of Southampton, Southampton

Professor Peter Sandercock, Professor of Medical Neurology, Department of Clinical Neurosciences, University of Edinburgh

Dr Susan Schonfield, Consultant in Public Health, Hillingdon PCT, Middlesex

Dr Eamonn Sheridan, Consultant in Clinical Genetics, Genetics Department, St James's University Hospital, Leeds

Professor Sarah Stewart-Brown, Professor of Public Health, University of Warwick, Division of Health in the Community Warwick Medical School, LWMS, Coventry

Professor Ala Szczepura, Professor of Health Service Research, Centre for Health Services Studies, University of Warwick

Dr Ross Taylor, Senior Lecturer, Department of General Practice and Primary Care, University of Aberdeen

Mrs Joan Webster, Consumer member, HTA – Expert Advisory Network

Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

The National Coordinating Centre for Health Technology Assessment,
Alpha House, Enterprise Road
Southampton Science Park
Chilworth
Southampton SO16 7NS, UK.
Fax: +44 (0) 23 8059 5639 Email: hta@hta.ac.uk
http://www.hta.ac.uk

ISSN 1366-5278