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Title: Ezetimibe for the treatment of hypercholesterolaemia

Produced by The University of Sheffield, School of Health and Related Research (ScHARR)

Authors Roberta Ara, Operational Research Analyst
Indra Tumur, Research Fellow
Abdullah Pandor, Research Fellow
Alejandra Duenas, Research Associate
Robert Williams, Placement Student
Anna Wilkinson, Information Officer
Suzy Paisley, Research Scientist
Jim Chilcott, Technical Director, ScHARR TAG

Correspondence to

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Contributions of authors

Abdullah Pandor and Indra Tumur carried out the review of the background information and the clinical effectiveness review. Roberta Ara, Alejandra Duenas, Robert Williams and Jim Chilcott carried out the cost effectiveness review. Anna Wilkinson and Suzy Paisley undertook the electronic literature searches. Rachel German, Suzy Paisley and Jim Chilcott investigated the role of problem structuring methods in the assessment.

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1. DEFINITION OF TERMS 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.

DEFINITION OF TERMS

Acute coronary syndrome	Symptoms compatible with acute myocardial ischaemia (primarily unstable angina or MI)
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
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 of time (usually 15 minutes).
Anorexia nervosa	An eating disorder characterized by low body weight (less than 85 percent 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 narrow 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
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 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 characterized 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 number of genes combined with dietary and other factors
Premature death	Death before the age of 75
Primary (familial) hypercholesterolaemia	High cholesterol level caused by 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 characterized 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	Total cholesterol is 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's stored in the fat tissue to be used as energy.

LIST OF ABBREVIATIONS

ACS	Acute Coronary Syndromes
ALT	Alanin aminotranspherase
AST	Aspartat aminotranspherase
BMI	Body mass index
CAD	Coronary artery disease
CHD	Coronary heart disease
CI	Confidence interval
CK or CPK	Creatine kinase (CK) or creatine phosphokinase (CPK)
CV	Cardiovascular
CVD	Cardiovascular disease
DM	Diabetes Mellitus
HDL-c	High-density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolaemia
HIV	Human immunodeficiency virus
HRQoL	Health Related Quality of Life
ICER	Incremental cost utility ratio
IHD	Ischemic Heart Disease
LDL-c	Low-density lipoprotein cholesterol
LYG	Life years gained
MI	Myocardial infarction
MSD/SP	Merck Sharp and Dohme Limited/Schering-Plough Limited
OR	Operational Research
PSM	Problem structuring methods
QALY	Quality adjusted life year
QoL	Quality of life
QUOROM	Quality Of Reporting Of Meta-analyses
RR	Relative risk
SA	Stable angina
Str	Stroke
TG	Triglycerides
TIA	Transient ischaemic attack
Total-c	Total cholesterol
RCT	Randomised controlled trial
RR	Relative risk
UKPDS	The United Kingdom Prospective Diabetes Study
UA	Unstable angina
VLDL-c	Very low-density lipoprotein cholesterol

2. EXECUTIVE SUMMARY

Background

Cardiovascular disease (CVD) is a disease of the heart and blood vessels, which can lead to cardiovascular events such as myocardial infarction (MI), angina (chest pain) and stroke. The most common form of CVD is coronary heart disease (CHD). Other forms of CVD are stroke, transient ischaemic attack and peripheral arterial disease. CVD is the most common cause of death in the UK, accounting for 216,000 deaths in 2004 (nearly half of these were from CHD and about a quarter from stroke) and is a major cause of illness, disability and reduced quality of life.

High levels of cholesterol in the blood (hypercholesterolaemia) are associated with an increased risk of CHD and stroke. The UK population has one of the highest average serum cholesterol levels in the world, with about 27% and 70% of people having a serum cholesterol level $\geq$ 6.5 mmol/L and $\geq$ 5.0 mmol/L, respectively. Serum cholesterol is an important determinant of cardiovascular risk. Lowering concentration of total cholesterol (Total-c) and low-density lipoprotein cholesterol (LDL-c), and raising high-density lipoprotein cholesterol (HDL-c) can reduce the risk of cardiovascular events, morbidity and mortality.

Primary hypercholesterolaemia is associated with an underlying genetic predisposition; this can be due to a single genetic mutation, or, much more commonly, to the interaction of a number of genes with dietary and other factors. Secondary hypercholesterolaemia is caused by another disease or by drug therapy. The majority of people with hypercholesterolaemia have plasma-cholesterol concentrations that are only mildly or moderately elevated, and they exhibit no clinical symptoms.

Factors which influence the degree of disease in people with hypercholesterolaemia include diet, obesity, smoking and lack of physical activity. Dietary and lifestyle changes are therefore important components in the management of the condition. Lipid regulating drugs may also be indicated and statins are the first choice drugs. However, lipid goals are frequently not achieved due to the initiation of low doses of lipid-lowering medications, inadequate response to therapy, non-adherence to drug treatment and adverse effects.

Ezetimibe is a novel, orally active selective inhibitor of intestinal absorption of cholesterol and related plant sterols. Its mechanism of action differs from that of other classes of cholesterol lowering drugs in that ezetimibe selectively inhibits the absorption of dietary and biliary cholesterol and related plant sterols. It does not affect the absorption of fat soluble vitamins or triglycerides in the intestine.

Objectives

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

Methods

A review of the evidence for clinical effectiveness was undertaken systematically following the general principles recommended in the QUOROM statement. A second review of the evidence on the relationship between cholesterol reductions and CVD events was undertaken to inform the economic evalution.

Identification of studies: Searches were carried out to inform three aspects of the assessment; the reviews of clinical and cost effectiveness and the development of the independent economic assessment. In all, 12 electronic databases were searched and current research registers of various health services research related organisations were consulted via the World Wide Web. The sponsor submissions of evidence to the National Institute for Health and Clinical Excellence (NICE) and the reference lists of key papers and conference proceedings were hand-searched.

Inclusion/exclusion criteria: Two reviewers independently screened all titles and/or abstracts including economic evaluations. The full manuscript of any study judged to be relevant by either reviewer was obtained and assessed for inclusion or exclusion. Any disagreements were resolved through discussion. Randomised controlled trials that compared the following were included in the assessment of clinical effectiveness (1) ezetimibe in combination with statins compared to statin monotherapy or statin plus other lipid lowering drugs (nicotinic acid, bile acid resins or fibrates) (2) ezetimibe monotherapy compared to placebo or other lipid lowering drugs (nicotinic acid, bile acid resins or fibrates). For the assessment of cost effectiveness, a broader range of studies was considered, which initially included all economic and cost-related studies relevant to the assessment. Studies were excluded if they did not assess the cost effectiveness of ezetimibe in combination with a statin or ezetimibe monotherapy, were not reported in sufficient detail or were considered methodologically unsound.

Data extraction and quality assessment: Data from included studies were extracted by one reviewer and independently checked for accuracy by a second reviewer. Where multiple publications of the same study were identified, data were extracted and reported as a single study. Individual studies were assessed for quality by one reviewer and independently checked for accuracy by a second. Any discrepancies were resolved through consensus.

Methods of analysis/synthesis: Details of the extracted data and quality assessment for each individual study of clinical effectiveness were presented in structured tables and as a narrative summary. The possible effects of study quality on the effectiveness data and review findings were discussed. Data were

reported separately for each outcome measure. In addition, results of eligible studies were statistically synthesised (meta-analysed) if appropriate (there was more than one trial with similar populations, interventions and outcomes) and possible (there were adequate data). All analyses were by intention-to-treat. For the cost effectiveness section of the assessment, details of each identified published economic evaluation, together with a critical appraisal of its quality, were presented.

Handling the company submission: In terms of clinical effectiveness, the MSD/SP submission provided no data additional to the publications identified from the literature searches. All economic evaluations (including accompanying models) included in the company submission were assessed and a detailed assessment of the assumptions underlying the submitted analyses was undertaken. An economic model was developed to assess the costs and benefits associated with ezetimibe treatments. Probabilistic methods were used to generate information regarding the uncertainty in the cost effectiveness results.

Results of clinical effectiveness

To date, there have been no published clinical outcome trials (>12 weeks) examining the cardiovascular benefit of ezetimibe, either alone or in combination with statins. In the absence of clinical endpoint data from trials, we identified and included 13 (of which five were multi-arm) phase III multicentre RCTs (of varying methodological quality) of 12 to 48-weeks duration with surrogate endpoint data, such as LDL-c, Total-c. All trials involved patients with primary hypercholesterolaemia with average baseline LDL-c levels ranging from 3.36 mmol/L to 6.50 mmol/L.

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 incremental reduction in LDL-c of 13.94%, 95% CI (-14.90, -12.98), $p<0.00001$, and Total-c of 10.36%, 95% CI (-11.09, -9.63), $p<0.00001$ compared to statin alone and the direction of effect was consistent across all studies. No RCTs were identified that compared ezetimibe plus statin versus statin plus other lipid lowering drugs (nicotinic acid, bile acid resins or fibrates).

Titration studies: Four studies (not eligible for meta-analysis) that titrated (either forced or step-wise) the statin doses to LDL-c targets showed that the co-administration of ezetimibe and statin was significantly more effective in reducing plasma LDL-c concentration than statin monotherapy. One study showed that the addition of ezetimibe to simvastatin significantly reduced LDL-c by 27% ($p<0.05$) compared to simvastatin monotherapy; one study showed the addition of ezetimibe plus simvastatin reduced LDL-c by 6.9% compared with atorvastatin monotherapy ($p<0.05$); and two studies found that the addition of ezetimibe plus atorvastatin reduced LDL-c by 9.8% ($p<0.05$) and 12.9%, ($p<0.05$) compared atorvastatin alone.

No RCTs were identified that compared ezetimibe plus statin versus 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 to 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 from baseline to endpoint by 18.56%, 95% CI (-19.68, -17.44), $p<0.00001$ compared to placebo. This effect was generally consistent across all trials. No RCTs were identified that directly compared ezetimibe versus 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 CHD or other vascular disease, people with or without diabetes, different ethnic groups and patients with or without heterozygous familial hypercholesterolaemia.

Safety and tolerability

Overall, the majority of the adverse events were considered to be of mild or moderate intensity. No particular trend was found for any adverse event category in either treatment groups. There were no clinically meaningful differences in combination and monotherapy groups for the incidence of adverse events or in the number of discontinuations due to adverse events. The low frequency of adverse events observed in the current review may be explained by the relatively short time periods of the studies (majority were 12-weeks). Long term adverse events are unknown.

Discussion of clinical effectiveness

The key issues identified in this review are follows: the populations described in the primary studies were not fully representative of the population specified in the scope. It was not clear whether the populations in the primary studies are the target population i.e. either individuals whose lipids are not adequately controlled with current statin treatment or those who are intolerant of statins.

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 and evaluated as a class drug. Particularly, because of the complex administration, it was not possible to establish in the titration studies how many patients reached target LDL-c levels on each statin dose.

No studies reported objective clinical endpoints (mortality and morbidity) and the effectiveness obtained from the reviewed studies relate to surrogate outcomes such as LDL-c. It has been widely accepted that surrogate outcomes such as LDL-c level are directly correlated to CVD mortality and morbidity.

However, it is unclear if ezetimibe induced changes in LDL-c will translate to observed reductions in CV events.

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

Quality of life

No ezetimibe studies reported data on quality of life (QoL).

The relationship between cholesterol and CVD events

A large body of epidemiological evidence has demonstrated a strong correlation between LDL-c, and the risk of CVD. Numerous clinical outcome trials have established that lowering LDL-c is associated with a reduced risk of events in people with or at high risk of CVD. A meta-analysis of data from 90,056 patients in 14 randomised trials of statins, found a one mmol/L reduction in LDL-c was associated with a 21% reduction in the five-year incidence of a major coronary event (non fatal MI or CHD death), coronary revascularisation, or stroke. A more recent meta-analysis, which assessed the relationship between LDL-c and CHD risk using data from patients receiving either non-statin treatments or statins, 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 suggested that the pleiotropic effect of statins does not contribute to additional CHD risk reduction beyond that expected from the degree of LDL-c lowering seen in other trials. More importantly, the absolute risk for an individual depends on a range of cardiovascular risk factors such as smoking, diabetes and hypertension, and treatment decisions are generally based on overall risk as opposed to LDL-c levels.

Summary of cost effectiveness evidence

A review was undertaken to identify and evaluate published studies exploring the cost effectiveness of ezetimibe in individuals with primary hypercholesterolaemia. The two studies reviewed described country specific adaptations of a core model. Results for Canada were reported to be £45.8k per quality adjusted life year (QALY) for patients with an average age of 65 years with no history of CHD when comparing ezetimibe plus atorvastatin 10mg versus titrated atorvastatin monotherapy. When comparing ezetimibe co-administered with current statin compared to current statin treatment with no titration in Germany, the results for adults with a history of CHD were £7.7k per life year while the results for adults with diabetes but no history of CHD in Spain were estimated to be £50.7k per life year when comparing ezetimibe co-administered with current statin treatment with current statin treatment titrated by one dose. An abstract, which provided insufficient detail for review, reported results to be approximately £8.0k per

QALY for patients with an average age of 65 years with a history of CVD when comparing ezetimibe plus current statin versus titration of current statin treatment in Scotland. However, it is uncertain if the model used in the studies is robust.

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 existing model used in the studies identified in the literature search. The second (referred to as the Basic model) is described as a basic model which was built and submitted to lend credence to the results generated by the more complex model. The Cook model uses the Framingham risk 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 corresponding reductions in cardiovascular events. Effectiveness rates are derived from meta-analyses of published data.

Several treatment regimens are explored and the basecase 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 £8.8k per QALY for South Asian males aged 60 years at high risk of a CHD event with a baseline Total-c of 6.5 mmol/L, to £122k per QALY for females aged 80 years with no history of CVD with a baseline Total-c of 4.5 mmol/L. However, several key errors were identified and the results are not considered to be robust.

ScHARR economic model

A Markov model has been developed to explore the costs and health outcomes associated with ezetimibe treatment in individuals with primary hypercholesterolaemia who have not achieved target lipid levels on optimal statin therapy. Several treatment regimens are explored including: ezetemibe plus current statin treatment compared with current statin treatment titrated by one dose for individuals who tolerate statin therapy, and ezetimibe monotherapy versus no treatment for individuals in whom statin therapy is contra-indicated or those who do not tolerate statins.

Age dependent state transition matrices are used and CVD risk is updated annually based on natural increases in risk derived from patient level data from the Heath Survey for England 2003. UK epidemiological data are used to model age and gender specific prevalence and incidence rates. The model utilises published evidence on the link between chemically induced reductions in LDL-c and corresponding reductions in cardiovascular events. Effectiveness rates are derived from meta-analyses of published data. Probabilistic analyses are used to describe the uncertainty in the cost effectiveness results.

Results for the ScHARR economic evaluation

The effectiveness rate of adding ezetimibe to ongoing statin treatment is assumed to be constant irrespective of the baseline statin treatment and is derived from a meta-analysis of data pooled from ezetimibe RCTs comparing treatment strategies involving different statins at various doses. The effectiveness rate for either switching to a more potent statin or titrating the current statin to a higher dose is assumed to be constant irrespective of baseline statin treatment based on published evidence. There is currently insufficient data to determine if the percentage reduction in LDL-c differs between alternative regimens involving ezetimibe co-administered with a statin. There is also insufficient data to determine if the incremental percentage reduction in LDL-c differs according to the treatment strategies being compared. Consequently, the results of the economic evaluation are entirely dependent on the incremental cost of the treatment strategies being compared.

For individuals who tolerate statin treatment, using a threshold of £30k per QALY, the results of the probabilistic analyses range from cost-effective when comparing ezetimibe plus generic simvastatin with atorvastatin monotherapy, to not cost-effective when comparing ezetimibe plus current weighted statin treatment with current statin treatment titrated by one dose irrespective of age, gender, CVD history or diabetes status. Using a threshold of £20k per QALY, the results for individuals with heterozygous familial hypercholesterolaemia are not cost-effective when comparing ezetimibe plus atorvastatin with rosuvastatin monotherapy. For individuals who do not tolerate statin treatment and those in whom statins are contra-indicated, using a threshold of £30k per QALY, none of the results of the probabilistic analyses for the treatment regimen ezetimibe monotherapy versus no treatment are cost effective, irrespective of age gender or CVD history.

The univariate sensitivity analyses suggest that the results are sensitive to changes in the effectiveness of ezetimibe plus statin treatment, the evidence used to link reductions in LDL-c to events avoided, and changes in utility measurements. All the results are robust to changes in the costs assigned to the health states.

Limitations of the cost-utility estimates

There are several major limitations associated with the economic evaluation. First, the lack of robust clinical effectiveness evidence derived from patients who fail to achieve lipid goals on optimal statin treatment or patients who are intolerant of statins increases the uncertainty associated with ezetimibe treatment. Second, 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. 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, long-term adverse event data associated with

ezetimibe monotherapy or ezetimibe combination treatment is not available and could have a large impact on the cost effectiveness results. The direction / magnitude of the impact on the results is not known.

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 effectiveness data there is a great deal of uncertainty in the cost effectiveness of ezetimibe. The results range from being highly cost effective to highly not cost effective. 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 reaching target lipid levels. Due to inclusion and exclusion criteria and the washout periods used in the study designs, the populations in the RCTs may not accurately represent the target population. The effectiveness of adding ezetimibe to existing treatment regimens in routine clinical practice could be either underestimated or overestimated.

Suggested research priorities

The main area for further research should focus on long term studies of ezetimibe powered to evaluate CV outcomes. Studies of ezetimibe in patients who are intolerant of statins and those in whom statins are contra-indicated are required. Studies recruiting patients who fail to achieve lipid goals on statin treatment are also required. Further studies of ezetimibe are needed to inform on subgroup populations who are likely to require additional treatments to achieve target goals such as individuals with extremely high baseline lipid profiles. Head to head studies are also required to ascertain the long term effectiveness and safety profile of ezetimibe using combinations of lipid lowering treatments such as ezetimibe plus statin plus a resin compared with statin plus a resin.

Research is required on the attitudes to commitments to lifetime adherence to combination therapy which includes ezetimibe; particularly the relatively healthy younger and asymptomatic patients with no history of CVD. Further research is required to establish if reductions in lipids to pre-determined targets provide additional reductions in cardiovascular events. The findings from these studies could inform on the most appropriate methods of explaining risks and benefits of treatments to patients who potentially have the most to gain from treatments.

3. BACKGROUND

3.1 Description of health problem

3.1.1 Introduction

Cardiovascular disease (CVD) is a disease of the heart and blood vessels, which can lead to cardiovascular events such as myocardial infarction, angina and stroke. The most common form of CVD is coronary heart disease (CHD). Other forms of CVD are stroke, transient ischaemic attack 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 stroke.[3] Serum cholesterol is an important determinant of cardiovascular risk. The increased risk is due mainly to raised low-density lipoprotein cholesterol (LDL-c). Lowering concentration of total cholesterol (Total-c) and LDL-c, and raising high-density lipoprotein cholesterol (HDL-c) can reduce the risk of cardiovascular events, morbidity and mortality. The absolute risk for an individual depends on a range of cardiovascular 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, onset of CHD is not uncommon during the second and third decade 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).

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 (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 TG) for people who require lipid regulating treatment.

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) 1:1million (homozygous)
		Familial defective apo-B	0.2	1:1000 (heterozygous) 1:4 million (homozygous)
		Polygenic hypercholesterolaemia	20 to 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	-
Hypoαlipoproteinaemia	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 to 0.1	-

[a] Among European adults

LDL, low density lipoprotein cholesterol; HDL, high density lipoprotein cholesterol; IDL, intermediate density lipoprotein cholesterol (VLDL remnants); VLDL, very low density lipoprotein cholesterol

3.1.2 Epidemiology

3.1.2.1 Blood lipid levels in the UK

Lipid levels vary in an individual from day to day; additionally, levels vary across different populations.[8,6] 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's (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) with the remainder being 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 social-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 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 are marginally lower than 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]

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

	Age (years)							
	16-24	25-34	35-44	45-54	55-64	65-74	75+	Total
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

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.

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

3.1.3 Aetiology, pathology and prognosis

3.1.3.1 Aetiology

Genetic predisposition, concomitant diseases (e.g. diabetes mellitus 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 (saturated fatty acid) are the major determinants of the serum total cholesterol 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. Heterozygous 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, more than 150 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. Half of the offspring of a familial cholesterolaemic parent could have severely elevated plasma LDL-c from birth onwards, with males and females equally affected.[17] Table 4 provides a list of other modifiable and non-modifiable risk factors for CVD.

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	

A further disussion of the relationship between cholesterol and CVD is provided in section 4.1.5.

3.1.3.2 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.

3.1.3.3 Prognosis

A number of complications may occur if high cholesterol levels in blood is left untreated. As mentioned earlier (section 3.1.3.2), 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 a myocardial infarction (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]

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 yr (per 1000)
<5	25
5-6	30
6-7	43
7-8	55
8-9	74
>9	130
HeFH	500

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

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

3.1.4 Impact of health problem

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

In the UK, CVD (CHD, stroke and other vascular diseases) accounted for nearly 216,000 deaths in 2004, about half (49%) of these were from CHD, and about a quarter (28%) from stroke.[1] CVD is one of the main causes of premature death (death in people aged under 75). 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. 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 North and South Thames regions; stroke 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 stroke 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 nonfatal events) and 56% of global ischaemic heart disease. 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]

3.1.4.2 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.

3.2 Current service provision

3.2.1 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 to 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 National Service Framework 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] recommend 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 $\geq$ 20% over 10 years). Although, the lipid targets in the National Service Framework 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 US, 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. A summary of the UK, European and US guidelines for best practice is summarised in Table 6. It is noteworthy that although lowering cholesterol has been shown to reduce the risk of cardiovascular events, the optimal guideline targets are based on expert consensus agreement and have not been tested *a priori* by clinical trials.[6]

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	2005[3]	Established atherosclerotic disease; CHD, stroke or peripheral arterial disease; CVD risk ≥20% over 10 years; diabetes mellitus	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,[34] 2000[30]	With CHD (myocardial infarction); 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; stroke/transient ischaemic attack; diabetes mellitus	<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,[34] 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% [moderate high risk]; zero to 1 risk factor [lower risk]	-	<1.8 (optional in very high risk patients) <2.6 (high risk) <3.4 (moderate to moderate 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)

At present, statins are the cholesterol-regulating drugs of choice for both primary and secondary prevention of CVD.[3,31,35,27,33,28,36,29,30] In comparison to other lipid regulating agents (e.g. anion exchange resins, nicotinic acid, or fibrates) statins are the most effective drugs for lowering surrogate endpoints (Total-c by approximately 20 to 30% and LDL-c by about 25 to 50%)[37] and reducing coronary events, all cardiovascular 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 National Health Service (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, 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]

Table 7: Comparative features of other lipid regulating drugs[40,7]

Drug class, agents and daily dose[38]	Main indication and use	Lipid/lipoprotein effects	Adverse -effects	Contra-indications	Comments
Anion exchange resins [a]	Hypercholesterolaemia	LDL-c: Decreased by 15 to 30% HDL-c: Increased by 5 to 15% Triglycerides: No change or increase	Gastrointestinal dysfunction (e.g. constipation, nausea and flatulence)	Hypertriglyceridaemia, peptic ulcer, haemorrhoids	Poor tolerability and unpalatability often limits 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. familial hypercholesterolaemia)[6]
Fibrates [b]	Hypertriglyceridaemia, mixed hyperlipidaemia	LDL-c: Decreased by 5 to 20% (may be increased in patients with high triglycerides) HDL-c: Increased by 10 to 20% Triglycerides: Decreased by 20 to 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.[42] 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 dysbetalioproteinaemia[6]
Nicotinic acid and analogues [c]	Hypertriglyceridaemia	LDL-c: Decreased by 5 to 25% HDL-c: Increased by 15 to 35% Triglycerides: Decreased by 20 to 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,[43] 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 to 24g/d; maximum 36g/d); Colestipol hydrochloride (5 to 10g/d; maximum 30g/d)
[b] Bezafibrate (400 to 600mg/d); Ciprofibrate (100mg/d); Fenofibrate (160 to 267mg/d); Gemfibrozil (1200mg/d)
[c] Nicotinic acid (standard release, 300mg to 6g/d; modified release, 375mg to 2g/d); Acipimox (500 to 750mg/d)

3.2.2 *Current service cost*

Statins represent the largest drug spend in the NHS budget, costing £578 million in England[44] and £40 million in Wales in 2005.[45] The estimated cost of statins in England in 2006 is approximately £389 million (Data not available for Wales), based on prescribing rates (Table 8).

Table 8: Statin and Ezetimibe prescribing rates for 2005 in England[44] (Data not available for Wales)

Statin		**% of patients**	**Annual cost[a] (£000s)**	**Statin**		**% of patients**	**Annual cost[a] (£000s)**
Simvastatin	10mg	9.019%	5,511	Simvador	10mg	0.242%	148
Simvastatin	20mg	19.296%	15,241	Simvador	20mg	0.499%	394
Simvastatin	40mg	17.798%	25,412	Simvador	40mg	1.034%	1,477
Simvastatin	80mg	0.878%	7,137	**Simvador**		**1.775%**	**2,019**
Simvastatin		**46.991%**	**53,301**				
				Lipostat	10mg	0.038%	193
Atorvastatin	10mg	19.754%	120,234	Lipostat	20mg	0.070%	652
Atorvastatin	20mg	11.752%	97,752	Lipostat	40mg	0.126%	1,171
Atorvastatin	40mg	6.181%	58,857	**Lipostat**		**0.233%**	**2,015**
Atorvastatin	80mg	1.337%	12,731				
Atorvastatin		**39.024%**	**289,574**	Zocor	10mg	0.055%	335
				Zocor	20mg	0.103%	1,027
Pravastatin	10mg	1.002%	1,154	Zocor	40mg	0.055%	546
Pravastatin	20mg	1.804%	2,569	Zocor	80mg	0.005%	48
Pravastatin	40mg	3.532%	5,472	**Zocor**		**0.217%**	**1,956**
Pravastatin		**6.337%**	**9,195**				
				Ranzolont	10mg	0.002%	6
Rosuvastatin	10mg	3.210%	19,536	Ranzolont	20mg	0.004%	17
Rosuvastatin	20mg	0.566%	3,444	Ranzolont	40mg	0.002%	11
Rosuvastatin	40mg	0.109%	1,093	**Ranzolont**		**0.008%**	**35**
Rosuvastatin	5mg	0.001%	15				
Rosuvastatin		**3.886%**	**24,087**	**Ezetimibe**	**10mg**		**17,391**
Fluvastatin	20mg	0.480%	2,061	Sim/Eze	10mg/20mg	1.269%	287
Fluvastatin	40mg	0.725%	3,111	Sim/Eze	10mg/40mg	0.989%	261
Fluvastatin	80mg	0.324%	1,747	Sim/Eze	10mg/80mg	0.177%	49
Fluvastatin		**1.528%**	**6,919**	**Sim/Eze**			**598**

[a]Total costs according to prescribed doses, prescribing rates as per 2005 and costs as per 2006.

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 to statins, the current prescribing growth rate is high (see section 7.1). 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. The literature suggests that 72% of individuals on statins are at target in the UK.[46] 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 a) evidence from long term studies demonstrating effectiveness in terms of hard clinical outcomes; b) evidence of long term adverse event rates; c) the rate of effectiveness in reducing lipids in clinical practice and d) identification of subgroups likely to benefit from ezetimibe treatment.

3.2.3 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 to variations in statin prescribing rates. Statin prescribing has been shown to vary between[47,48] and within countries,[49,50] between health authorities and general practitioners[51,49,52,53] and between patients on the basis of gender,[54,55,49,56,50] demographics,[49,57] ethnicity[58] and deprivation.[59] 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.[60] Other UK studies in patients with CHD or at high CHD risk suggest a figure of around 50%.[61,62,63,64]

A survey evaluating statin prescribing in UK general practice[65] 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[65] 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. Other studies have also found that the failure to achieve target levels may be due to either the use of suboptimal doses of statins[66] or observed reductions in clinical practice are less than those projected by package insert guidelines.[67] 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.[68] (e.g. a three step titration, equivalent to increasing the dose from 10 to 80mg simvastatin, will result in an additional 18% reduction in LDL-c approximately).

Prescription cost analyses[44] and data from the Primary Care Data Quality audit[60] 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, 40mg simvastatin in high risk individuals) may be more common in secondary care than in primary care, but the reason for this is unknown.[69] 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 increase intolerability), and the limited availability of time and resources are perceived to be key barriers for statin titration.[70] 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.[69,71]

While 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.[72] In addition, more than 30% of patients receiving statins switch from their initial therapy within the first year of treatment[73] and more than 50% of patients discontinue statin therapy within three years.[74,75] 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 suggest 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.[60] A more recent figure of 72% has been quoted by Kirby *et al*.[46] which is based on data from the Quality and Outcomes Framework (QOF) within the General Medical Services Framework (GMF).

3.3 Description of technology under assessment

Ezetimibe has been proposed for the treatment of patients with primary hypercholesterolaemia. The following 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).

3.3.1 Summary of interventions

3.3.1.1 Ezetimibe

a) 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

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.

b) Licensed indications

Ezetimibe monotherapy (Ezetrol®, 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.

c) Dosage and administration

The recommended dose of ezetimibe monotherapy is 10mg once daily, which may be taken orally at anytime 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 mg 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 cardiovascular complications.

d) Contra-indications

Ezetimibe monotherapy is contra-indicated 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 contra-indicated 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.

3.3.2 Identification of important sub-groups

Current guidelines recommend prescribing lipid regulating interventions based on patients' CVD status or risk.[39] The current study is reviewing the role of ezetimibe treatment in individuals with primary hypercholesterolamia 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 diabetics 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 sub-groups 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 section 3.2.3, and the growth in prescribing rates for ezetimibe (see section 7.1) 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.[46] 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, literature suggests a clinical diagnostic criteria is frequently used which includes: Total-c level above 7.5 mmol/L or an LDL-c level above 4.9 mmol/L (Simon Broome Register Group definition and Dutch lipid clinical network diagnosis cited in Marks *et al*.)[19]

3.3.3 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[44] and £2 million in Wales.[45]

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 cardiovascular 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 health care structures within the UK it is unlikely that the variation between geographical areas will reduce.

3.3.4 Anticipated costs associated with intervention

Assuming 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.[69] For those individuals whose treatment strategy is changed, monitoring costs are likely to increase and a recent article suggested a follow-up and review of patients at three months would be required to monitor progress, side effects and the need for up or down titration of statin treatment.[46] 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 reduction in cardiovascular events, then treatment costs could also be offset by the costs saved through events avoided.

4. DEFINITION OF THE DECISION PROBLEM

4.1 Decision problem

4.1.1 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 ahieve 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

4.1.2 Population including sub-groups

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 ischaemic heart disease or other vascular disease, people, with or without diabetes and for different ethnic groups.

4.1.3 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

4.1.4 Outcomes

The following outcomes are assessed

- Survival
- Fatal and non-fatal cardiovascular events
- Adverse effects of treatment
- Health-related quality of life

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.

4.1.5 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] have 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),[79,80,81] particularly LDL cholesterol, 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 five-year incidence of a major coronary event (non-fatal MI or CHD death), and a 21% reduction in major coronary events, coronary revascularisation, and stroke.

Although the majority of evidence for the benefits of lowering LDL-c is derived from RCTs investigating statin treatment, treatment to lower LDL-c levels is associated with cardiovascular 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 *et al*.[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 *et al*.,[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 ten 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 *et al*.,[84] and the CTTC[79] analysis. It is noteworthy that the study by Robinson *et al*.,[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, these authors[85] 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 five years.

4.1.6 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 endpoints, a literature review was conducted to identify the most robust methodology to link the changes in surrogate measures (the lipid profile) to clinical events (Appendix 21). The searches identified several possible methods including the Framingham, UKPDS or PROCAM equations, evidence based on the WOSCOPS study and the results of a meta-analyses performed by the Cholesterol Treatment Trialists (CTT) Collaborators.[79,86,77,87,88]

A combination of soft Operational Research (strategic choice approach, cognitive maps) and hard quantitative techniques were used to examine the choice of modelling methods.[89] A selection of pre-defined 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 12.

The Framingham Heart Study

The Framingham study, based on individuals from the general population of Framingham in Massachusetts, USA is well known and the cardiovascular risk engines generated as a result of this study are used to predict a one-off risk for individuals world-wide[77,87] However, the data was collected decades ago (from the 1970s) and incidence of coronary disease has changed in the interim for example there has been a 50% drop in male coronary heart disease mortality over this period.[91] The sensitivity and specificity of the algorithms have been extensively studied in differing 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.[92,93,94,95,96] 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.

While the Framingham risk engines have been used to predict events before and after treatment in previous economic evaluations[99,100,101] 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 CTTCs 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 mmol/L[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 stroke 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 there was an approximate linear relationship between absolute reductions in LDL-c and the proportional reductions in major vascular events. At one year the mean LDL-c differences in the trials ranged from 0.35 mmol/L to 1.77 mmol/L. When sub-grouped by

changes in LDL-c over time, the analysts found that a sustained reduction in LDL-c of one mmol/L over five 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 this particular meta-analysis has over previously published data are 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 is difficult when using published data. The data demonstrated that the proportional risk reduction increased over the five year period (14% vs 29% for CHD events, 4% vs 21% for stroke) 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 anlayses (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]

4.1.7 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 12). An important criteria 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 while the results of the CTTC meta-analysis is 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.

4.2 Overall aims and objectives of assessment

The main aim of this review is to systematically evaluate and appraise the clinical 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 endpoints is unavailable

- Evaluate the adverse effect profile and toxicity

- Evaluate the cost effectiveness of ezetimibe in terms of incremental cost per quality-adjusted life years

- Advise on the patient groups for whom ezetimibe might be particularly appropriate

- Estimate the possible overall cost in England and Wales

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

5. 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]

5.1 Methods for reviewing effectiveness

5.1.1 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 sections 6.1.1 and 6.3.2.

5.1.1.1 Identification of studies for the review of clinical effectiveness

The aim of the search was to provide as comprehensive retrieval as possible of randomised controlled trials (RCTs) of ezetimibe for the treatment of hypercholesterolaemia.

a) 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 World Wide Web (WWW). Keyword searching of the WWW was undertaken using the Google search engine. The submissions of evidence to NICE by sponsors were hand-searched as well as references of retrieved papers. A list of the sources searched is provided in Appendix 1.

b) 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. hypercholesterolemia, hypercholesterolaemia). Keyword strategies for all electronic databases are provided in Appendix 1.

c) 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 to June 2006.

5.1.2. Inclusion and exclusion criteria

Two reviewers independently screened all titles and abstracts. Full paper manuscripts of any titles/abstracts that were considered relevant by either reviewer were obtained where possible. The relevance of each paper was assessed according to the criteria set out below. Trial flow chart is presented in Appendix 2. Any disagreements were resolved by discussion.

a) 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.

b) 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)

c) 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.

d) Outcomes

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

e) Study design

Phase III randomised controlled trials 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 endpoint data from trials, we identified and included data from RCTs of sufficient duration (i.e. at least 12 weeks) for surrogate endpoints were included. This decision was then validated by clinical experts' opinion and meta-analysis (see section 5.3).

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 are reported to allow critical appraisal of the study quality.

5.1.3 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. Any

discrepancies were resolved by consensus. Where multiple publications of the same study were identified, data were extracted and reported as a single study.

5.1.4 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.[107] 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.

5.1.5 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 intention-to-treat or modified intention-to-treat (analysis of subset of patients who received treatment as planned or at least some treatment). Efficacy results were reported as least squares (LS) mean percent change from baseline to study endpoint for comparison groups. Where appropriate, the standard deviations (SD) and 95% confidence intervals (CI) were calculated using the method documented in the Cochrane Handbook to perform meta-analyses of the published literature.[108]

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 visualization of the results and, in statistical terms, by chi^2 test for homogeneity and the I^2 measure. The chi^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. Chi^2 is not a particularly sensitive test: a cut-off of $p<0.10$ is often used to indicate significance, but lack of statistical significance does not mean 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.[109]

5.1.6. Handling of the company submission

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

5.2 Results

5.2.1 Quantity and quality of research available

5.2.1.1 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 2.

5.2.1.2 Number and type of studies included

To date, there have been no published clinical outcome trials (>12 weeks) examining the cardiovascular benefit of ezetimibe, either alone or in combination with statins. In the absence of data from hard clinical endpoint trials, we identified and included 13 phase III randomised controlled trials with surrogate endpoints in the review.

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

Fixed dose: From six identified studies four compared combination of ezetimibe and simvastatin with simvastatin alone,[110,111,112,113] one study compared combination of ezetimibe and atorvastatin with atorvastatin alone[114] and one study compared combination of ezetimibe and pravastatin with pravastatin alone.[115]

Titration studies: Of the five included studies two compared combination of ezetimibe and atorvastatin with atorvastatin alone.[116,117] One study compared combination of ezetimibe and simvastatin with atorvastatin alone.[118] One study compared combination of ezetimibe and simvastatin with simvastatin alone[119] and one study compared combination of ezetimibe and statin with combination of niacin and statin.[120]

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

Seven studies compared ezetimibe monotherapy with placebo[121,114,122,115,110,111,112]

5.2.1.3 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, non-RCTs, systematic reviews/meta-analyses, or ongoing studies. After a more detailed examination two studies[123,124] were excluded from the review as one had a mixed hyperlipidaemic[123] population and other reported results only for the first five weeks.[124] A full list of the excluded publications with rationale is presented in Appendix 3.

a) 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 by 2008-2010 (Table 9).

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)16860	Multi-centre, double-blind RCT	2.5	Approximately 10,000 high risk patients (planned recruitment) with coronary artery disease presenting with ACS	Fixed dose combination of ezetimibe (10mg/d) and simvastatin (40mg/d)	Simvastatin (40mg/d)	Composite of CV death, MI, non-fatal stroke, hospitalisation for ACS or revascularisation
SEAS trial (Simvastatin and Ezetimibe in Aortic Stenosis)[125,126]	Multi-centre, double-blind, placebo RCT	4	Patients (n=1873 subjects aged between 45 to 85 years) with asymptomatic moderate aortic stenosis (defined by Doppler-measured peak flow velocity of 2.5 to 4.0m/s)	Ezetimibe (10mg/d) co-administered with simvastatin (40mg/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 stroke)
SHARP trial (Study of Heart And Renal Protection)[127]	Multi-centre, double-blind, placebo RCT	4	Patients aged ≥40 years with chronic disease (planned recruitment approximately 9000 subjects [around 6000 on pre-dialysis and 3000 on dialysis])	Ezetimibe (10mg/d) co-administered with simvastatin (20mg/d)	Placebo	Composite of major vascular events (non fatal MI, cardiac death, non-fatal or fatal stroke, or revascularisation)

CV, cardiovascular; ACS, acute coronary syndromes; MI, myocardial infarction

5.2.1.4 Summary of included trials

Thirteen phase III multicentre RCTs of 12 to 48-weeks duration with sample sizes ranging from 246[116] to 1528[110] were included. All trials involved patients with primary hypercholesterolaemia with average baseline LDL-c levels ranging from 3.36 mmol/L to 6.50 mmol/L. A summary of the design and study characteristics of the included studies is summarised 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. Data on other lipid profiles (HDL-c and TG) are provided in the Appendix 6 (Tables 59-62).

Table 10: Summary of design and study characteristics of included studies

Study	Population with primary hypercholesterolaemia	Study design	Active treatment duration	Number randomised	Intervention (Daily dosage)	Primary outcome (Mean % change)	Funding	Comments
Ballantyne *et al*. 2003[114] USA	N=628 LDL-c, 3.77 to 6.50 mmol/L TG ≤ 3.85 mmol/L	Randomised double-blind, placebo controlled, balanced-parallel group trial	12 week	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[116] USA	N=246 LDL-c, 3.77 to 6.50 mmol/L TG ≤ 3.85 mmol/L	Multinational, randomised placebo-controlled double-blind trial	24 week	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[118] USA	N=788 LDL-c, 3.38 to 6.50 mmol/L TG ≤ 3.85 mmol/L	Multicenter, randomised active-controlled, double-blind trial	24 week	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[110] USA	N=1528 LDL-c, 3.77 to 6.50 mmol/L TG ≤ 3.85 mmol/L	A multicenter, randomised, double-blind, placebo-controlled, factorial design study	12 week	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[111] USA	N=668 LDL-c, 3.77 to 6.50 mmol/L TG ≤ 3.85 mmol/L	Randomised placebo controlled trial	12 week	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	
Dujovne *et al*.	N=892	Multicenter, double	12 week	T1= 666	T1:Ezetimibe (10mg/d)	LDL-c	Schering-Plough	

Study	Population with primary hypercholesterolaemia	Study design	Active treatment duration	Number randomised	Intervention (Daily dosage)	Primary outcome (Mean % change)	Funding	Comments
2002[121] USA	LDL-c, 3.38 to 6.50 mmol/L TG ≤ 3.85 mmol/L	blind, placebo-controlled trial		T2= 226	T2: Placebo		Research Institute	
Goldberg *et al*. 2004[112] USA	N=887 LDL-c ≥ 3.77 and ≤ 6.50 mmol/L TG ≤ 3.85 mmol/L	Multicenter randomised, double-blind, placebo-controlled	12 week	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[122] USA	N=827 LDL-c, 3.36 to 6.47 mmol/L TG ≤ 3.95 mmol/L	Multicenter, randomised double blind, placebo-controlled trial.	12 week	T1= 622 T2= 205	T1: Ezetimibe (10 mg/d) T2 : Placebo	LDL-c	Schering-Plough Research Institute	
Masana *et al*. 2005[119] International	N=433 LDL-c ≥ 3.77 and ≤ 6.50 mmol/L TG ≤ 3.85 mmol/L	Multicenter, randomised, double blind, placebo-controlled trial	48 week	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[120] USA	N=292 LDL-c, 5.12 mmol/L, TG, 1.86 mmol/L,	Multicenter, randomised controlled trial	12 week	NR	T1: Ezetimibe (10 mg/d)/ Simvastatin (20, 40 mg/d) T2: Niacin (1000mg/d)/ Atorvastatin (20,40 mg/d) T3: Niacin (1000mg/d)/ Rosuvastatin (20, 40 mg/d) T4: Rosuvastatin (20,40 mg/d)	LDL-c	Kos Pharmaceuticals, Inc	Conference abstract
Melani *et al*. 2003[115] USA	N= 538 LDL-c ≥ 3.8 and ≤ 6.5	Multicenter, double-blind, randomised,	12 week	T1=64 T2=204 T3=205	T1: Ezetimibe (10 mg/d) T2 : Ezetimibe (10 mg/d)/ Pravastatin (10-40 mg/d)	LDL-c	Merck and Schering-Plough Pharmaceuticals	

Study	Population with primary hypercholesterolaemia	Study design	Active treatment duration	Number randomised	Intervention (Daily dosage)	Primary outcome (Mean % change)	Funding	Comments
	mmol/L TG ≤4.0 mmol/L	placebo-controlled, balanced-parallel-group, 2x4 factorial design study		T4=65	T3 : Pravastatin (10-40 mg/d) T4 : Placebo			
Rodney *et al*. 2006[113] USA	N=247 LDL-c ≥ 3.77 and ≤ 6.50 mmol/L TG, ≤ 3.85 mmol/L	Multicenter, double-blind, randomised controlled trial	12 week	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[117] International	N=621 LDL-c ≥ 3.8 mmol/L TG ≤ 4.0 mmol/L	Randomised, double-blind, multicenter, double-dummy, active controlled comparator study	14 week	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 pts achieving a LDL-c level ≤100 mg/dl to study endpoint	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)

LDL-c= Low density lipoprotein cholesterol; TG= Triglycerides; 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; HeFH Heterozygous familial hypercholesterolaemia; pt(s) –patient(s)

5.2.2.1 Quality and characteristics of identified studies

A table summarising data on quality assessment can be found in Appendix 4. All thirteen studies were described as large multicentre randomised controlled trials and were published in peer-reviewed journals. McKenney *et al.*[120] reported in conference abstract form 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 LDL-c concentration of 3.38 to 6.50 mmol/L and 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 six months of study entry; history of unstable or severe peripheral artery disease within 3 months of study entry; unstable angina pectoris; disorders of the haematologic, digestive, or central nervous system, uncontrolled or newly diagnosed diabetes mellitus, uncontrolled endocrine or metabolic disease 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[111] 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 (six 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 pre-trial treatment history and previous treatment success (whether the subjects did reach 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. Twenty eight per cent (between 19%[117] and 36%)[119] of the overall population was identified as elderly patients aged 65 and over (Appendix 5).

The patient demographics and baseline characteristics of the included studies are presented in Appendix 4. Where reported, baseline performance status was generally well-balanced. The trials

were conducted among patients both with primary and secondary CVD. All trials consisted of mixed (primary and secondary) populations. Patients in each study were mainly subdivided into those who had family history of CHD, risk factors of CHD/CVD, history of hypertension, diabetes mellitus, 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 diabetes mellitus 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 Ballantyne *et al.*[114] and Stein *et al.*[117] 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 *et al.*[113] was conducted exclusively on African Americans. Ballantyne *et al.*[118] Davidson *et al.*[111] and Goldberg *et al.*[112] did not report baseline information on 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 TG level of ≤ 3.85 mmol/L. Only Stein and colleagues[117] 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,[118] single computer generated[111,115,112,113] or computer random schedule.[121,122] However none of the trials reported method of allocation concealment. It was not clear whether the assessors were blinded to the treatment allocation in trials by Dujovne *et al.,*[121] Knopp *et al.,*[122] Masana *et al.*[119] Rodney *et al.*[113] and Stein *et al.*[117] It was not clear whether the individuals who administered the intervention were blinded to the treatment allocation in Davidson *et al.*[111] and Dujovne *et al.*[121] Patients were all blinded, however none of the studies assessed the success of the blinding. All trials used intention-to-treat or modified intention-to-treat analyses apart from Stein *et al.*[117] 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.[122,114,118,111,115,113,117]

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

5.2.2.2 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:

- Fixed dose studies

  Comparison 1: Ezetimibe plus statin versus statin alone

  Comparison 2: Ezetimibe plus statin versus statin plus other lipid lowering drugs (nicotinic acid, bile acid resins or fibrates)

- Titrated studies

  Comparison 1: Ezetimibe plus statin versus statin alone

  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:

Comparison 1: Ezetimibe versus placebo

Comparison 2: Ezetimibe versus other (non-statin) lipid lowering drugs (nicotinic acid, bile acid resins or fibrates)

Safety and tolerability

Quality of life

5.2.2.3 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 the Figures 1 and 2. Six studies[110,111,112,113,114,115] with a total sample size of 3610 were identified as eligible for this comparison.

Figure 1: For patients whose condition is not adequately controlled with a statin alone: Mean % change in LDL-c (mmol/L)

Review: Ezetimibe
Comparison: 01 Ezetimibe + Statin versus Statin alone
Outcome: 01 Low density lipoprotein cholesterol (LDL-c) non-titrated 12 week studies

Study or sub-category	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	604	-53.00(14.75)	612	-39.00(14.84)		33.59	-14.00 [-15.66, -12.34]
Davidson	274	-49.90(14.90)	263	-36.10(14.60)		14.92	-13.80 [-16.30, -11.30]
Goldberg	353	-53.20(17.20)	345	-38.50(14.20)		17.00	-14.70 [-17.04, -12.36]
Rodney	124	-45.60(15.78)	123	-28.30(15.72)		6.02	-17.30 [-21.23, -13.37]
Subtotal (95% CI)	1355		1343			71.53	-14.40 [-15.54, -13.26]
Test for heterogeneity: Chi² = 2.60, df = 3 (P = 0.46), I² = 0%							
Test for overall effect: Z = 24.77 (P < 0.00001)							
02 Ezetimibe + Atorvastatin versus Atorvastatin							
Ballantyne	255	-54.50(15.01)	248	-42.40(14.96)		13.54	-12.10 [-14.72, -9.48]
Subtotal (95% CI)	255		248			13.54	-12.10 [-14.72, -9.48]
Test for heterogeneity: not applicable							
Test for overall effect: Z = 9.05 (P < 0.00001)							
03 Ezetimibe + Pravastatin versus Pravastatin							
Melani	204	-37.70(12.85)	205	-24.30(12.89)		14.93	-13.40 [-15.89, -10.91]
Subtotal (95% CI)	204		205			14.93	-13.40 [-15.89, -10.91]
Test for heterogeneity: not applicable							
Test for overall effect: Z = 10.53 (P < 0.00001)							
Total (95% CI)	1814		1796			100.00	-13.94 [-14.90, -12.98]
Test for heterogeneity: Chi² = 5.31, df = 5 (P = 0.38), I² = 5.8%							
Test for overall effect: Z = 28.35 (P < 0.00001)							

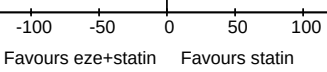
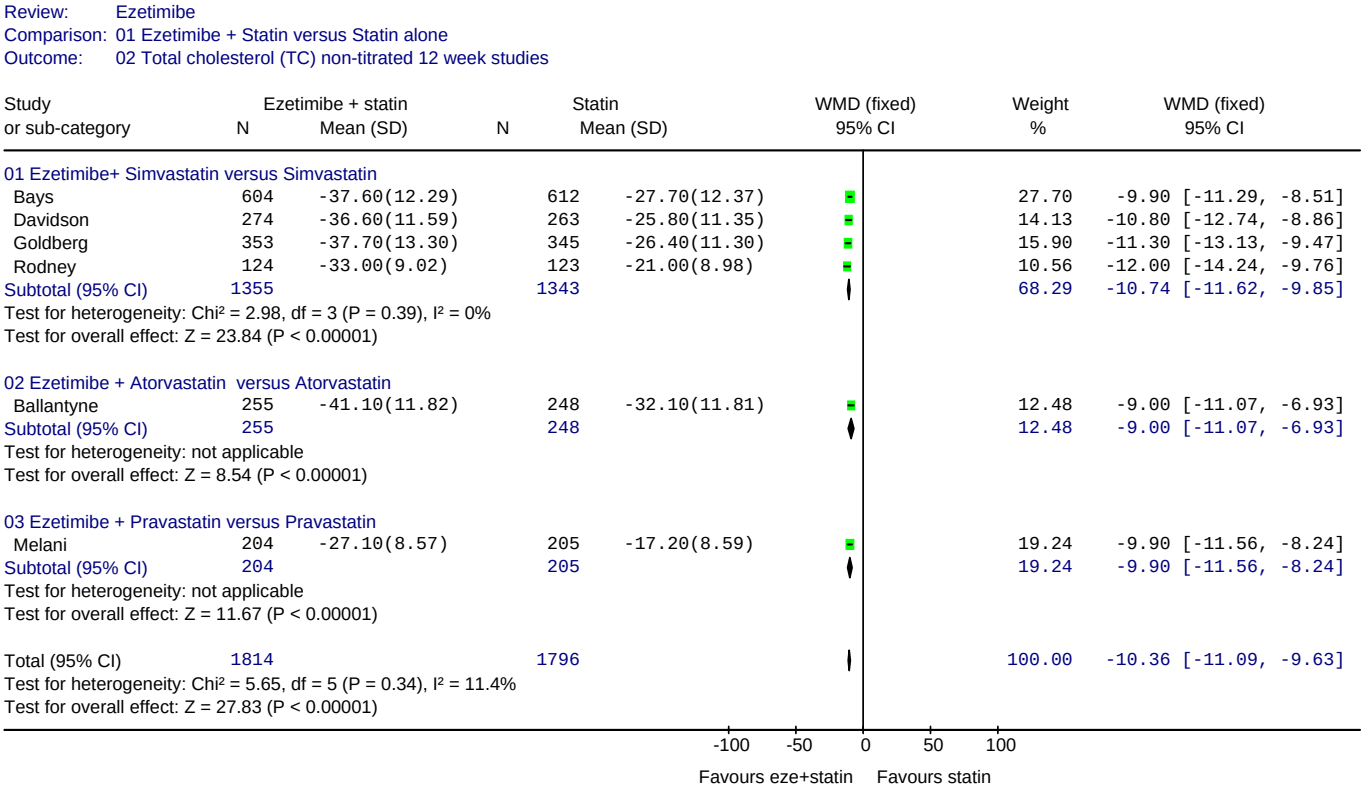


Figure 2: For patients whose condition is not adequately controlled with a statin alone: Mean % change in Total-c (mmol/L)



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 to statin alone and a direction of effect was consistent across all studies. There were low heterogeneity (LDL-c: Chi^2=5.31, p=0.38, I^2=5.8%; Total-c: Chi^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 randomised controlled trials 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.

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)	Mean % reduction (SD)	Between treatment Mean % difference*
		Ezetimibe+ Atorvastatin	Atorvastatin	
Ballantyne *et al.* 2004 a[116]	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[117]	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[118]	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[119]	LDL-c	-23.7 (33.67)	3.30 (22.96)	-27
	Total-c	-1.9 (22.45)	2.5 (15.90)	-18.4

*All comparisons are statistically significant ($p<0.05$)

A total of 1800 patients participated in the four studies. In three[117,116,119] studies, 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[118] 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[116,117] compared the LDL-clowering effect of co-administered ezetimibe and atorvastatin against atorvastatin monotherapy in patients with primary hypercholesterolaemia. One study[119] compared ezetimibe plus simvastatin with simvastatin, and one trial[118] looked at a combination of ezetimibe and simvastatin against atorvastatin. The source of heterogeneity may be due to differences in the type statin, dose titration and duration of the studies. Therefore the results were tabulated and discussed accordingly (Table 11). For more detailed information see Appendix 7 (Table 56).

Due 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 the current 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[116,117] demonstrated that administration of

ezetimibe with atorvastatin have significantly greater LDL-c lowering effect compared to atorvastatin alone (between treatment mean % difference -9.8%, $p<0.05$ and -12.9%, $p<0.05$). One trial[118] compared ezetimibe coadministered with simvastatin to atorvastatin monotherapy found that ezetimibe plus simvastatin reduced LDL-c by 59.4% vs. 52.5% with atorvastatin (difference of 6.9%, $p<0.05$). One trial[119] compared the LDL-c lowering effect of co-administration of ezetimibe and simvastatin against simvastatin monotherapy and found between treatment mean % difference to be 27%, $p<0.05$. A smilar pattern of efficacy was observed in plasma Total-c concentration (Table 11).

Stein and colleagues,[117] 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% vs. 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 compared with the atorvastatin monotherapy arm (29% vs. 11%, $p<0.01$). Further evidence on HeFH and non-HeFH subgroups is described in section 5.2.2.4.

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.[120] The treatments of interest in McKenney *et al.*[120] were ezetimibe plus statin vs. niacin plus statin.

McKenney *et al.*[120] 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 to 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 summarized in Figures 3 and 4. Seven studies[114,110,111,121,112,122,115] with a total of 2577 participants were included in this category.

Figure 3: For patients in whom a statin is considered inappropriate, or is not tolerated: Mean % change in LDL-c (mmol/L)

Comparison: 02 Ezetimibe versus Placebo
Outcome: 01 Low Density Lipoprotein cholesterol (LDL-c) 12 week studies

Study or sub-category	Ezetimibe N	Ezetimibe Mean (SD)	Placebo N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
Dujovne	666	-16.86(14.19)	226	0.36(12.48)		32.89	-17.22 [-19.17, -15.27]
Ballantyne	65	-18.40(14.92)	60	5.90(14.87)		4.59	-24.30 [-29.53, -19.07]
Knopp	621	-17.69(14.70)	204	0.79(12.43)		29.50	-18.49 [-20.55, -16.43]
Melani	64	-18.70(12.80)	65	1.30(12.90)		6.37	-20.00 [-24.43, -15.57]
Bays	148	-18.90(14.60)	146	-2.20(14.50)		11.32	-16.70 [-20.03, -13.37]
Davidson	61	-18.10(14.84)	70	-1.30(14.22)		5.02	-16.80 [-21.80, -11.80]
Goldberg	89	-19.80(10.50)	92	2.70(13.30)		10.31	-22.50 [-25.98, -19.02]
Total (95% CI)	1714		863			100.00	-18.56 [-19.68, -17.44]

Test for heterogeneity: Chi² = 13.44, df = 6 (P = 0.04), I² = 55.4%
Test for overall effect: Z = 32.50 (P < 0.00001)

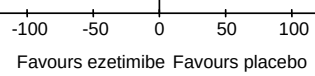
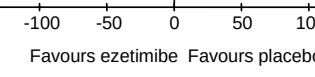


Figure 4: For patients in whom a statin is considered inappropriate, or is not tolerated: Mean % change in Total-c (mmol/L)

Comparison: 02 Ezetimibe versus Placebo
Outcome: 02 Total Cholesterol (Total-c) 12 week studies

Study or sub-category	Ezetimibe N	Ezetimibe Mean (SD)	Placebo N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
Dujovne	666	-12.48(9.81)	226	0.84(8.42)		35.49	-13.32 [-14.65, -11.99]
Ballantyne	65	-13.50(12.34)	60	3.50(11.85)		3.47	-17.00 [-21.24, -12.76]
Knopp	621	-12.40(9.47)	204	0.57(8.57)		32.24	-12.97 [-14.36, -11.58]
Melani	64	-13.20(9.60)	65	0.20(9.67)		5.65	-13.40 [-16.73, -10.07]
Bays	148	-13.30(10.95)	146	-1.40(10.87)		10.04	-11.90 [-14.39, -9.41]
Davidson	61	-13.30(11.72)	70	-0.60(11.71)		3.86	-12.70 [-16.72, -8.68]
Goldberg	90	-13.70(7.90)	92	2.20(9.90)		9.25	-15.90 [-18.50, -13.30]
Total (95% CI)	1715		863			100.00	-13.41 [-14.20, -12.62]

Test for heterogeneity: Chi² = 8.21, df = 6 (P = 0.22), I² = 26.9%
Test for overall effect: Z = 33.26 (P < 0.00001)



Efficacy analyses showed that ezetimibe reduced the plasma concentration of LDL-c from baseline to endpoint by a mean 18.56%, (95% CI -19.68, -17.44, p < 0.00001) compared to 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 to 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 versus other lipid-lowering (nicotinic acid, bile acid resins or fibrates) combinations.

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[37,128] and was around 25% to 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 to 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.[129,130,131]

5.2.2.4 Efficacy and safety of ezetimibe across different patient subgroups

Four studies have demonstrated[110,122,112,113] (Table 12a, b) LDL-c lowering effects of the treatment across different subgroups such people with or without existing CHD or other vascular disease, people with or without diabetes, different ethnic groups and patients with or without heterozygous familial hypercholesterolaemia. 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.

Table 12a: Mean % LDL-c reduction by patient subgroups

SUBGROUPS	ARMS	STUDY 1	STUDY 2
		Bays *et al.* 2004[110]	Goldberg *et al.* 2004[112]
Gender			
Male	Eze+Statin	-53	-51
	Statin	-39	-39
Female	Eze+Statin	-53	-53
	Statin	-39	-39
Age			
<65	Eze+Statin	-52	-52
	Statin	-38	-39
≥65	Eze+Statin	-45	-55
	Statin	-56	-40
Race			
White	Eze+Statin	-52	-52
	Statin	-39	-39
Non-white	Eze+Statin	-59	-43
	Statin	-38	-35
CVD risk factors			
Hypertension			
Yes	Eze+Statin	-54	-53
	Statin	-42	-39
No	Eze+Statin	-53	-52
	Statin	-37	-39
Established CVD			
Yes	Eze+Statin	NR	NR
	Statin	NR	NR
No	Eze+Statin	NR	NR
	Statin	NR	NR
Diabetes Mellitus			
Yes	Eze+Statin	-56	-56
	Statin	-38	-35
No	Eze+Statin	-53	-54
	Statin	-39	-39

All subgroup comparisons were not significant

Table 12b: Between treatment mean % LDL-c reduction by patient subgroups

	STUDY 3	STUDY 4
SUBGROUPS	Rodney *et al.* 2006[113]	Knopp *et al.* 2003[122]
	Eze+Statin vs.Statin	Eze vs. Placebo
Gender		
Male	-18	-17.5
Female	-17	-18
Age		
<65	-15	-18
≥65	-19	-18
Race*		
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

Rodney *et al.* 2006[113]was conducted only on African-Americans
All subgroup comparisons were not significant

Pooled analyses of three similarly designed 12-week double blind RCTs showed that superior lipid-altering effects of ezetimibe plus simvastatin vs. simvastatin observed in the entire cohort were consistent across all subgroups.[132] However, a recent meta-analysis[133] found that the LDL-c lowering effect of combination of ezetimibe and statins (simvastatin, atorvastatin, pravastatina and lovastatin) was lower in African –Americans compared to Caucasians. A study by Rodney *et al.*[113] 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 significant incremental reduction of 17.30% in LDL-c concentration compared to simvastatin alone. This reduction was also consistent to that observed in Caucasian population (average LDL-c reduction of 14%). However, 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 to 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 *et al*.,[117] it provided limited data. Further unpublished data obtained from the authors allowed a full 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, apart from that HeFH group were younger, proportionately greater male and lighter (Table 12). In terms of the baseline lipid profiles, the differences between the two groups were not as large as expected. After 14 weeks of treatment, ezetimibe plus atorvastatin treatment (Table 13) demonstrated consistent, significant favourable changes in both groups. LDL-c level reduced by reduced by 34.6% in HeFH group and 31.1% in non-HeFH group. Total-c level reduced by 27% in HeFH group and 24.7% in non-HeFH group. TG level was reduced by 16.3% and 23.4% in HeFH and non-HeFH groups respectively. 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 8), and were evaluated for statistical significance using a two-sample t-test (independent samples t-test). Although the HeFH group performed better in lowering LDL-c than the non-HeFH group, the analysis indicated that there was no statistically significant difference between the two estimates of clinical 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 was 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 no such evidence.

Table 13: Baseline characteristics of the HeFH and non-HeFH groups *(Obtained by personal communication from Stein et al. 2004[117])*

		HeFH group		Non- HeFH group	
		Atorva N=181	Eze+Atorva N=181	Atorva N=135	Eze+Atorva 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	< 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 Info	Yes[$]	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%)

[$] Subjects may appear in more than one category

Table 14: Changes in plasma lipid/lipoprotein concentrations (mmol/L) in HeFH vs. non-HeFH groups[117] *(Obtained by personal communication from Stein et al. 2004[117])*

Lipid profiles (mmol/L)	Baseline		End of treatment	
	HeFH	Non-HeFH	HeFH	Non-HeFH
	Mean (SD)	Mean (SD)	Mean % change (SD)	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 detail of the titration process of this trial is reported in Appendix 9

5.2.2.5 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 10. Meta-analyses were considered inappropriate due to insufficient data and low occurrences of the adverse events.

Ezetimibe alone (compared to 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 10, Table 64). 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 Aminotranspherase and Aspartate Aminotranspherase) 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 10, Table 65). Sixty three percent and 65% of participants reported as 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 as treatment-related adverse events. Serious treatment-related adverse events were not statistically

significant between statin group and the combination group. The number 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 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 ≥ 3x Upper Limit of Normal (ULN) were uncommon apart from Ballantyne *et al.* 2004b[118] study, which reported 2.3% vs. 2.4% for ALT and 1.2% vs. 0.8% for AST in the ezetimibe plus statin vs. statin monotherapy arms respectively. CK values ≥ 10 times 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 ≥ 10 times, ULN and liver function tests show no pattern of relationship with respect to ezetimibe, administered either alone or with statins. No particular trend was found for any adverse event category in either treatment groups. There were no clinically meaningful differences in 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.[134]

It is established that myopathy and rhabdomyolysis are known adverse events with statins, and occur more commonly at higher doses.[135] The low frequency of adverse events observed in the current review may be explained by the relatively short time periods of the studies.

5.2.2.6 Quality of life

No evidence was found which assessed health related quality of life (HRQoL) directly in individuals receiving ezetimibe monotherapy or coadministered with a statin.

5.3. Discussion

Thirteen RCTs (one of which was published as an abstract) assessing the clinical effectiveness of ezetimibe 10 mg/d 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 cardiovascular events or mortality. Main outcomes of all trials were percentage decrease in LDL-c during the study period. The evidence suggests that (1) for patients whose condition is not adequately controlled with a statin alone the combination treatment of ezetimibe with statins provides significantly more benefit by reducing LDL-c level by 13.94% compared to statin monotherapy; (2) for patients in whom a statin is considered inappropriate, or is not tolerated, ezetimibe monotherapy is associated with a significant decrease of LDL-c concentration of 18.56% compared to placebo arm. There is no evidence that the LDL-c lowering effect of ezetimibe differs across various patient subgroups such as people with higher CVD risk factors and established CVD. Although concerns were raised about the relatively short period of the studies, ezetimibe was generally considered to be well tolerated and combination of ezetimibe/statin has a safety profile similar to a statin alone.

All studies were described as multicentre, 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 as adequate. The number of withdrawals and reasons were presented. Study groups were comparable at baseline and overall likelihood of confounding bias was considered as moderate to low.

Only four trials reported the LDL-c lowering effect by different subgroups in section 5.2.2.4. 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 to those with established CVD. Even if the authors could make such comparisons (as has been discussed in HeFH vs. non-HeFH comparison, section 5.2.2.4), 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.

An abstract[120] reporting a statistical significance between two treatment groups (ezetimibe plus statin vs. niacin plus statin) provided limited information. Without examination of the detailed study method and outcomes it was not possible to fully evaluate and validate the results.

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. Particularly, 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.

It should be noted that 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 intolerant to statin treatment. No information was given in the primary studies about pre-trial medication of the participants.

Based on the meta-analysis (Appendix 11) it was evident that the short term studies (<12 weeks) are unlikely to adequately inform on sustainable effect over time, in terms of lipid lowering (incremental decrease of LDL-c of the ezetimibe was 22% and 14% in the 6-week and 12-week studies, respectively). While most of the 12 week studies initiated co-administration of ezetimibe and statin at the same time after washout of the ongoing lipid-altering drugs, patients in the six-week studies received ezetimibe in addition to their ongoing statin therapy.

No studies reported objective clinical endpoints (mortality and morbidity) and the effectiveness obtained from the reviewed studies relate to surrogate outcomes such as LDL-c. It has been widely accepted that surrogate outcomes such as LDL-c level are directly correlated to CVD mortality and morbidity. However, it is unclear if the ezetimibe induced changes in LDL-c will translate to observed reductions in CV events.

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, it has been 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 is unknown.

Although ezetimibe co-administered with statins appears well tolerated in clinical trials, there is no long term evidence that this strategy is any safer than maximising the dose of a statin. However, high dose statins are associated with increase adverse effects;[136,137,138,139,140] thus the incidence of those who cannot tolerate the drugs may also increase.[141] In order to avoid the risk of potentially serious adverse with high dose statin, a useful treatment option will include the addition of ezetimibe to a low dose of a statin. Moreover, if the long-term data of ezetimibe co-administered with statin shows a good or low adverse event profile, this strategy could be preferable to high dose or more potent statin treatments.

To date, there is limited evidence assessing effectiveness, safety and tolerability for co-administration of ezetimibe with other lipid lowering drugs. There is also a need for evidence on patients who are on treatment but haven't reached the lipid goals and patients with very high levels of plasma cholesterol. Studies of longer duration and head-to head comparison with nicotinic acid, resins, or fibrates are required to fully assess the efficacy of ezetimibe.

6. ASSESSMENT OF COST EFFECTIVENESS

6.1 Systematic review of existing cost effectiveness evidence

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

6.1.1 Search strategy

Studies were identified through searches of the following databases: Medline, Embase, Cochrane Library, NHSEED, 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 WWW. 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 31.

6.1.2 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 saved (LYS) or quality adjusted life-years (QALYs)
- Adult population (aged 18 years and over)

Exclusion criteria

- Studies that do not report results in terms of ICERs

6.1.3 Quality assessment strategy

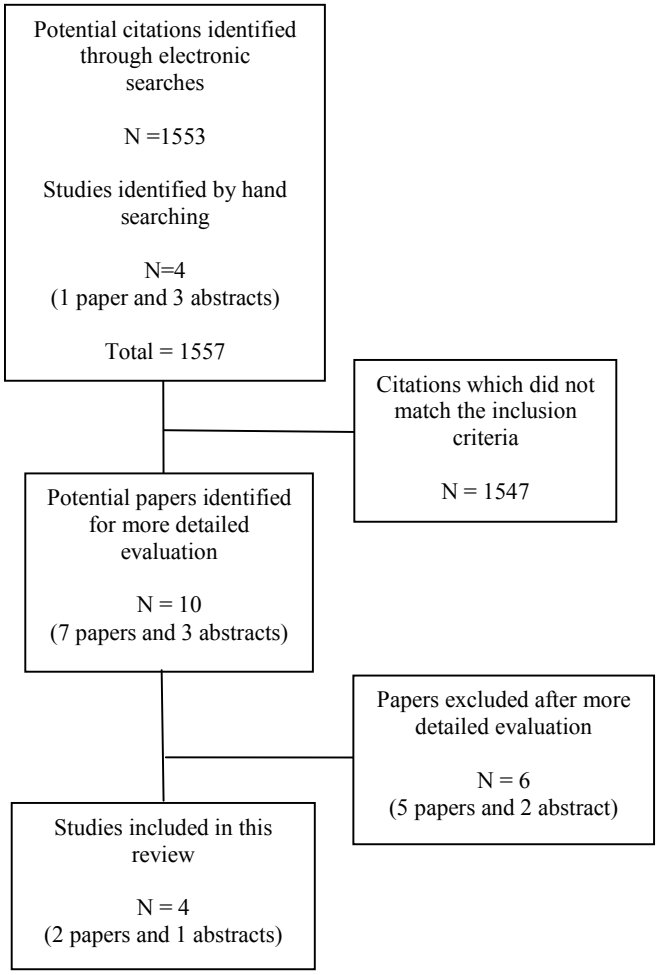
The Eddy checklist on mathematical models for technology assessments[142] in combination with the British Medical Journal checklist for economic evaluations[143] was used to assess the quality of studies.

6.1.4 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.[144,145,146,147,148,149] After more detailed evaluations of the full papers, it was found that one of the studies[146] was not a cost effectiveness analysis and two did not meet all the inclusion criteria because they were discussion about the use of ezetimibe and clinical practice.[144,149] Two studies were excluded as the results were presented as the drug cost versus percentage of LDL-c reduction.[147,148] One article satisfied all inclusion and exclusion criteria (Figure 5).[145] One additional potentially relevant study[150] and three abstracts were identified by random hand searching. One of the identified abstracts has not yet been published.[151] Two full articles and one abstract have been included in this review.[145,150,152,153] The abstract provides insufficient detail for review but is retained for information as it is the only UK (Scotland) based evidence.

Figure 5: Studies eliminated/selected for the review after applying the inclusion/exclusion criteria



Published cost effectiveness analyses

The two papers[145,150] and the abstract[152] included in the review describe country specific evaluations using a core economic model developed by Cook *et al.*[145] Only one study[152] 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 section 6.2, a very brief synopsis (Table 15) of the differences in the assumptions, parameter values and the reported results for the four studies identified in the literature searches is provided in the following 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 Great Britain pound using the Purchasing Power Parities,[154] and results are adjusted to 2006 using the Pay and Prices annual percentage increase (1.9%).[155]

Table 15: Summary of the cost effectiveness studies identified

Author (year)	Setting	Population	Treatment goal	Treatment strategies	Cost effectiveness Range (£)
Cook *et al.* (2004)[145]	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 to £49,867 (cost per LY)
Cook *et al.* (2004)[152] (Abstract only)	Scotland	Patients aged 65 years with no 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 to £8,511 £8,735 to £9,118 (cost per QALY)
Kohli *et al.* (2006)[150]	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 to £45,867 (cost per QALY)

Further details of the core model (originally published by Cook *et al.*[145]) are provided in section 6.2

Cook et al. Cost effectiveness of ezetimibe co-administration in statin-treated patients not at cholesterol goal: application to Germany, Spain and Norway. Pharmacoeconomics, 22 Suppl 3 (2004), 49-61.[145]

This study[145] evaluates the cost effectiveness of ezetimibe in three different countries: Germany, Spain and Norway. A health insurance perspective was used for the Germany evaluation while 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.

The cost effectiveness ratios for patients with CHD were under £18.9k per life-year gained (LYG) for ezitimibe plus statin versus statin monotherapy; and under £27.3k per LYG for ezitimibe plus statin versus 'titrate to goal'. The cost effectiveness ratios for diabetic patients with no history of CHD were under £27.3k per LYG for ezitimibe plus statin versus statin monotherapy and under £50.4k per LYG for ezitimibe plus statin versus against 'titrate to goal'.

Kohli et al. Cost Effectiveness of Adding Ezetimibe to Atorvastatin Therapy in Patients Not at Cholesterol Treatment Goal in Canada. Pharmacoeconomics, 24(8)(2006), 815-830.[150]
Kohli *et al.*[150] evaluated the cost effectiveness of ezetimibe treatment in a Canadian population. 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 (coronary artery disease) 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 cost effectiveness ratios for ezetimibe plus statin compared to atorvastatin monotherapy or atorvastatin titration ranged from £26.2k to £45.9k per QALY. The cholestyramine plus statin treatment was dominated by the ezetimibe plus statin treatment.

Cook et al. The cost effectiveness in CHD and CHD equivalent patients not at total cholesterol goal on statin monotherapy in Scotland. Abstract (2004) European Society of Cardiology Annual Meeting (ESC), August 28 – September 1, Munich, Germany.[152]
This abstract[152] presented a cost effectiveness analysis of ezetimibe plus statin treatment for patients with CHD not reaching their Total-c goal of < 5mmol/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 £8.9k while for ezetimibe plus statin versus statin monotherapy the cost per QALY was £8.3k.

Based on the information provided within the manuscripts, 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 CTTCs. 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 £45.8k per QALY for patients with an average age of 65 years with no history of CHD when comparing ezetimibe plus atorvastatin 10mg versus atorvastatin titrated. When comparing ezetimibe co-administered with current statin compared to current statin treatment with no titration in Germany the results for adults with a history of CHD were £7.7k per life year while the results for adults with diabetes but no history of CHD in Spain were estimated to be £50.7k per life year when comparing ezetimibe co-administered with current statin treatment compared with current statin treatment titrated by one dose. The results for Scotland were estimated to be approximately £8.0k per QALY for patients with an average age of 65 years with a history of CVD when comparing ezetimibe plus current statin therapy versus titration of current statin.

6.2 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, while 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 section 6.1. 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.

6.2.1 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 stroke, secondary MI, secondary angina, no event in previous 12 months, CHD death, and non CHD death (Appendix 14). The probability of non-fatal strokes are 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 weighted according to the distribution of secondary events observed in the Framingham cohort.[87] The UK Prospective Diabetes Study (UKPDS) algorithms are used to calculate probabilities of events for diabetic patients with no history of CHD.[156] The predicted risk for primary CHD diabetic patients is distributed across fatal CHD and non fatal MI using a combination of UKPDS equations.[86,157,158] The UKPDS 60 is used to predict the probability of a stroke.[159]

A one 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 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 cardiovascular 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.[160] 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.

Table 16: Treatment scenarios evaluated in the MSD/SP economic evaluation

Population[a]	Treatment 1	Treatment 2
Basecase a: ezetimibe plus current statin vs. double the dose of current statin **Basecase 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 20mg & 50% simvastatin 40mg		
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 20mg & 50% on simvastatin 40mg	50% on atorvastatin 20mg & 50% on atorvastatin 40mg
Alternative Scenario 2: titration of high cost statin vs. switch to low cost statin plus ezetimibe Assumes current statin therapy: 50% atorvastatin 10mg & 50% atorvastatin 20mg		
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 20mg & 50% on atorvastatin 40mg	ezetimibe plus 50% on simvastatin 20mg & 50% on simvastatin 40mg
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 pharmacologic treatment

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

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

Table 17: Baseline lipid levels and additional risk factors modelled in MSD/SP economic evaluation

	HDL-c	SBP	DM	Smoke	HbA1c	Risk engine
	mmol/L	mm.Hg	%	%		
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

SBP = systolic blood pressure; DM = diabetes mellitus

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).

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 17)	[redacted]	[redacted]
Ezetimibe monotherapy Source: MSD/SP meta-analysis (Appendix 17)	[redacted]	[redacted]
Double statin dose Knopp *et al*.[68] McKenney *et al*.[161]	[redacted]	[redacted]

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.[135] The costs of the CHD events (but not the monitoring costs) are inflated to 2006 costs using a 3.8% annual inflation rate.

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	£4,792	£184
Fatal CHD	£1,256	n/a
Monitoring costs	£124	£33.42

Costs of treatments used in the Cook model

All treatment costs (Table 61 Appendix 14) 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 (Table 62 Appendix 15) are used to derive a weighted average (Table 20) cost of statin for the basecase analyses.

Table 20: Weighted average 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 10mg (20mg)	£0.1001	
Atorvastatin 10mg (20mg)	£0.945[a]	
Ezetimibe 10mg	£0.94	

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

Utilities used in the Cook model

The health state quality of life utilities and the utility by age is 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.[162,163,164,165] 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 nonfatal 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 nonfatal CHD event and the benefit of lipid lowering.

6.2.2 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 risk.[79] The objective of this model was to test if the ICERs generated were comparable with 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[68,161]
- Ezetimibe co-administered with statin treatment gives an [redacted] in LDL-c compared to 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 (at £0.94 per day) plus a weighted average dose of: generic and branded simvastatin (10mg, 20mg, 40mg, 80mg), atorvastatin (10mg, 20mg, 40mg, 80mg), generic and branded pravastatin (10mg, 20mg, 40mg, 80mg), and rosuvastatin (5mg, 10mg, 20mg, 40mg (at £0.4162 per day) versus a weighted average dose of generic and branded simvastatin (20mg, 40mg, 80mg), atorvastatin (20mg, 40mg, 80mg), generic and branded pravastatin (20mg, 40mg), and rosuvastatin (10mg, 20mg, 40mg) (at £0.6733 per day)
2) Ezetimibe (at £0.94 per day) plus with 50% of individuals on simvastatin 20mg and 50% of individuals on simvastatin 40mg (at £0.1001 per day) versus 50% of individuals on atorvastatin 20mg and 50% of individuals on atorvastatin 40mg (at £0.945 per day).

6.2.3 Cost effectiveness results estimated by the MSD/SP models

Results from the Cook MSD/SP model

The results are presented in terms of incremental cost effectiveness ratios (ICERs) and are summarised in Table 21. The basecase (a) evaluates ezetimibe plus current statin therapy compared to titration of current statin therapy. The results range from £8.8k per QALY (for South Asian males at high risk of a CHD event aged 60 with a baseline Total-c of 6.5 mmol/L), to £122k per QALY (for females with no history of CVD aged 80 with a baseline Total-c of 4.5 mmol/L).

Table 21: Summary of results from the Cook model[a]

Population	Patient profile[b]	Disc ICER £,000
Basecase (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
Basecase (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	M, 60, 6.5	9.9
Maximum: Females with no history of CVD	F, 80, 4.5	131.1
Alt 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
Alt 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 18 [b]patient profile = gender (M=male, F=female), age, baseline Total-c

Results from the Basic MSD/SP model

The authors conclude the simplified model "gives results of a similar order to those calculated using 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 £21.1k 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 £2.0k 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 £20k 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 £20k per QALY none of the treatment regimens are cost effective (Appendix 19).

6.2.4 Critique of the MSD/SP economic models

The authors of the MSD/SP economic evaluation were approached at an early stage of the review regarding a number of potential issues identified (Appendix 18). These included a) the treatment regimens compared in the alternative scenarios 1 and 2, b) the large differences in the ICERs for the male and female populations, c) the method used to distribute predicted risk across event type, and d) the CEACs presented. The full responses are provided in Appendix 18 and are summarised below. This is followed by a more detailed review of the submitted models (see Table 21).

a) The MSD/SP analysts agreed that the treatment regimens compared in Scenario 1 were the same as the treatment regimens compared in Scenario 2 (Table 15), i.e. Each Scenario compares the cost effectiveness of regimen 1 with regimen 2. The analysts explained the differences in the ICERs was due to a rounding down of the treatment costs used in one of the scenarios which was noticed at a late stage in the submission process. As the regimens compared are the same in both scenarios then one set of results must have both a negative incremental cost and a negative incremental benefit, implying dominance. This is not discussed in the MSD/SP report. It should be noted that a slightly different cost is used for weighted statin treatment in the Basic model (Table 19).

b) In response to the query regarding the large differences in the ICERs generated for the male and female primary prevention analyses, the MSD/SP analysts suggested "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". However, the calculations they provide to support their explanation appear to have been estimated outside the model (Appendix 18). The clarification does not sufficiently explain the large differences in the reported results. The calculations used in the model have been examined in

more detail and the findings are discussed below (Table 22 and Appendix 19). In summary, an error in the MSD/SP code means that the risks and thus the number of events avoided in the female analyses are underestimated. This error has a large impact on the results.

c) In response to the query regarding the allocation of predicted risk across event type, the analysts stated "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", and "when a negative result does occur, we set the risk of Angina to 0". Allocating zero events to the angina health state does not reflect the expected distribution of events observed in either individuals at high risk or those with a history of CVD. The method used has been examined in more detail and the findings are discussed below (Table 22 and Appendix 19). In summary, this methodology biases the results in favour of ezetimibe treatment and the magnitude of the error could be substantial.

d) The MSD/SP analysts clarified that the CEACs labelled "people" in the submission document were the results for the male cohorts only and provided the corresponding plots for the female cohorts (Appendix 18).

Table 22: Summary of the review of the methods and assumptions used in the Cook model

	Method/Variable	Method	Issue	Implication on results generated
1	Modelling benefit from treatment regimens	CHD/stroke risk for all treatment arms in the model are predicted using Framingham & UKPDS risk engines. Predicted risks in each arm are based on changes in Total-c:HDL-c due to treatment.	These algorithms were not formulated to predict changes in cardiovascular risk based on chemically induced changes in lipid profiles. Evidence is now available to link chemically induced changes in lipids (i.e. statin) to reductions in cardiovascular risk based on the meta-analysis performed by the CTTCs[79]	This method is used in every analysis and thus affects every result from the sophisticated model. It is possible that this methodology will overestimate the number of events avoided in which case both the cost offsets and benefits from events avoided could be overestimated. As the majority of scenarios modelled compare two treatments it is not possible to estimate the magnitude of the impact on the ICERs generated.
2	Primary risk for females	d'Agostino primary event algorithm	Risks estimated using the d'Agostino primary CHD event algorithm for females are incorrectly calculated. The predicted risks are underestimated. It is interesting to note that while detailed explanations and worked examples are provided for the primary CHD diabetic and the secondary CHD calculations, an example is not provided for the primary CHD non diabetic calculations.	As the predicted risks are underestimated the number of events in both arms of the model is underestimated. It is probable that the incremental number of events avoided is also underestimated. While it is believed the benefits and costs associated with the treatments could be underestimated it is not possible to estimate the magnitude of the impact on the ICERs generated, but it is thought this could be substantial.
3	Reported, predicted and modelled risks	Anderson d'Agostino code Markov traces	The risks reported in the results tables do not correspond to the risks predicted using the MSD code or the risks modelled (calculated from the Markov traces). The risks modelled are greater than the values predicted using the code, thus the number of	All the analyses examined exhibited this anomaly suggesting that the full set of analyses may be using the incorrect risk. If the error between the predicted and modelled risk is cumulative over the whole horizon modelled, the impact on the ICERs could be considerable.

			events are overestimated.	As the modelled risk is greater than the risk predicted by the code the benefits of treatment are possibly overestimated.
4	Modelled risk	The minimum possible time horizon in the d'Agostino algorithms is 4 years. To use this risk in the annual transitions in the model, the analysts have assumed that an annual risk is 1/4 of a 4 year risk.	This is a crude assumption and is mathematically incorrect. The correct annual rate is larger than the annual rate estimated using this assumption.	As this assumption is used for every analysis and each time the risks are updated (annually) this affects every results presented. As the actual risk is underestimated the number of events avoided could be underestimated. As the errors are cumulative the total incremental costs and benefits due to the treatments could be underestimated and the magnitude of the error in the ICERs generated could be substantial.
5	Distribution of risk across event type	Anderson equations for individual events are used to estimate the distribution across events with the balance assigned to angina.	The methodology used is flawed. The summed probabilities for the individual events are frequently larger than the overall risk. If the summed probabilities are larger than the predicted risk a mechanism within the code sets the probability of angina equal to zero. Setting the probability of angina to zero does not reflect the distribution of coronary events in the UK. Markov traces from the model show that patients receiving treatment have more angina events than those who receive no treatment.	The benefits of treatment are overestimated as the distribution across event type is unequal in both arms – patients on no treatment are distributed across the more serious events while those receiving treatment are distributed across all event types. Hence costs in the treatment arms are underestimated and benefits are overestimated. It is unknown how many of the analyses are affected by this error. The magnitude of the impact on the ICERs is unknown but as the benefits of treatment are overestimated the ICERs could be higher than estimated.
6	Data used	Health state costs	The inflation rate used for the health state costs is not referenced and appears to be high 3.8%.	The cost offsets due to events avoided are underestimated thus the ICERs should be lower than estimated
7		Monitoring costs	Incorrect costs used and incorrectly applied.	The monitoring costs are overestimated. As these are applied to all patients in the majority

				of the analyses, depending on the ratio of cost and benefits, the errors may cancel. For the analyses exploring the ezetimibe monotherapy with no treatment the costs associated with treatment are overestimated.
8		Treatment costs	As stated previously, three different costs have been used for the scenarios involving atorvastatin treatment.	The rounding will have a minimal impact on the results generated.
9		Treatment costs	Drug tariffs are used as opposed to BNF.	Treatment costs in all the evaluations are underestimated. However, as they are underestimated in both arms in the majority of analyses (with the exception of the comparison against no treatment), the impact is likely to be small.
10	Diabetic analyses	UKPDS	Evaluate the costs and benefits associated with MI and fatal CHD events only. The benefits due to changes in treatment are different when using the UKPDs and Anderson equations. Evidence suggests that there is no significant difference in the benefits received from lipid therapies for diabetic and non diabetic patients.	As only MI and fatal CHD events are modelled for diabetics, the ICERs generated are not directly comparable with those for the non diabetic patients. It is possible that the ICERs are overestimated for the primary diabetic patients. (i.e. they should be lower)

[a] more detailed discussion is provided in Appendix 19

Summary of the review of the MSD/SP models and the validity of the results

It is acknowledged that when the Cook model was originally constructed, the algorithms from the Framingham study was potentially the most appropriate methodology for predicting future cardiovascular events in economic models when only surrogate outcome measures were available. However, this methodology has been superseded by the evidence published by the Cholesterol Treatment Trialists Collaborators (CTTCs) which enables chemically induced changes in lipids to be linked to reductions in cardiovascular risk based on evidence from lipid lowering RCTs (section 3.1.1).[79]

In addition, the calculations and assumptions used to predict risks in the Cook model are inaccurate (Appendix 20). Some of the errors under predict risk and benefit from treatment while others over predict risk and benefits from treatment. The methods used to distribute predicted risks to event type are flawed and do not represent the observed distribution of events. These errors overestimate benefits of treatment. The health state, monitoring and treatment costs are incorrect. Some of the errors underestimate costs while others overestimate the costs associated with the disease.

The evidence which links treatment induced changes in LDL-c and cardiovascular risk was used by the MSD/SP analysts in the Basic model. While 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 (page 242 Appendix 28 of the industry submission report) using several strong assumptions. In addition treatment and health state costs are incorrect.

The reviewers have not attempted to either correct the errors detected or modify the methods and simplifying assumptions used in the models. Furthermore, since there are several errors acting on conflicting directions it is impossible to estimate the full magnitude or direction of errors in the reported ICERs for each of the individual analyses and subgroups. The results generated using the MSD/SP models are therefore not considered to be robust.

6.3 Independent economic assessment by ScHARR

6.3.1 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) 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.

6.3.2 Methods

A Markov model was developed to explore the costs and health outcomes associated with a lifetime of treatment using a UK NHS perspective. The Framingham risk equations are used to derive baseline risks.[77,87] Effectiveness of treatments is modelled using a reported link between chemically induced LDL-c reductions and cardiovascular 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. Input parameters are characterised by probability distributions and Monte Carlo simulations performed to reproduce this uncertainty in the results. Results are presented in terms of cost per quality-adjusted life years (QALYs).

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 23. Individual sources are referenced, as appropriate, in the report. An overview of the methods used to identify evidence base supporting the model is presented in Appendix 30.

Table 23: Key sources of evidence used to inform 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. BNF)

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 (3 mmol/L), moderate (3.5 mmol/L), and high (4 mmol/L) baseline LDL-c measurements

Population subgroup analyses, diabetic cohort

There is limited evidence on the effectiveness of ezetimibe in diabetics and the evidence available is not reported in sufficient detail to establish if there is any significant difference in the effectiveness of ezetimibe treatment on diabetic and non diabetic patients. However, diabetics are at an increased risk of CHD and incidence rates are thought to be twice as high as non diabetic patients. As in the Statin NICE appraisal, it is assumed that primary event rates are twice as high for diabetics as non diabetics (Personal communication Dr Wilf Yeo, Consultant Physician & Senior Lecturer in Clinical Pharmacology & Therapeutics, Royal Hallamshire Hospital).[39]

Population subgroup analyses, HeFH cohort

Individuals with HeFH have a history of premature CHD and form a high risk sub-group. Robust epidemiological data describing event rates in untreated patients is scarce and as the effectiveness of preventing coronary morbidity and mortality by treating with statins is now established in patients with elevated cholesterol levels, clinical evidence in patients with FH is scarce due to the ethical implications of not treating these individuals. A recent review suggests that the elevated serum cholesterols concentrations lead to a greater than 50% risk of a fatal or non fatal coronary event by the age of 50 years in males and to a greater than 30% risk by the age of 60 years in females. Although a SMR as high as 100-fold at ages 20-39 years has been reported, this was based on a very small number of deaths (n=6),[166] and a relative risk of death of 3-4 fold in untreated patients has been reported.[19]

The Framingham risk equations[77] have not been shown to be valid for this population[167] and it has been assumed that the baseline risk is two times that of individuals without HeFH. However, the probability of subsequent events is likely to be similar to those used in the basecase (Personal

communication Dr Wilf Yeo, Consultant Physician & Senior Lecturer in Clinical Pharmacology & Therapeutics, Royal Hallamshire Hospital).

A recent Dutch study exploring the impact of environmental and genetic factors on individuals with FH reported mean baseline LDL-c levels of 8.38 mmol/L (SD 2.13) after a 6 week washout period.[168] It is assumed that baseline LDL-c levels will be lower than those reported in the Dutch study as the majority of patients with HeFH will be on current lipid lowering treatments and the baseline LDL-c measurements modelled for this cohort are 4.0 (5.0, 6.0 and 7.0) mmol/L.

Aggressive LDL-c therapy in the form of multiple treatments is more frequent in patients with HeFH but due to lack of robust data it is not possible to model combination treatments compared to ezetimibe plus a statin. It is assumed that these patients will require more potent statin treatment than patients without HeFH and the analyses use the treatment regimen described in scenario 4, i.e. ezetimibe co-administered with atorvastatin compared with switching to an equivalent dose of the more potent rosuvastatin.

Although the results of the subgroup analyses comparing the HeFH and non HeFH cohorts in the Stein study[117] are not statistically significant (Appendix 11), they suggest that patients with HeFH could gain more in terms of reductions in LDL-c. As the observed percentage reductions are smaller in this study than observed in the main studies (see Figure 1) the results (HeFH mean reduction in LDL-c = 14.50%; non-HeFH mean reduction in LDL-c = 10.60%) are adjusted using the results of the meta-analysis of the main studies (mean reduction in LDL-c = 13.94%; Figure 1): percentage reduction for HeFH = 14.5%*13.94%/10.6% = 19.07%.

Non-European groups

Patients of non-European descent and in particular British Asian have an incidence rate that is approximately 1.5% higher than the basecase. However, it is thought that transitions between health states will be similar to that modelled for the basecase and utilities and costs are unlikely to differ (Personal communication Dr Wilf Yeo, Consultant Physician & Senior Lecturer in Clinical Pharmacology & Therapeutics, Royal Hallamshire Hospital, Sheffield, September 2004). Non-European groups are not modelled explicitly as there is no direct evidence of a difference of effectiveness for this population from the clinical studies.

Treatment / Comparator

NICE guidance recommends statin treatment for individuals with existing CVD and those with a 10 year CVD risk ≥ 20%[39] with therapy initiated with a drug with a low acquisition cost. 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.[169] However, it is likely that more aggressive lipid lowering strategies will prevail due to the anticipated changes to both the GMS contract and the QOF, and a shift towards payment by result.[46] Consequently the proportion of individuals who would have remained on current statin therapy without modification are expected to decrease.

Comparator literature search

A systematic literature search (reported in Appendix 21) was undertaken to identify possible comparators. Published systematic reviews and meta-analyses of lipid lowering therapies identified in the systematic review described in section 5, were used to identify studies on the possible comparators. New evidence and studies excluded from the existing reviews were identified through a berrypicking technique[170] 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.

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

- nicotinic acid, bile acid resin, a fibrate or a comibination 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 contra-indicated and those in whom statins are not tolerated the results of the literature searches suggest 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: 2.51%, 0.17% and 0.02%[44] of patient days of lipid-lowering therapy in the UK possibly due to poor tolerability and palatability, moderate effects on LDL-c levels, and a high prevalence of intolerable side effects (section 3.2). These treatments are generally reserved for individuals with hypertriglyceridaemia, mixed hyperlipidaemia, HeFH or diabetes.

Based on expert opinion [personal communication W. W. Yeo, May 2006], small prescribing rates, and the conflicting evidence on the effectiveness of fibrates [personal communication S Robins, 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 (24g/d) involving over 3,800 individuals.[171] 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. [personal communication P. Durrington, June 2006]

Niacin is very rarely prescribed in the UK and is not generally used to achieve an LDL-c target [personnel communication P Durrington, October 2006]. This treatment can also cause unpleasant adverse events[43] particularly when taken in the larger doses that would be required to achieve targets. The minimum dose that would be applicable is 1g/d [personnel communication P Durrington, October 2006]. A placebo controlled trial by Knopp *et al.*[68] using niacin 1.5g/d 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 contra-indicated 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: for individuals who are tolerant of statins

Scenario 1 compares ezetimibe co-administered with current statin therapy versus titration of current statin therapy to the next dose.

Current statin therapy and the corresponding weighted cost is based on published data on prescribing rates in the UK and Wales.[44,45] Co-administered with ezetimibe (10 mg/d), this treatment regimen is compared with titrating to the next dose of statin therapy.

Scenario 2: for individuals who are either contra-indicated for statin treatment or in whom statin therapy is not tolerated

Scenario 2 explores the costs and benefits in individuals who are either contra-indicated for statin treatment or in whom statin therapy is not tolerated. The treatment regimens are ezetimibe (10 mg/d) monotherapy compared with no treatment.

Scenario 3: for individuals who are tolerant of statins

Scenario 3 compares ezetimibe co-administered with generic simvastatin to "switching" to a more potent dose of atorvastatin.

The UK guidelines for statin treatment recommend initial therapy is based on the lowest acquisition cost.[39] Prescribing data suggests that this recommendation is adhered to in general with almost 50% of patient days of treatment in England being generic simvastatin.[44] The majority of the balance is accounted for by atorvastatin therapy.[44] Based on this, scenario 3 compares ezetimibe (10 mg/d) co-administered with generic simvastatin (50% of individuals receiving simvastatin 20 mg/d and 50% receiving simvastatin 40 mg/d) with atorvastatin (50% of individuals receiving atorvastatin 20 mg/d and 50% receiving atorvastatin 40 mg/d).

Scenario 4: For individuals who are tolerant of statin who require more potent treatments to achieve targets

Scenario 4 compares ezetimibe co-administered with atorvastatin versus switching to an equivalent dose of the more potent rosuvastatin.

The prescribing data demonstrates that a large proportion of individuals receive atorvastatin.[44] RCT evidence suggests rosuvastatin is potentially the most potent statin currently available. While current prescribing rates for rosuvastatin are comparatively small, it is possible that a larger proportion of individuals, who have very high baseline LDL levels (such as those with HeFH) may require rosuvastatin treatment to achieve target lipid levels. Scenario 4 compares ezetimibe (10 mg/d) co-administered with atorvastatin (75% of individuals receiving atorvastatin 20 mg/d and 25% receiving atorvastatin 40 mg/d) versus switching to a more potent dose of rosuvastatin (75% of individuals receiving rosuvastatin 20 mg/d and 25% receiving rosuvastatin 40 mg/d).

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 (Figure 6). 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.[172,173,174] 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

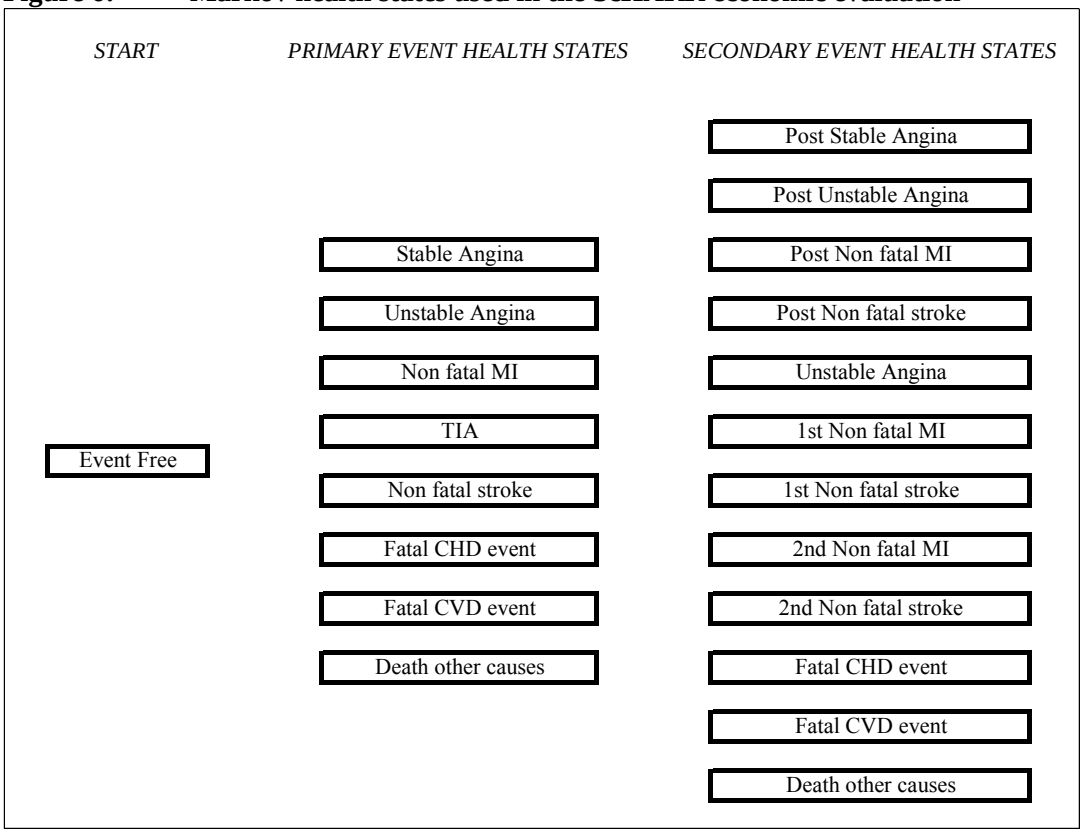
When assessing the impact of treatments on reducing major events such as MIs, strokes and cardiovascular deaths, a lifetime horizon is appropriate to explore the full costs and benefits accrued through events avoided. However, in the current evaluation, this requires two large assumptions: a) the surrogate outcomes (changes in lipids) will translate to reductions in cardiovascular events and b) that the extremely short-term surrogate outcomes will be sustained over long time horizons. Unless otherwise stated the analyses are presented using a time horizon of 20 years. However, additional results are reported a) assessing the costs and benefits accrued when using a 5 year or a lifetime horizon, b) truncating treatment at 2, 5 or 10 years but accruing the costs and benefits associated with events avoided over 20 years.

Markov health states modelled

For the purposes of this evaluation, a CVD event is defined as onset of stable angina (SA), unstable angina (UA), a non fatal MI (MI), death from CHD related causes (FCHD), a transient ischaemic attack (TIA), a non fatal stroke (ST) or death from stroke/TIA related causes (FCVD). 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. 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, stroke, CVD death or death through other causes while the remainder remain in the event free state.

Figure 6: Markov health states used in the ScHARR economic evaluation



A full list of the possible transitions are provided in Appendix 24

For the secondary prevention analyses all patients commence in either post stable angina, post MI, post TIA or post stroke health states. In each subsequent cycle, patients in a non-fatal health state move to an equivalent or more severe non-fatal health state, die through CHD, CVD or other

causes, or move to a post health state. The secondary analyses allow a maximum of two secondary events, while primary analyses also allow one primary event. A full list of possible transitions is provided in Appendix 24.

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.[175] As per current NICE guidance, discount rates of 3.5% are applied to both costs and health benefits.[175,39] However, to fully inform decision makers, the basecase results are also reported undiscounted. Costs are at 2006 prices. Half cycle correction is used for both costs and benefits.

Baseline LDL-c measurements

In the clinical effectiveness review (section 5), most of the included studies required washout or discontinuation of all ongoing lipid regulating drug therapy for up to 12 weeks prior to randomisation and initiation of study treatments. These trials are not reflective of routine clinical practice and do not accurately represent the target population.

As the population considered in the current evaluation are prescribed ezetimibe in addition to ongoing treatment, data was sought from studies where subjects received ezetimibe treatment without a washout period. This data was derived from a meta-analysis (Appendix 11, raw data not reported) of short-term six to eight week studies which suggested that baseline LDL-c levels for individuals on ongoing lipid lowering treatment ranged from 3.1 mmol/L (SD=0.38)[123] to 3.6 mmol/L (SD=0.10).[176] For the main analyses three different baseline LDL-c measurements are assumed: mild (3.0 mmol/L), moderate (3.5 mmol/L), and high (4.0 mmol/L).

Baseline CVD risks modelled in the ScHARR economic model

The HSE patient level data are used to generate typical profiles (age, gender, TC, HDL-c, SBP, smoking status) of individuals in the UK whose 10 year CVD risk is greater than 20%.[177] These are then used to generate a 10 year CVD risk using the Anderson primary CVD risk equation.[77] An annual rate is then derived using the formula: annual rate = 1-(1-10 year probability) ^ (1/10). For example, a 10 year risk of 31.1% has an annual rate = 1-(1-31.1%)^(1/10) = 3.66%.

There is currently no risk equation to predict the probability of a secondary CVD event for individuals with a history of CVD. The probability of a secondary CVD event is calculated as

follows: predict the risk of a secondary CHD event using the d'Agostino secondary CHD risk equation, increase the predicted CHD risk to a corresponding CVD risk by using the ratio of CHD:CVD risk derived when predicting risks using Anderson's primary CHD and CVD risk equations.[77,87] For example, for a non smoking male aged 60 years (with SBP=144 mg/Hg, HDL-c=46 mg/dL, Total-c=270 mg/dL) the 10 year primary CHD risk is 20% (annual rate = 2.2%), and the primary CVD risk is 26.1% (annual rate = 3.0%). The secondary CHD annual risk is 5.15% and the secondary CVD annual risk is 7.1% (7.1% = 5.18% X 3.0% / 2.2%).

While the primary baseline risks modelled are approximately equal for males and females of corresponding ages, the female secondary CVD risk is smaller than the corresponding male risk for each age group (Table 24). The increases in risks by age reflect the trends observed in the HSE data and thus rise steeply for the oldest age groups. The baseline risks are updated annually using gender specific regressions derived from analyses of the HSE 2003 data. The natural increase by age is less rapid for females than males reflecting the trends observed in the HSE data.

Table 24: Baseline 10 year CVD risk and corresponding annual CVD rate used in the ScHARR economic evaluations

Age	10 year CVD risk	Primary Annual CVD rate	Secondary Annual CVD Rate	10 year CVD risk	Primary Annual CVD rate	Secondary Annual CVD Rate
	Males			Females		
45	20%	2.2%	5.8%	20%	2.2%	4.1%
55	23%	2.6%	6.7%	24%	2.7%	3.8%
65	28%	3.3%	7.6%	28%	3.2%	4.8%
75	34%	4.1%	8.6%	34%	4.0%	7.1%

Distribution of risk across health states

As per recommendations,[175] UK specific data are utilised where possible and UK epidemiological data (Table 25) are used to apportion the total predicted risk to event type and to allocate starting distributions for the secondary analyses.

The HSE data suggests distributions across event types have changed in recent years and published data on incidence rates[178,179,180,181] is calibrated (Table 25) to obtain a more accurate reflection of the observed trends in the HSE 2003 data.[182,182]

Table 25: Distribution across primary events in the ScHARR economic evaluation

Age	Stable Angina[a]	Unstable Angina[a]	MI[a]	Fatal CHD[a]	TIA[b]	Stroke[c]	Fatal CVD[b]
Male							
45	28.2%	7.7%	22.8%	6.3%	11.6%	22.8%	0.5%
55	26.5%	8.3%	22.1%	8.1%	8.9%	22.1%	4.0%
65	23.3%	8.5%	21.8%	9.1%	7.0%	21.8%	8.6%
75	20.0%	8.6%	21.6%	9.7%	5.4%	21.6%	13.2%
Female							
45	45.9%	12.1%	11.2%	6.4%	8.5%	11.2%	4.8%
55	33.3%	8.3%	13.2%	7.8%	11.3%	13.2%	13.0%
65	26.5%	6.3%	14.0%	8.4%	12.2%	14.0%	18.8%
75	22.2%	5.0%	14.4%	8.7%	12.6%	14.4%	22.7%

[a] Sutcliffe *et al.*[178], [b] Dennis *et al.*[179] and Bamford *et al.*[180], [c] Rothwell *et al.*[181]

It is assumed that individuals do not move from a more severe health state to a less severe health state (see Appendix 24 for full set of transitions) hence angina and TIA are not included in the distribution of secondary risk (Table 26).

Table 26: Distribution across secondary events in the ScHARR economic evaluation

Age	Unstable Angina	MI	Fatal CHD	Stroke	Fatal CVD
Male					
45	13%	38%	11%	38%	1%
55	13%	34%	12%	34%	6%
65	12%	31%	13%	31%	12%
75	11%	29%	13%	29%	18%
Female					
45	27%	25%	14%	25%	11%
55	15%	24%	14%	24%	24%
65	10%	23%	14%	23%	31%
75	8%	22%	13%	22%	35%

Prevalence data from the Health Survey for England[182] is used to distribute individuals across the post angina, MI and stroke health states for the secondary evaluations (Table 27). In the absence of relevant data, the prevalence for TIA is estimated as 25% of the stroke rate. Uncertainty is explored using beta distributions.

Table 27: Starting distributions for secondary analyses in the ScHARR economic evaluation (prevalence data)[182]

Age	Post Stable Angina	Post MI	Post TIA	Post Stroke
Males				
45	31%	43%	5%	21%
55	31%	46%	4%	18%
65	28%	42%	5%	25%
75	25%	38%	5%	32%
Females				
45	39%	27%	7%	28%
55	32%	26%	8%	34%
65	32%	27%	8%	33%
75	33%	28%	8%	31%

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 CTTCs analysts established there was an approximate linear relationship between absolute reductions in LDL-c and the proportional reductions in major vascular events (section 3.1). When sub-grouped 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 major vascular events of about 23% as opposed 21% when using the weighted analysis. The proportional reduction varies according to event type and the relative risks corresponding to a reduction of one mmol/L LDL-c are provided in Table 28.

Table 28: Proportional effects on major vascular events per mmol/L LDL-c reduction

Event	RR	95% CI	Source
Non fatal MI	0.74	0.70 – 0.79	Table 2, CTTCs[79]
Angina	0.74	0.70 – 0.79	see text below
CHD death	0.81	0.75 – 0.87	Table 1, CTTCs[79]
Any stroke	0.83	0.78 – 0.88	Table 2, CTTCs[79]
TIA	0.83	0.78 – 0.88	see text below
Fatal stroke[a]	0.91	0.74 – 1.11	Table 1, CTTCs[79]
Any major vascular event	0.79	0.77 – 0.81	Table 2, CTTCs[79]

[a] assumed relative risk (RR) = 1, see text below, RR = relative risk

A number of assumptions were used to apply the link in the model:

- 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 stroke
- The RR for fatal stroke is equal to one, as the CI cross one and evidence from a recent meta-analysis of RCT event rates was also inconclusive[39]
- 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, CTTCs)
- The proportional reduction in event rate per mmol/L in LDL-c is independent of baseline prognostic factors (Figure 5, CTTCs) such as age, sex, diabetes status or CVD history

The CTTC findings suggest a highly significant 10% proportional reduction in major vascular events per unit 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,[183,184,185] no benefits are modelled in the first year of treatment. This is possibly a conservative assumption and the affect of varying the time delay in treatment effects is explored in sensitivity analyses.

It has been assumed that treatments have no impact on the relative risk of fatal stroke. 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 stroke and while the reported RR from the CTTCs is used in the basecase, the impact of modelling no benefits on stroke 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 cardiovascular 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 cardiovascular events remains unknown.

When conducting the analyses for individuals with HeFH who have very high baseline LDL-c levels the link between LDL-c and CV events is extrapolated beyond the majority of data used in the meta-analysis (see Figure 5 in CTTC article[79]).

Benefits of treatments

The benefits of treatment regimens modelled are derived from published data on reductions in LDL-c. The effectiveness of ezetimibe monotherapy and ezetimibe in combination with statin therapy are based on the meta-analyses in section 5.2. It is assumed that statin titration of one dose provides an additional reduction of 6% based on meta-analysis of RCT evidence.[68]

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 the population considered in the current evaluation are prescribed ezetimibe in addition to ongoing treatment, a sensitivity analysis is conducted using evidence of a meta-analysis of shorter studies where subjects received ezetimibe treatment without a washout period (Appendix 11).

Table 29: Mean change in LDL-c for treatment regimens used in the ScHARR economic evaluation

Treatment regimen	% LDL-c change[a] mean (95% CI)	Source
Ezetimibe 10 mg monotherapy (versus placebo)	-18.56 (-19.68 to -17.44)	meta-analysis Figure 3
Ezetimibe 10 mg plus statin therapy (versus statin therapy)	- 13.94 (-14.90 to -12.98)	meta-analysis Figure 1
Sensitivity analysis: Ezetimibe 10 mg plus statin therapy (versus statin therapy)	-22.16 (-23.19 to -21.13)	meta-analysis of 6 week data Appendix 11
Titration of statin by one dose and / or switch to a similar dose of a more potent statin	-6.0	Knopp *et al*[68]

[a] Mean percentage reduction in LDL-c

Applying the benefits of treatments

The relative risk 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 relative risk of an event is then calculated by multiplying the absolute reduction in LDL-c by the relative risk 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 21 and Appendix 22). 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,[186] costs for GP contact are taken from Netten, 2005,[187] and other costs are adjusted to 2006 £s using the Pay and Prices annual percentage increase (1.9%).[155] First year and subsequent year costs are assigned for each of the health states modelled.

Table 30: Cost of health states in ScHARR cost effectiveness model

Health State	Cost £(2006)	Assumption/Source
Stable Angina (year 1)	£201	3 times 15 min GP contact plus medication costs
Stable Angina (subsequent year)	£201	3 times 15 min 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 min GP contact plus medication costs
MI (year 1)	£4,934	Palmer 2002[188] inflated to 2006 (£4,457) + primary care and medication costs as unstable angina (£477)
MI (post-year 1)	£201	3 times 15 min GP contact plus medication costs
MI (fatal event)	£1,261	Clarke 2003[156] inflated to 2006
TIA (year 1)	£1,104	£1064 inflated to August 2006
TIA (subsequent year)	£274	£264 inflated to August 2006
Stroke (year 1)	£8,070	Youman *et al.*[189] weighted by severity & inflated to 2006
Stroke (subsequent year)	£2,169	Youman *et al.*[189] weighted by severity & inflated to 2006
Stroke (fatal event)	£7,425	Youman *et al.*[189] inflated to 2006

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 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 fist 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 one is taken from Palmer *et al.*[188] (£4,070) 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 the costs is the same as for stable angina.

Fatal MI: The cost of fatal MI is taken from Clarke *et al.*[156] (£1,152) and inflated to 2006.

TIA: While 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. Assuming that the patient attends an outpatient visit and undergoes appropriate tests (including an ultrasound, CT scan and an angiography); a small number of patients will also require an 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 ACE inhibitor and a diuretic at an evaluated cost of £264.[39] First year costs are estimated to be £1,104 (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 stroke for the first year are based on the costs of acute events taken from Youman *et al.*[189] weighted by the distribution of severity of stroke. The costs of acute events are £5,009 for mild stroke, £4,816 for moderate stroke, and £10,555 for severe stroke. The cost of non-fatal stroke for subsequent years is based on the costs of ongoing care at home (£326) or in an institution (£3,872)[189] weighted by the distribution of severity of stroke and discharge locations.

Fatal stroke: The cost of fatal stroke is also taken from Youman *et al.*[189] (£6,781) and inflated to 2006.

Treatment costs: Annual treatment costs (Table 31) for the different regimens modelled are taken from the BNF. The weighted cost for current statin therapy is based on published prescribing rates for 2005.[44] The proprietary tablet, ezetimibe 10 mg plus simvastatin 20mg (40mg) are not

considered as the cost is higher than for ezetimibe plus a generic statin (e.g. ezetimibe plus generic simvastatin 40mg = £30.54 while 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 80mg (£41.21 per 28 tablet pack) was prescribed as opposed to ezetimibe plus a generic simvastatin 80mg (£50.38 per 28 tablet pack).

Table 31: Annual cost of treatments used in the ScHARR economic evaluation

Treatment	Annual cost
Ezetimibe monotherapy	£343
Ezetimibe plus weighted dose of current statin treatment	£493[a]
Weighted dose of current statin treatment titrated by one dose	£226[a]
Ezetimibe plus 50% on simvastatin 20mg & 50% on simvastatin 40mg	£386
Ezetimibe plus 75% on atorvastatin 20mg & 25% on atorvastatin 40mg	£676
50% on atorvastatin 20mg & 50% on atorvastatin 40mg	£344
75% on rosuvastatin 10mg & 25% on rosuvastatin 20mg	£273

[a] statin costs weighted as per the BNF prescribing rates for 2005[44]

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, 12 months then annually thereafter. In addition, it is assumed 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 (2*£2.17+£13+0.1*£1.66) for subsequent years. The costs for the practice nurse are taken from Netten,[187] and the cost for tests are taken from the NHS reference costs.[190]

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 21). Published literature on HRQoL is sparse and as no new evidence was identified, the data used in the recent statin HTA has been retained.[39]

The studies identified in the original review 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 UK-5D instrument is the recommended instrument (Nice reference case)

Stable Angina

Only one study was identified which reported a mean quality of life specifically for individuals with stable angina. This was an economic study which included a quality of life sub-study.[191] The Bypass Angioplasty Revascularization Investigation,[192] a US study enlisted 553 patients with multivessel coronary artery disease and angina or documented ischemia assessed the quality of life in 387 patients using the time trade-off method. Patients with angina had a mean time trade-off score of 7.03, which is likened to a mean score of 8.7 patients without angina. The variance in these scores represents the decrement due to stable angina that is used in the ScHARR model. However, the baseline in this study that is patients with CAD is not analogous to the baseline in the ScHARR model, (general population). The score for patients without angina was consequently scaled up to a score of one; the score for stable angina was scaled up by the same multiplier. Therefore, the value for stable angina used in the ScHARR model is 0.81.

Unstable angina

Only one study was identified that provided a mean utility value for unstable angina.[193] This was carried out in the emergency department of the Northern General Hospital in Sheffield and was a randomised controlled trial comparing care in a chest pain clinic observation unit with routine care. As part of a cost effectiveness analysis EQ-5D questionnaires were given to 676 patients following treatment at 6 months. A chronicle of patient diagnosis at entry included MI and unstable angina. The mean utility score at 6 months for unstable angina was 0.77 based on questionnaires from 209 patients (Personal communication, Steve Goodacre, Senior Clinical Lecturer in Health Service Research and Emergency Medicine, Medical Care Research Unit, School of Health and Related Research, University of Sheffield, November 2004).

MI

Two studies were identified which reported mean utility values for MI.[193,194] The study by Bradley *et al*. reviewed and considered the quality of life of 176 patients enlisted in the Michigan State University Inter-Institutional Collaborative Heart Study (MICH study) by utilising the Health and Activities Limitations Index (HALex). The study by Goodacre *et al*. discussed above meets the criteria for the population setting; it also uses a more validated quality of life instrument. Therefore, this study was favoured to provide the utility for MI (0.76).

TIA

The TIA utility score is assumed to be the same as the population norm.[195]

Stroke

Mean utility estimates were found in two studies. In one study, data was collected in the Evaluation of Dutch Integrated Stroke Service Experiment.[196] The study was carried out between 1999 and 2000. A total of 598 stroke patients, from eight hospitals in six areas of the Netherlands all with consecutive stroke were included. Interviews with patients were directed at 2 and 6 months after stroke using the EQ-5D instruments.

The second study by Tengs *et al*. was a meta-analysis of quality of life estimates for stroke.[197] Similar studies were found from the NHS Economic Evaluations Database; Medline bibliographies of review articles were looked at as well as citation searching. 20 articles were found containing 53 quality of life estimates. The best pooled estimates for stroke were found using a meta-regression, which also assessed the impact of study design features on the pooled quality of life estimate. Only the severity of stroke and the sphere of the scale used were predictive of quality of life. The best predictor of quality of life estimates was found to be the scale of death to perfect health compared to the scales of death to normal health, death to excellent health and worse possible health to perfect health. The method of elicitation and respondents were not found to be of statistical significance in terms of quality of life predictors. This study was based on a meta-analysis of all known utilities. Elicitation methods and respondents were not predictive outcomes. Therefore, the estimates are considered to more accuately reflect quality of life for stroke patients than estimates from van Exel *et al*.[196] The values from this study are utilised in the ScHARR cost effectiveness model and are, mild stroke 0.87, moderate stroke 0.68 and severe stroke 0.52. The ScHARR model uses an overall non-fatal stroke health state that does not differentiate between severities. Therefore, the above utilities were combined. A study by Youman *et al*.[189] estimated the proportion of patients that experienced strokes of differing severity from the data set of a UK trial researching stroke outcomes in 290,000 newly diagnosed patients. The proportion of those that survived after experiencing a mild, moderate or severe stroke were 0.19, 0.27 and 0.54 respectively. A combined utility of 0.63 was estimated after weighting the above utilities at each severity by the proportion of stroke patients in the respective severity.

Table 32: Health state HRQoL utilities

Health state	mean (se)	Source
Stable angina	0.808	Meslop[191]
Unstable angina	0.770 (0.038)	Goodacre[193]
MI	0.760 (0.018)	Goodacre[193]
TIA	1	assumed no disutility
Stroke	0.629 (0.04)	Tengs[197]

HRQoL utility by age: A study by Kind and Dolan[195] 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 33. It is acknowledged that by including a baseline utility adjusted for age there will be a small element of double counting as a proportion of individuals in the sample used in the Kind study will have a history of CVD. However, using the alternative of a constant utility of 1 across all ages would bias the results in favour of ezetimibe treatment. The overestimation of benefits would come from 2 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. However a sensitivity analysis is conducted where baseline utility is set to 1 for all ages.

Table 33: Utility values by age[195]

age	utility
45	0.869
50	0.848
55	0.826
60	0.805
65	0.784
70	0.763
75	0.741

Utility = 1.060 – 0.004*Age

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 to 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 is 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 to treatment is required if target cholesterols are to be achieved. While the literature has shown that the discontinuance rates during the first 5 years of lipid-lowering treatment can be as high as 50%,[198] the authors of a recent study on the issues and implications of switching statins state that 72% patients nationally are to target and suggest this may be due in part to tighter follow-up.[46] The impact on compliance rates of switching treatments, titrating doses and multi-drug therapies uncertaint. There is no robust evidence to suggest that compliance to ezetimibe in combination with a statin would be any different to compliance to 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 are not modelled.

Mortality

To account for the proportion of patients dying from non-vascular causes, interim life tables published by the UK Government Actuary Department are adjusted using CVD deaths cited in the national mortality statistics for England and Wales.[199]

Key modelling assumptions

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

Cost Effectiveness Ratios

Incremental cost effectiveness ratios (ICERs) demonstrate the additional cost per QALY gained of Treatment A versus Treatment B:

$$\text{Incremental cost effectiveness ratio} = \frac{\text{Cost Treatment A} - \text{Cost Treatment B}}{\text{Utility Treatment A} - \text{Utility Treatment B}}$$

6.3.3 Results

The following section presents the results estimated by the ScHARR model for cohorts of 1,000 individuals. All analyses use a time horizon of 20 years, a baseline LDL-c of 3.5 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, sex and baseline LDL-c.

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

The results are generated using different time horizons as shown in Table 34. The ICERs decrease as the time horizon increases as would be expected. When examining the costs and benefits accrued over a full lifetime horizon, the ICERs increase by age and are slightly higher for the females than males of the same age. The results suggest it is more cost effective to commence treating patients at younger ages than older ages. However, when looking at the ICERs using a 20 year horizon the results are of a similar magnitude across all ages: approximately £88k (£104k) per QALY for males (females) with no history of CVD; and approximately £154k (£210k) per QALY for males (females) with a history of CVD.

The ICERs increase by age as an event saved at the age of 45 years accumulates more benefits in terms of life years gained and costs avoided than an event saved at a later age. The ICERs for the cohorts with a history of CVD (secondary prevention) are approximately double those for the equivalent cohorts with no history of CVD (primary prevention). Again this is to be expected as all individuals with a history of CVD have costs and disutilites associated with the health state they are in, consequently if a primary event is saved this accumulates more benefits in terms of life years gained and costs avoided than an equivalent secondary event.

Table 34: Scenario 1, discounted ICERs (£,000) using different time horizons and a baseline LDL-c of 3.5 mmol/L

	Primary prevention			Secondary prevention		
Age	5 yr[a]	20 yr[a]	life	5 yr[a]	20 yr[a]	life
Male						
45	£564	£90	**£48**	£763	£140	**£104**
55	£515	£82	£53	£687	£129	£105
65	£441	£78	£63	£719	£146	£131
75	£427	£100	£96	£815	£202	£196
Female						
45	£631	£102	£53	£1,091	£177	£121
55	£605	£101	£65	£1,421	£229	£168
65	£564	£98	£78	£1,197	£214	£184
75	£540	£115	**£108**	£920	£217	**£210**

[a] truncating the costs and benefits associated with events avoided at 5,(20) years.
Lowest ICER in bold text and highest in shaded text.

The incremental costs (Table 35) increase as the time horizon increases as would be expected as the cost offsets accrue over a longer period. The incremental costs decrease slightly as age increases as events avoided in older cohorts have less time to accrue benefits in terms of the costs avoided than events avoided in younger cohorts. The incremental costs are smaller for the secondary cohorts than the primary cohorts. As all individuals with a history of CVD incur ongoing treatment costs, saving a secondary event for an individual with a history of CVD saves less costs than saving an event for an individual with a no history of CVD.

Table 35: Scenario 1, discounted incremental costs (£,000) using different time horizons and a baseline LDL-c of 3.5 mmol/L

	Primary prevention			Secondary prevention		
Age	5 yr[a]	20 yr[a]	life	5 yr[a]	20 yr[a]	life
Male						
45	£1,224	£3,567	£4,807	£1,188	£3,410	£4,595
55	£1,214	£3,382	£4,135	£1,171	£3,153	£3,817
65	£1,193	£3,029	£3,343	£1,151	£2,815	£3,084
75	£1,151	£2,459	£2,507	£1,113	£2,296	£2,337
Female						
45	£1,230	£3,576	£4,744	£1,206	£3,368	£4,329
55	£1,216	£3,373	£4,103	£1,199	£3,220	£3,855
65	£1,196	£3,022	£3,331	£1,169	£2,819	£3,071
75	£1,153	£2,448	£2,496	£1,107	£2,196	£2,230

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

The incremental QALYs (Table 36) increase as the time horizon increases as would be expected as the QALYs accrue over a longer time period. Looking at the incremental QALYs accrued over a lifetime, the total QALYs decrease steeply as age increases. This is because an event saved at the age of 75 years saves less life years compared to one saved at 45 years. However, when looking at the incremental QALYs accrued over just 20 years the results are comparable for all cohorts except the older age (75 years). As all individuals with a history of CVD have a disutility associated with their health state, an avoided secondary event gains less in terms of QALYs saved than an equivalent primary event. This is illustrated in the results as the total incremental QALYs gained in the cohorts with a history of CVD are much smaller (approximately half) than those gained by the cohorts with no history of CVD of the same age.

Table 36: Scenario 1, discounted incremental QALYs using different time horizons and a baseline LDL-c of 3.5 mmol/L

	Primary prevention			Secondary prevention		
Age	5 yr[a]	20 yr[a]	life	5 yr[a]	20 yr[a]	life
Male						
45	2.2	39.6	99.3	1.6	24.4	44.1
55	2.4	41.1	78.3	1.7	24.5	36.5
65	2.7	39.0	53.5	1.6	19.3	23.6
75	2.7	24.5	26.2	1.4	11.4	11.9
Female						
45	2.0	35.2	89.6	1.1	19.0	35.7
55	2.0	33.3	62.8	0.8	14.1	23.0
65	2.1	30.9	42.9	1.0	13.2	16.7
75	2.1	21.3	23.1	1.2	10.1	10.6

[a] truncating the costs and benefits associated with events avoided at 5,(20) years.

When varying the baseline LDL-c, the results (Table 37) are more cost effective for cohorts with higher baseline LDL-c levels. The discounted ICERs for cohorts with no history of CVD range from £67k per QALY for males aged 65 years and a baseline LDL-c of 4.0 mmol/L to £135k per QALY for females aged 75 years with a baseline LDL-c of 3.0 mmol/L. Looking at the baseline LDL-c values, in general the results are comparable for all ages except for cohorts aged 75 years, which less cost effective. As discussed earlier this is because the events avoided in these cohorts save less in terms of the cumulative life years gained.

The results suggest that the ICERs for cohorts with no history of CVD (primary prevention) are approximately £100k per QALY while the ICERs for cohorts with a history of CVD (secondary prevention) are approximately 150k per QALY. The corresponding costs and QALYs are provided in Appendix 28.

Table 37: Scenario 1, discounted 20 year ICERs (£,000) when varying the baseline LDL-c value

	Primary prevention			Secondary prevention		
	baseline LDL-c (mmol/L)					
Age	3.0	3.5	4.0	3.0	3.5	4.0
Male						
45	£106	£90	£78	£165	£140	£121
55	£97	£82	£71	£152	£129	**£111**
65	£92	£78	**£67**	£173	£146	£126
75	£118	£100	£87	£238	£202	£175
Female						
45	£119	£102	£88	£208	£177	£154
55	£119	£101	£88	£269	£229	£199
65	£115	£98	£85	£252	£214	£186
75	**£135**	£115	£100	**£256**	£217	£189

Lowest ICER in bold text and highest in shaded text.

The effectiveness rates used in the analyses are based on data from short term studies, which is extrapolated over very long time periods in the model. Unless stated otherwise the analyses presented assume that treatment continues to death with a corresponding benefit. A series of analyses were performed to examine the impact on the ICERs if treatment is stopped and additional benefits from treatment are truncated at 2 (5 or 10) years while accruing costs and benefits from the events avoided during the treatment period over a 20 year time horizon.

As in the basecase, the ICERs generated when truncating benefits at shorter time points (Table 38) are dependent on age, are higher for the cohorts with a history of CVD than those with no history of CVD and are all greater than £50k per QALY. From Tables 39 and 40 it can be seen that the marginal costs and QALYs gained tend towards the basecase scenario. The difference in convergence rates means that the ICER decreases up to 10 years and then increases towards the basecase. This analysis demonstrates the cost effectiveness if the choice to treat is not viewed as a lifetime decision but rather a short term (e.g. 2 years) option to be revisited in light of external and lifestyle changes.

Table 38: Scenario 1, discounted ICERs (£,000) when truncating treatment but accruing costs and benefits over a 20 year period using baseline LDL-c of 3.5mmol/L

	Primary Prevention				Secondary Prevention			
Age	Basecase	2yr	5yr	10yr	Basecase	2yr	5yr	10yr
Male								
45	£90	£126	£79	£65	£140	£173	£111	£98
55	£82	£115	£72	£60	£129	£160	£104	**£93**
65	£78	£108	£68	**£58**	£146	£186	£122	£110
75	£100	£126	£85	£81	£202	£247	£170	£165
Female								
45	£101	£130	£84	£73	£177	£221	£144	£128
55	£101	£134	£87	£75	£229	**£299**	£195	£171
65	£98	£133	£86	£74	£214	£289	£188	£166
75	£115	**£144**	£98	£94	£217	£279	£191	£182

Lowest ICER in bold text and highest in shaded text.

Table 39: Scenario 1, discounted incremental costs (£,000) when truncating treatment but accruing costs and benefits over a 20 year period using a baseline LDL-c of 3.5 mmol/L

	Primary Prevention				Secondary Prevention			
Age	Basecase[a]	2yr[b]	5yr[c]	10yr[d]	Basecase	2yr[b]	5yr[c]	10yr[d]
Male								
45	£3,567	£509	£1,181	£2,124	£3,410	£501	£1,151	£2,055
55	£3,382	£508	£1,171	£2,080	£3,153	£500	£1,138	£1,990
65	£3,029	£506	£1,152	£1,993	£2,815	£502	£1,126	£1,913
75	£2,459	£504	£1,120	£1,846	£2,296	£501	£1,096	£1,767
Female								
45	£3,576	£515	£1,203	£2,166	£3,368	£513	£1,187	£2,105
55	£3,373	£514	£1,191	£2,113	£3,220	£515	£1,184	£2,074
65	£3,022	£512	£1,170	£2,020	£2,819	£512	£1,155	£1,954
75	£2,448	£509	£1,130	£1,854	£2,196	£505	£1,095	£1,730

Table 40: Scenario 1, discounted incremental QALYs when truncating treatment but accruing costs and benefits over a 20 year period using a baseline LDL-c of 3.5 mmol/L

	Primary Prevention				Secondary Prevention			
Age	Basecase[a]	2yr[b]	5yr[c]	10yr[d]	Basecase	2yr[b]	5yr[c]	10yr[d]
Male								
45	39.6	4.0	15.0	32.7	24.4	2.9	10.4	21.0
55	41.1	4.4	16.2	34.5	24.5	3.1	11.0	21.4
65	39.0	4.7	16.9	34.2	19.3	2.7	9.2	17.4
75	24.5	4.0	13.1	22.7	11.4	2.0	6.4	10.7
Female								
45	35.2	4.0	14.3	29.8	19.0	2.3	8.2	16.5
55	33.3	3.8	13.8	28.3	14.1	1.7	6.1	12.2
65	30.9	3.8	13.6	27.2	13.2	1.8	6.1	11.8
75	21.3	3.5	11.5	19.8	10.1	1.8	5.7	9.5

Probabilistic results for Scenario 1: Probability distributions are used to describe the uncertainty surrounding key input parameters to determine the impact of the imprecision of input values on decision uncertainty. A full list of variables and distributions used are provided in Appendix 24.

Using a threshold of £30k per QALY, the results (Figures 7 to 10) of the probabilistic analyses for the treatment regimen ezetimibe plus current statin treatment versus current statin treatment titrated by one dose are not cost effective using a threshold of £30k per QALY.

Figure 7: Scenario 1, CEAC for males with no history of CVD using a baseline LDL-c of 3.5 mmol/L

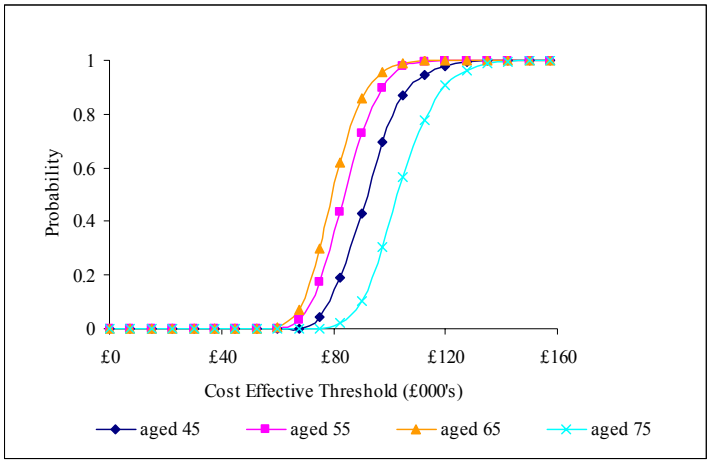


Figure 8: Scenario 1, CEAC for females with no history of CVD using a baseline LDL-c of 3.5 mmol/L

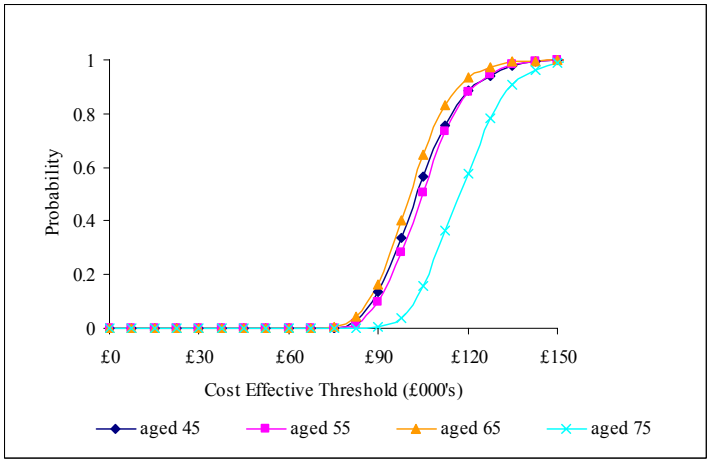


Figure 9: Scenario 1, CEAC for males with a history of CVD using a baseline LDL-c of 3.5 mmol/L

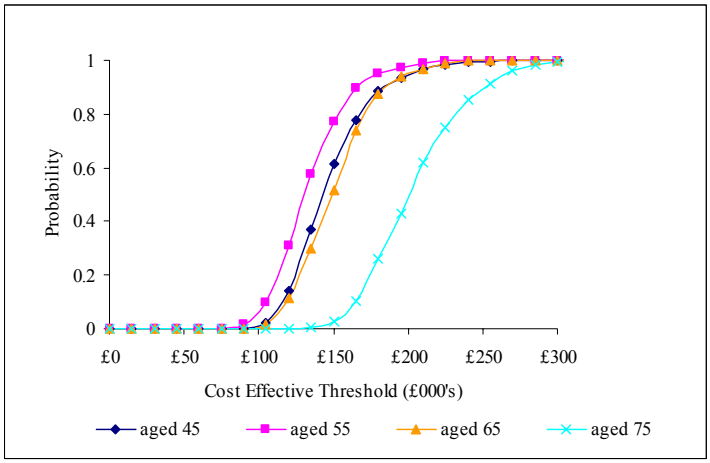
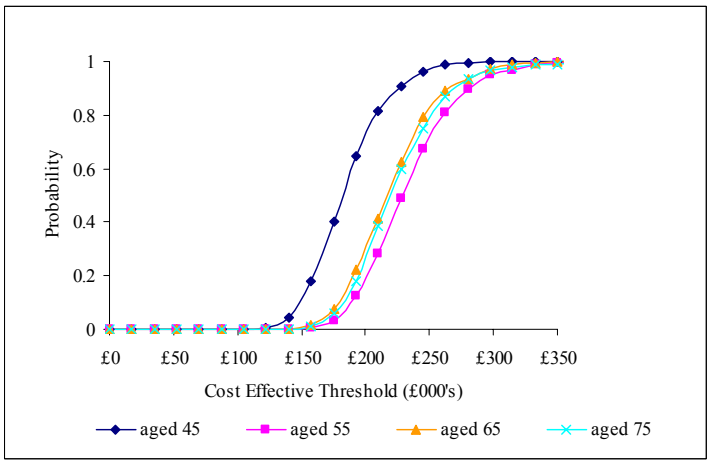


Figure 10: Scenario 1, CEAC for females with a history of CVD using a baseline LDL-c of 3.5 mmol/L



Univariate sensitivity analysis for Scenario 1: A series of sensitivity analyses (using a baseline LDL-c of 3.5 mmol/L and a 20 year time horizon) were performed to explore the impact on the results of changing values used to represent key parameters. The variables which have the largest impact on the results are shown at the top of the Tornado diagrams (Figures 11 and 12). A full set of results for a male cohort are provided in Table 42. The results for a female cohort are provided in Appendix 28 together with the corresponding costs and QALYs.

Figure 11: Scenario 1, Tornado diagram illustrating the impact of varying key parameter values for males aged 45 years, with no history of CVD and a baseline LDL-c of 3.5 mmol/L

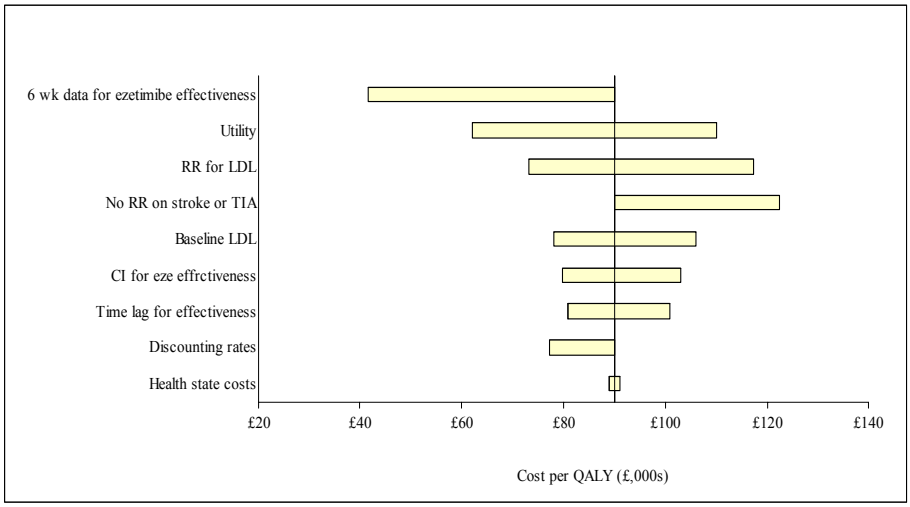
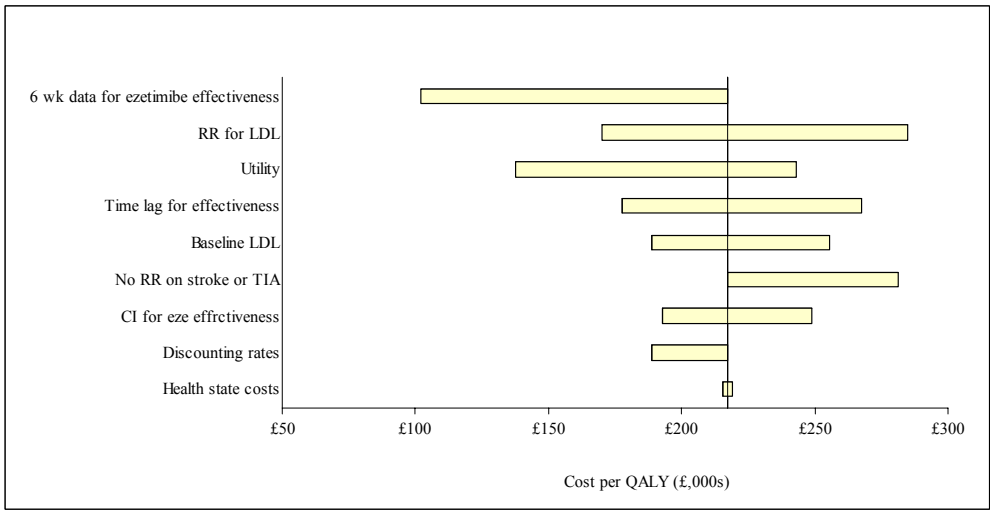


Figure 12: Scenario 1, Tornado diagram illustrating the impact of varying key parameter values for females aged 75 years with a history of CVD and a baseline LDL-c of 3.5 mmol/L



When using the results of the six week meta-analysis as opposed to the 12 week meta-analysis (Appendix 11) to represent the effectiveness of ezetimibe plus a statin the ICERs for all Scenario 1 analyses are almost halved. Varying the values used to translate reductions in LDL-c to CV events avoided also has a large impact on the results with ICERs varying by minus 20% when using the lower confidence intervals and increasing by approximately 30% when using the upper confidence interval (see Table 41).

When using a constant utility of one across all ages, the ICERs are reduced by approximately 20% for both the primary and secondary cohorts aged 45 years and by approximately 30% for both the primary and secondary cohorts aged 75 years. When decreasing the disutility for events by 10%, the results for individuals with a history of CVD increase by approximately 12% while the results for cohorts with no history of CVD decrease by approximately 14%.

Varying the time lag for applying effectiveness has a larger impact on the ICERs for the older cohorts: plus or minus approximately 20% for ages 75 years, compared to plus or minus approximately 10% for ages 45 years.

Table 41: Scenario 1, univariate results (£,000) for males with baseline LDL-c of 3.5 mmol/L

	Value	Primary Prevention				Secondary Prevention			
Age		45	55	65	75	45	55	65	75
Scenario 1 basecase		£90	£82	£78	£100	£140	£129	£146	£202
Discount rates for costs and utilities									
	0%	£77	£70	£67	£87	£123	£113	£128	£177
Time lag for effectiveness of treatment									
	0	£81	£73	£68	£84	£123	£112	£125	£165
	2 yr	£101	£93	£89	£121	£160	£149	£172	£249
Health state costs									
	Plus 20%	£89	£81	£77	£99	£138	£127	£144	£200
	Minus 20%	£91	£83	£79	£102	£142	£131	£148	£204
Health related quality of life (QoL) utilities									
	Plus 10%	£110	£98	£91	£117	£126	£116	£132	£183
	Minus 10%	£76	£71	£68	£88	£157	£144	£164	£226
	Constant utility by age	£73	£64	£57	£70	£114	£100	£108	£141
	Constant utility by age plus 10% on health state utilities	£90	£75	£66	£82	£103	£90	£97	£128
	Constant utility by age minus 10% on health state utilities	£62	£55	£50	£61	£128	£112	£121	£158
Relative risk on events corresponding to reduction in LDL-c									
	LCI	£73	£67	£63	£81	£108	£99	£113	£157
	UCI	£117	£107	£101	£131	£187	£171	£194	£267
Effectiveness of ezetimibe treatement									
	LCI	£80	£73	£69	£89	£124	£114	£129	£179
	UCI	£103	£94	£89	£115	£161	£148	£168	£232
No relative risk on stroke or transient iscaemic attack (TIA)									
		£123	£111	£104	£133	£212	£184	£202	£274
Baseline LDL-c (mmol/L)									
	3.0	£106	£97	£92	£118	£165	£152	£173	£238
	4.0	£78	£71	£67	£87	£121	£111	£126	£175
Using effectiveness rates from short term ezetimibe studies									
	6wk data	£42	£38	£36	£47	£63	£58	£66	£93

LCI = lower confidence interval, UCI = upper confidence interval

Results for Scenario 2: ezetimibe monotherapy versus with no treatment

The results are generated using different time horizons as shown in Table 42. The ICERs decrease (Table 42) as the time horizon increases as would be expected. When examining the costs and benefits accrued over a full lifetime horizon, the ICERs increase by age and are slightly higher for females than males of the same age. The lifetime results suggest it is more cost

effective to commence treating patients at younger ages than older ages. However, when looking at the ICERs using a 20 year horizon the results are of a similar magnitude across all ages: approximately £48k (£58k) per QALY for males (females) with no history of CVD (primary prevention); and approximately £85k (£118k) per QALY for males (females) with a history of CVD (secondary prevention). The corresponding costs and QALYs are provided in Appendix 28.

Table 42: Scenario 2, discounted ICERs (£,000) using different time horizons and a baseline LDL-c of 3.5 mmol/L (basecase)

	Primary prevention			Secondary prevention		
Age	5 yr[a]	20 yr[a]	life	5 yr[a]	20 yr[a]	life
Male						
45	£322	£50	**£26**	£427	£77	**£57**
55	£293	£45	£29	£384	£70	£57
65	£250	£43	£34	£402	£80	£72
75	£242	£56	£53	£457	£112	£109
Female						
45	**£361**	£57	£29	£620	£100	£68
55	£346	£57	£36	**£810**	£129	£95
65	£322	£55	£43	£680	£121	£103
75	£307	£64	£61	£520	£122	£118

[a] truncating the costs and benefits associated with events avoided at 5,(20) years.
Lowest ICER in bold text and highest in shaded text.

When varying the baseline LDL-c, the results (Table 43) are more cost effective for cohorts with higher baseline LDL-c levels. The discounted ICERs for cohorts with no history of CVD range from £37k per QALY for males aged 65 years and a baseline LDL-c of 4.0 mmol/L to £144k per QALY for females aged 75 years with a baseline LDL-c of 3.0 mmol/L. Looking at the baseline LDL-c values, in general the results are comparable for all ages except cohorts aged 75 years which less cost effective. As discussed earlier this is because the events avoided in these cohorts save less in terms of the cumulative life years gained.

The results suggest that the ICERs for cohorts with no history of CVD (primary prevention) are approximately £55k per QALY while the ICERs for cohorts with a history of CVD (secondary prevention) are approximately £100k per QALY. The corresponding costs and QALYs are provided in Appendix 28.

Table 43: Scenario 2, 20 year discounted ICERs (£,000) when varying the baseline LDL-c value

	Primary prevention			Secondary prevention		
	baseline LDL-c (mmol/L)					
Age	3.0	3.5	4.0	3.0	3.5	4.0
Male						
45	£59	£50	£43	£91	£77	£66
55	£54	£45	£39	£84	£70	**£60**
65	£51	£43	**£37**	£96	£80	£69
75	£66	£56	£48	£133	£112	£96
Female						
45	£67	£57	£50	£117	£100	£86
55	£67	£57	£49	**£152**	£129	£112
65	£65	£55	£47	£142	£121	£104
75	**£76**	£64	£56	£144	£122	£105

Lowest ICER in bold text and highest in shaded text.

As in Scenario 1, the ICERs generated when truncating benefits at shorter time points (Table 44) are dependent on age, are higher for the cohorts with a history of CVD than those with no history of CVD and are all greater than £30k per QALY. Again the marginal costs and QALYs gained tend towards the basecase scenario. The difference in convergence rates means that the ICER decreases up to 10 years and then increases towards the basecase.

Table 44: Scenario 2, discounted ICERs (£,000) when truncating treatment but accruing costs and benefits over a 20 year period using a baseline LDL-c of 3.5 mmol/L

	Primary Prevention				Secondary Prevention			
Age	Basecase	2yr	5yr	10yr	Basecase	2yr	5yr	10yr
Male								
45	£50	£71	£44	£38	£77	£96	£61	£55
55	£45	£65	£40	£35	£70	£89	£57	£53
65	£43	£60	£38	£33	£80	£104	£67	£62
75	£56	£71	£47	£46	£112	£139	£94	£94
Female								
45	£57	£74	£47	£43	£99	£125	£81	£75
55	£57	£76	£49	£44	£129	£170	£110	£100
65	£55	£76	£48	£43	£121	£164	£106	£97
75	£64	£82	£55	£54	£122	£158	£107	£105

Lowest ICER in bold text and highest in shaded text.

Probabilistic results for Scenario 2: Using a threshold of £30k per QALY, none of the results (Figures 13 to 16) of the probabilistic analyses for ezetimibe monotherapy versus no treatment are cost effective.

Figure 13: Scenario 2, CEAC for males with no history of CVD using a baseline LDL-c of 3.5 mmol/L

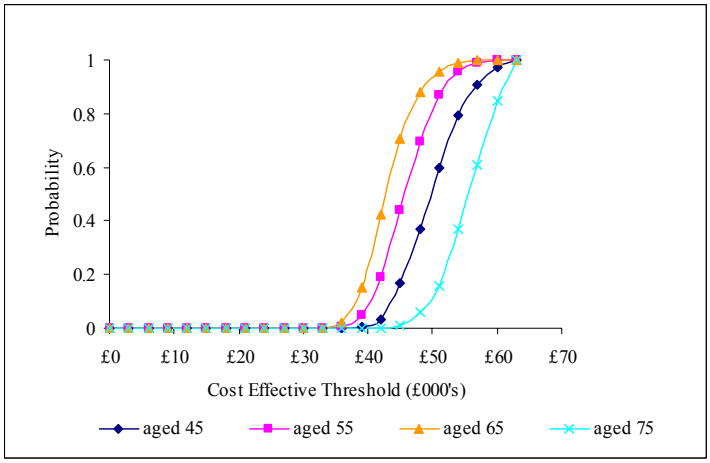


Figure 14: Scenario 2, CEAC for females with no history of CVD using a baseline LDL-c of 3.5 mmol/L

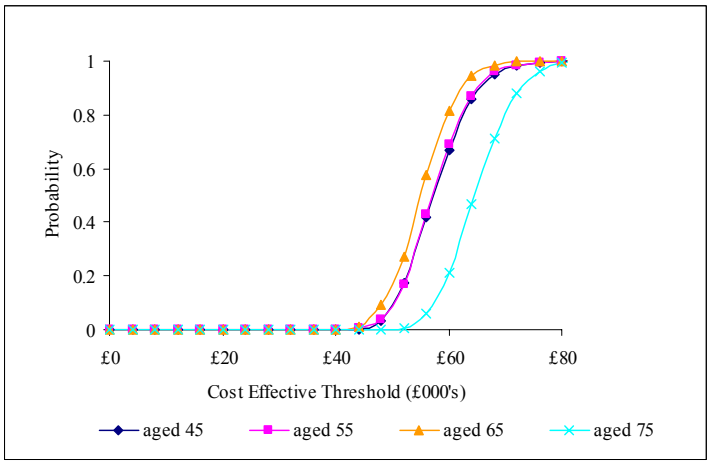


Figure 15: Scenario 2, CEAC for males with a history of CVD using a baseline LDL-c of 3.5 mmol/L

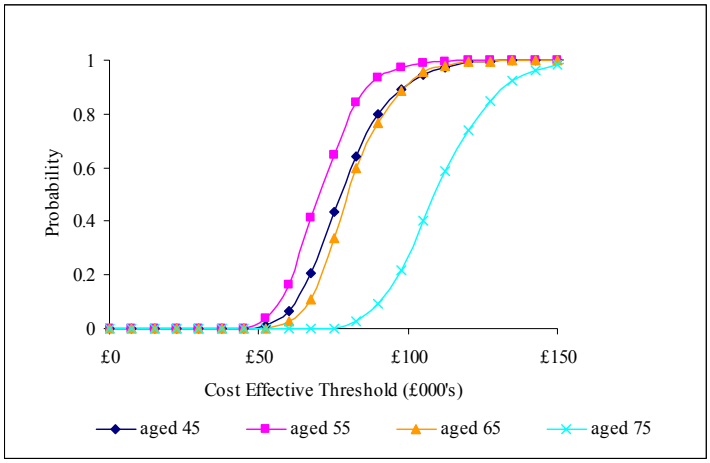
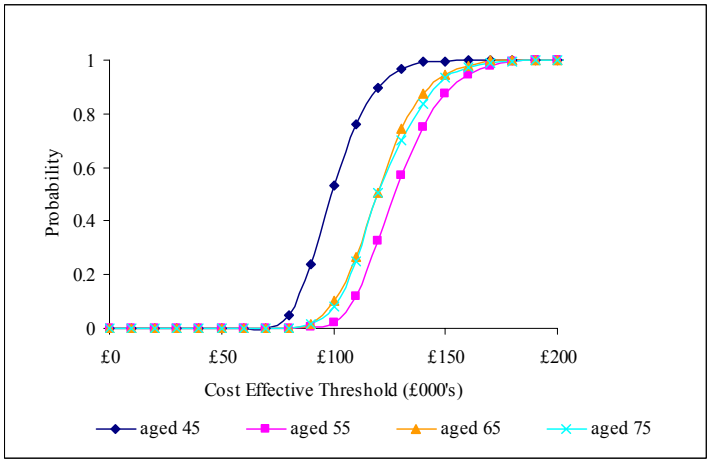


Figure 16: Scenario 2, CEAC for females with a history of CVD using a baseline LDL-c of 3.5 mmol/L



Univariate results for Scenario 2: A series of sensitivity analyses (using a baseline LDL-c of 3.5 mmol/L and a 20 year time horizon) were performed to explore the impact on the results of changing values used to represent key parameters. The variables which have the largest impact on the results are shown at the top of the Tornado diagrams (Figures 11 and 12). A full set of results for a male cohort are provided in Table 41. The results for a female cohort are provided in Appendix 28 together with the corresponding costs and QALYs.

Figure 17: Scenario 2, Tornado diagram illustrating the impact of varying key parameter values for males aged 45 years with no history of CVD and a baseline LDL-c of 3.5 mmol/L

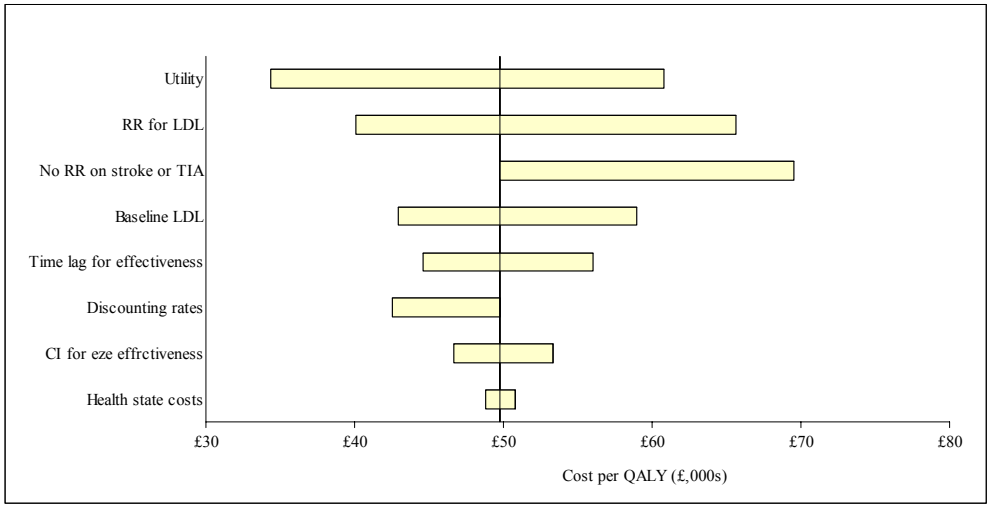
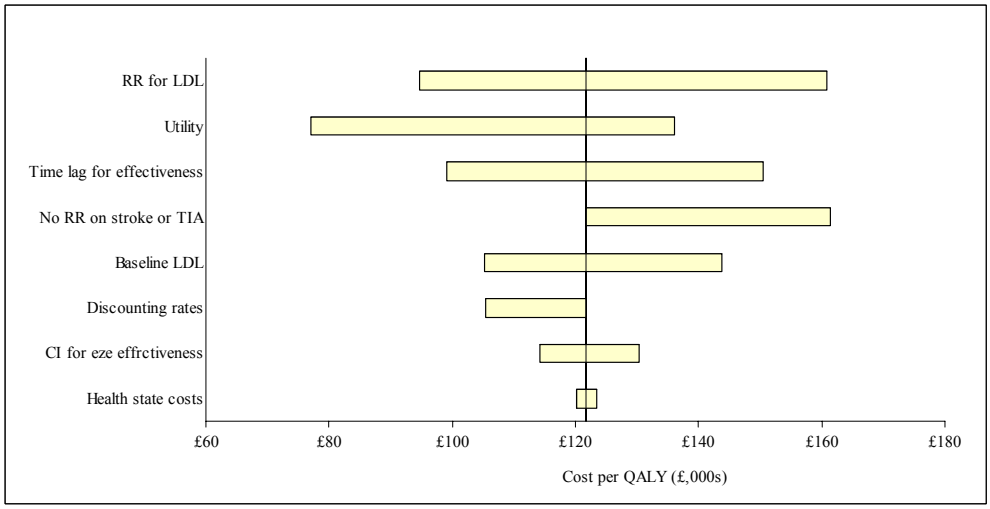


Figure 18: Scenario 2, Tornado diagram illustrating the impact of varying key parameter values for females aged 75 years with a history of CVD and a baseline LDL-c of 3.5 mmol/L



When using a constant utility of 1 across all ages, the ICERs are reduced by approximately 20% for both the primary and secondary cohorts aged 45 years and by approximately 30% for both the primary and secondary cohorts aged 75 years. When decreasing the disutility for events by 10%, the results for individuals with a history of CVD increase by approximately 12% while the results for cohorts with no history of CVD decrease by approximately 14%. Conversely, increasing the

disutility associated with events by 10% the ICERs for cohort with no history of CVD decrease by approximately 14% while those for cohorts with a history of CVD increase by 12%.

Figure 17 and 18 show that varying the values used to translate reductions in LDL-c to CV events avoided has a large impact on the results. ICERs decrease by approximately 20% when using the LCI and increase by approximately 30% when using the UCI .

Varying the time lag for applying effectiveness has a larger impact on the ICERs for the older cohorts: plus or minus approximately 20% for ages 75 years, compared to plus or minus approximately 12% for ages 45 years.

Table 45: Scenario 2, univariate results (£,000) for males with baseline LDL-c of 3.5 mmol/L

	Value	Primary Prevention				Secondary Prevention			
Age		45	55	65	75	45	55	65	75
Scenario 2 basecase		£50	£45	£43	£56	£77	£70	£80	£112
Discount rates for costs and utilities									
	0%	£43	£39	£36	£48	£67	£61	£70	£98
Time lag for effectiveness of treatment									
	0	£45	£40	£37	£46	£67	£61	£68	£91
	2 yr	£56	£51	£49	£68	£88	£82	£95	£139
Health state costs									
	Plus 20%	£49	£44	£42	£55	£75	£68	£78	£110
	Minus 20%	£51	£46	£44	£57	£79	£72	£82	£114
Health related quality of life (QoL) utilities									
	Plus 10%	£61	£54	£50	£65	£69	£63	£73	£101
	Minus 10%	£42	£39	£37	£49	£86	£79	£90	£125
	Constant utility by age	£41	£35	£31	£39	£63	£55	£59	£78
	Constant utility by age plus 10% on health state utilities	£50	£42	£36	£45	£57	£49	£53	£71
	Constant utility by age minus 10% on health state utilities	£34	£30	£27	£34	£70	£61	£66	£88
Relative risk on events corresponding to reduction in LDL-c									
	LCI	£40	£36	£34	£45	£58	£53	£61	£86
	UCI	£66	£60	£56	£73	£104	£95	£108	£150
Effectiveness of ezetimibe treatement									
	LCI	£47	£42	£40	£52	£72	£66	£75	£105
	UCI	£53	£49	£46	£60	£82	£76	£86	£120
No relative risk on stroke or transient iscaemic attack (TIA)									
		£70	£63	£59	£76	£122	£106	£116	£157
Baseline LDL-c (mmol/L)									
	3.0	£59	£54	£51	£66	£91	£84	£96	£133
	4.0	£43	£39	£37	£48	£66	£60	£69	£96

LCI = lower confidence interval, UCI = upper confidence interval

Results for Scenario 3: ezetimibe plus generic simvastatin versus a more potent dose of atorvastatin

The results are generated using different time horizons as shown in Table 46. The ICERs decrease as the time horizon increases as would be expected. When examining the costs and benefits accrued over a full lifetime horizon, the ICERs increase by age and are slightly higher for females than males of the same age. The life time results suggest it is more cost effective to commence

treating patients at younger ages than older ages. However, when looking at the ICERs using a 20 year horizon the results are of a similar magnitude across all ages: approximately £10k (£13k) per QALY for males (females) with no history of CVD (primary prevention); and approximately £16k (£27k) per QALY for males (females) with a history of CVD (secondary prevention). The corresponding costs and QALYs are provided in Appendix 28.

Table 46: Scenario 3, discounted ICERs (£,000) using different time horizons and a baseline LDL-c of 3.5 mmol/L

	Primary prevention			Secondary prevention		
Age	5 yr[a]	20 yr[a]	life	5 yr[a]	20 yr[a]	life
Male						
45	£80	£10	**£4**	£92	£14	**£10**
55	£72	£9	£5	£81	£12	£10
65	£60	£8	£6	£86	£15	£13
75	£57	£11	£11	£100	£22	£22
Female						
45	**£93**	£13	£6	£151	£22	£15
55	£88	£13	£8	**£201**	£30	£22
65	£80	£12	£9	£165	£27	£23
75	£76	£14	£13	£121	£27	£26

[a] truncating the costs and benefits associated with events avoided at 5,(20) years.
Lowest ICER in bold text and highest in shaded text.

When varying the baseline LDL-c, the results (Table 47) are more cost effective for cohorts with higher baseline levels. For cohorts with no history of CVD, all the results are below £20k per QALY irrespective of age or gender. With the exception of cohorts with a baseline LDL-c of 3.0 mmol/L, all the results for cohorts with a history of CVD are below £30k per QALY. The corresponding costs and QALYs are provided in Appendix 28.

Table 47: Scenario 3, 20 year discounted ICERs (£,000) when varying the baseline LDL-c value

	Primary prevention			Secondary prevention		
	baseline LDL-c (mmol/L)					
Age	3.0	3.5	4.0	3.0	3.5	4.0
Male						
45	£12	£10	£8	£18	£14	£11
55	£11	£9	£7	£16	£12	**£10**
65	£10	£8	**£6**	£19	£15	£12
75	£14	£11	£9	£28	£22	£18
Female						
45	£16	£13	£11	£27	£22	£19
55	£16	£13	£11	**£36**	£30	£25
65	£15	£12	£10	£33	£27	£23
75	**£17**	£14	£12	£33	£27	£22

Lowest ICER in bold text and highest in shaded text.

The ICERs generated when truncating benefits at shorter time points (Table 48) are comparable for each age cohort and are slightly higher for the cohorts with a history of CVD than those with no history of CVD. When using a threshold of £20k per QALY, all ICERs for cohorts with no history of CVD are cost effective (maximum £19k per QALY) while the ICERs for the cohorts with a history of CVD range from £8k per QALY to £42k per QALY. The marginal costs and QALYs (Appendix 28) tend towards the basecase scenario. The difference in convergence rates means that the ICERs decreases up to 10 years and then increases towards the basecase.

Table 48: Scenario 3, discounted ICERs (£,000) when truncating effectiveness but accruing costs and benefits over a 20 year period using a baseline LDL-c of 3.5 mmol/L

	Primary Prevention				Secondary Prevention			
Age	Basecase	2yr	5yr	10yr	Basecase	2yr	5yr	10yr
Male								
45	£10	£16	£9	£6	£14	£20	£10	**£8**
55	£9	£14	£8	£6	£12	£18	£10	£8
65	£8	£13	**£7**	£5	£15	£22	£12	£10
75	£11	£16	£9	£8	£22	£31	£18	£17
Female								
45	£13	£18	£11	£9	£22	£30	£18	£15
55	£13	£18	£11	£9	£30	£42	£26	£21
65	£12	£18	£11	£9	£27	**£40**	£24	£20
75	£14	**£19**	£12	£11	£27	£37	£23	£22

Lowest ICER in bold text and highest in shaded text.

Probabilistic results for Scenario 3: Using a threshold of £30k per QALY, the results (Figures 19 to 22) of the probabilistic analyses suggest that ezetimibe plus generic simvastatin versus atorvastatin monotherapy is cost effective for all cohorts irrespective of age, gender or CVD history, while using a threshold of £20k per QALY the majority of results are cost effective.

Figure 19: Scenario 3, CEAC for males with no history of CVD using a baseline LDL-c of 3.5 mmol/L

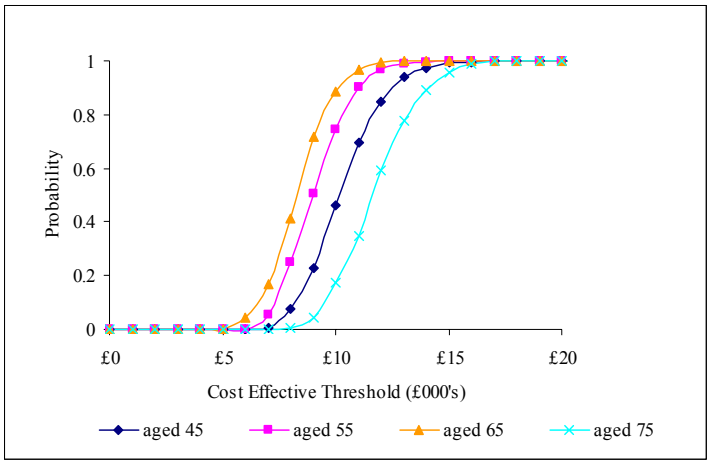


Figure 20: Scenario 3, CEAC for females with no history of CVD using a baseline LDL-c of 3.5 mmol/L

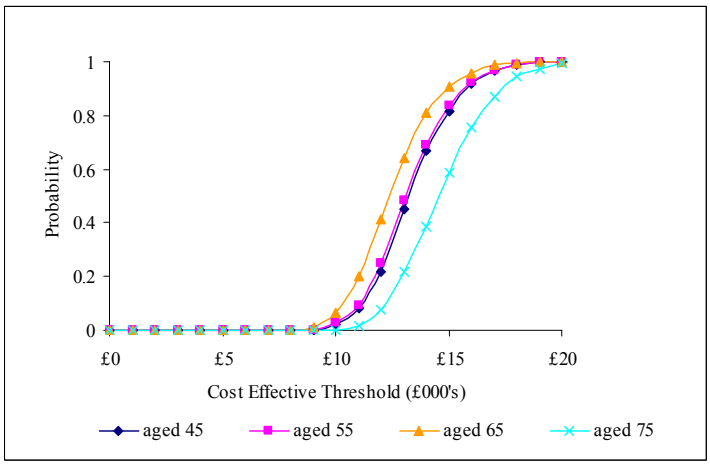


Figure 21: Scenario 3, CEAC for males with a history of CVD using a baseline LDL-c of 3.5 mmol/L

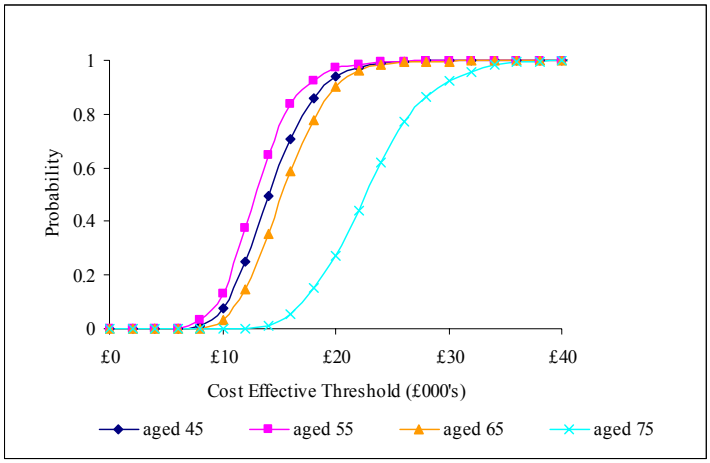
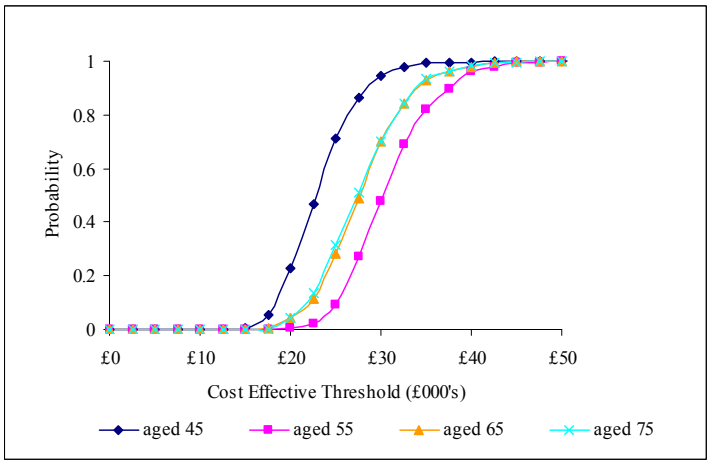


Figure 22: Scenario 3, CEAC for females with a history of CVD using a baseline LDL-c of 3.5 mmol/L



Univariate sensitivity analysis for Scenario 3: A series of sensitivity analyses (using a baseline LDL-c of 3.5 mmol/L and a 20 year time horizon) were performed to explore the impact on the results of changing values used to represent key parameters. The variables which have the largest impact on the results are shown at the top of the Tornado diagrams (Figures 23 and 24). A full set of results for a male cohort are provided in Table 49. The results for a female cohort are provided in Appendix 28 together with the corresponding costs and QALYs.

For scenario 3, the results are most sensitive (Appendix 28) to changes in the effectiveness data and the variable used to link changes in LDL-c to reductions in events.

Figure 23: Scenario 3, Tornado diagram illustrating the impact of varying key parameter values for males aged 45 years with no history of CVD and a baseline LDL-c of 3.5 mmol/L

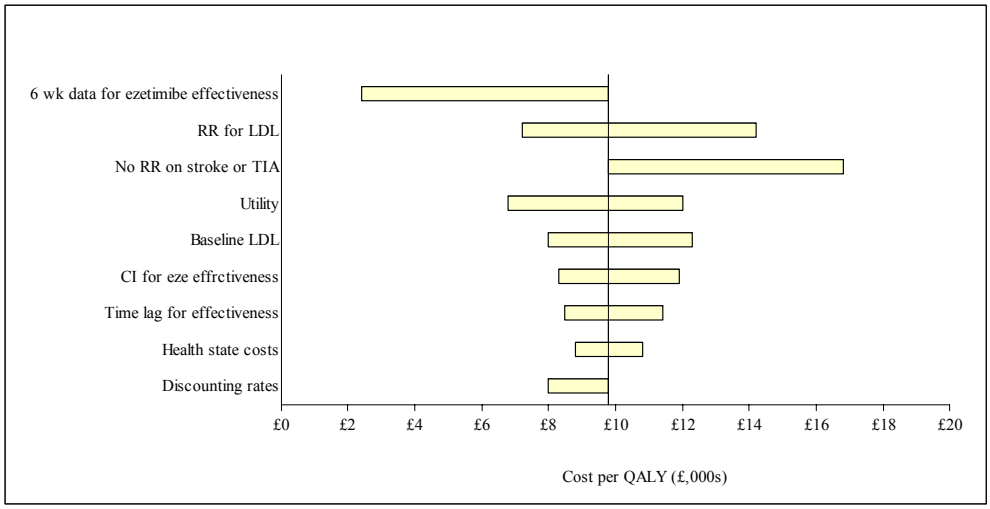
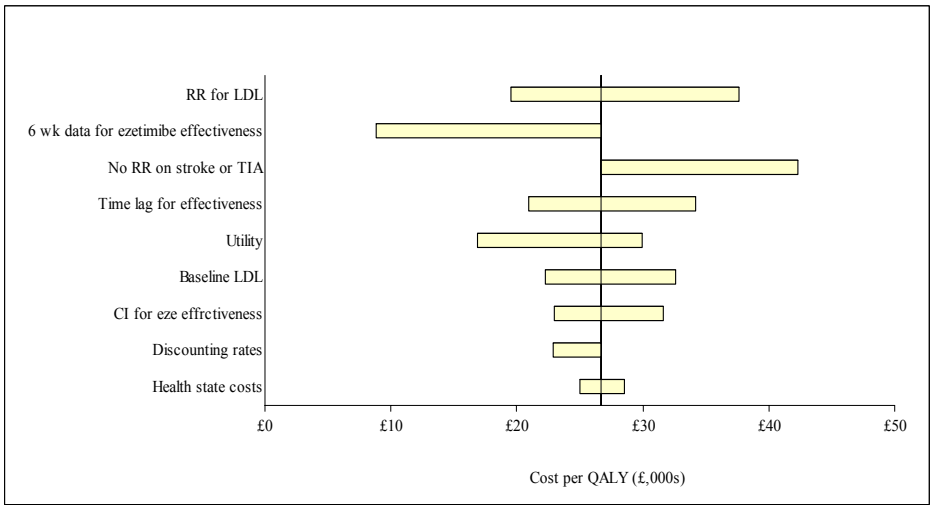


Figure 24: Scenario 3, Tornado diagram illustrating the impact of varying key parameter values for females aged 75 years with a history of CVD and a baseline LDL-c of 3.5 mmol/L



When using the results of the six week meta-analysis as opposed to the 12 week meta-analysis (Appendix 11) to represent the effectiveness of ezetimibe plus a statin the ICERs for all the analyses are reduced by over 75% with results ranging from £1.4k per QALY to £5.5k per QALY. Varying the values used to translate reductions in LDL-c to CV events avoided also has a large impact on the results with ICERs reducing by approximately 40-45% when using the LCI and increasing by approximately 30% when using the UCI.

When using a constant utility of one across all ages, the ICERs are reduced by approximately 20% for both the primary and secondary cohorts aged 45 years and by approximately 30% for both the primary and secondary cohorts aged 75 years. When decreasing the disutility for events by 10%, the results for individuals with a history of CVD increase by approximately 20% while the results for cohorts with no history of CVD decrease by approximately 10%. Conversely, increasing the disutility associated with events by 10% the ICERs for cohort with no history of CVD decrease by approximately 14% while those for cohorts with a history of CVD increase by 12%.

Varying the time lag for applying effectiveness has a larger impact on the ICERs for the older cohorts: plus or minus approximately 28% for ages 75 years, compared to plus or minus approximately 15% for ages 45 years.

Table 49: Scenario 3, 20 year ICERs for males with baseline LDL-c of 3.5 mmol/L

	Value	Primary Prevention				Secondary Prevention			
Age		45	55	65	75	45	55	65	75
Scenario 3 basecase		£9.8	£8.7	£8.0	£11.3	£13.6	£12.3	£14.8	£22.4
Discount rates for costs and utilities									
	0%	£8.0	£7.0	£6.4	£9.4	£11.5	£10.4	£12.6	£19.3
Time lag for effectiveness of treatment									
	0	£8.5	£7.4	£6.7	£8.9	£11.1	£9.9	£11.7	£16.9
	2 yr	£11.4	£10.2	£9.6	£14.3	£16.6	£15.3	£18.5	£29.3
Health state costs									
	Plus 20%	£8.8	£7.7	£7.0	£10.2	£11.6	£10.5	£12.8	£20.2
	Minus 20%	£10.8	£9.7	£9.0	£12.3	£15.5	£14.2	£16.7	£24.5
Health related QoL utilities									
	Plus 10%	£12.0	£10.3	£9.3	£13.1	£12.2	£11.1	£13.3	£20.2
	Minus 10%	£8.3	£7.5	£7.0	£9.8	£15.2	£13.8	£16.5	£25.0
	Constant utility by age	£8.0	£6.7	£5.9	£7.8	£11.1	£9.6	£10.9	£15.6
	Constant utility by age plus 10% on health state utilities	£9.8	£8.0	£6.8	£9.2	£10.0	£8.6	£9.8	£14.2
	Constant utility by age minus 10% on health state utilities	£6.8	£5.8	£5.1	£6.9	£12.4	£10.7	£12.2	£17.5
Relative risk on events corresponding to reduction in LDL-c									
	LCI	£7.2	£6.2	£5.6	£8.3	£8.6	£7.8	£9.6	£15.4
	UCI	£14.2	£12.7	£11.8	£16.1	£21.3	£19.4	£22.7	£32.9
Effectiveness of ezetimibe treatement									
	LCI	£8.3	£7.2	£6.6	£9.5	£11.0	£10.0	£12.1	£18.8
	UCI	£11.9	£10.5	£9.7	£13.5	£16.8	£15.3	£18.1	£26.9
No relative risk on stroke or transient iscaemic attack (TIA)									
		£16.8	£15.0	£14.1	£18.4	£31.5	£27.5	£30.3	£40.8
Baseline LDL-c (mmol/L)									
	3.0	£12.3	£10.9	£10.1	£14.0	£17.5	£16.0	£18.9	£27.9
	4.0	£8.0	£7.0	£6.4	£9.2	£10.6	£9.6	£11.7	£18.2
Using effectiveness rates from short term ezetimibe studies									
	6wks	£2.4	£1.9	£1.5	£3.0	£1.7	£1.4	£2.4	£5.5

LCI = lower confidence interval, UCI = upper confidence interval

Results for diabetic cohorts

Diabetic scenario 1, comparing ezetimibe plus current statin treatment versus current statin treatment titrated by one dose: When comparing the costs and benefits associated with ezetimibe plus current statin therapy versus current statin therapy titrated by one dose in diabetic patients,

all ICERs are greater than £38k per QALY for cohorts with no history of CVD (primary prevention) and are greater than £100k per QALY for cohorts with a history of events.

Table 50: Scenario 1, discounted ICERs (£,000) when varying the baseline LDL-c value with diabetic patients over a 20 year period

	Primary prevention			Secondary prevention		
	baseline LDL-c (mmol/L)					
Age	3.0	3.5	4.0	3.0	3.5	4.0
Male						
45	£54	£46	£39	£163	£137	£118
55	£53	£44	**£38**	£152	£128	**£110**
65	£53	£44	£38	£173	£146	£126
75	£67	£56	£48	£238	£202	£174
Female						
45	£62	£53	£45	£211	£179	£156
55	£67	£56	£48	**£270**	£230	£200
65	£68	£57	£49	£253	£215	£187
75	**£77**	£65	£56	£257	£219	£190

Lowest ICER in bold text and highest in shaded text.

Diabetic scenario 2, comparing ezetimibe monotherapy versus no treatment: When comparing the costs and benefits associated with ezetimibe monotherapy versus no treatment in diabetic patients, for individuals with no history of CVD (primary prevention) the ICERs are estimated to be approximately £30k per QALY (range £19k per QALY to £42k per QALY). All ICERs are greater than £58k per QALY for individuals with a history of CVD. The results for the secondary prevention cohorts are very similar to those for the non diabetic patients as it is assumed that diabetics do not have a greater risk of a secondary event.

Table 51: Scenario 2, discounted ICERs (£,000) when varying the baseline LDL-c value with diabetic patients over a 20 year period

	Primary prevention			Secondary prevention		
	baseline LDL-c (mmol/L)					
Age	3.0	3.5	4.0	3.0	3.5	4.0
Male						
45	£29	£24	£20	£88	£74	£63
55	£28	£23	**£19**	£83	£69	**£58**
65	£28	£23	£19	£94	£79	£67
75	£36	£30	£25	£131	£110	£94
Female						
45	£34	£29	£24	£118	£100	£86
55	£37	£31	£26	**£152**	£129	£111
65	£37	£31	£26	£142	£120	£104
75	**£42**	£35	£30	£144	£121	£105

Lowest ICER in bold text and highest in shaded text.

Results for individual with HeFH

HeFH scenario 4, comparing ezetimibe plus atorvastatin versus rosuvastatin: this analysis examines the costs and benefits associated with ezetimibe treatment in individuals with HeFH who may require more potent treatment to achieve lipid goals. The ICERs estimated for individuals with baseline LDL-c levels of 7.0 mmol/L are approximately half those for individuals with a baseline LDL-c level of 4.0 mmol/L. The ICERs for individuals with no history of CVD range from approximately £18k per QALY for individuals with a baseline LDL-c of 7.0 mmol/L to approximately £35k per QALY for individuals with a baseline LDL-c of 4.0 mmol/L. Using a threshold of £30k per QALY none of the ICERs for the individuals with a history of CVD are cost effective.

Table 52: Scenario 4, discounted ICERs (£,000) when varying the baseline LDL-c value over a 20 year period

	Primary Prevention				Secondary Prevention			
Age	4.0	5.0	6.0	7.0	4.0	5.0	6.0	7.0
Male								
45	£31	£23	£19	£15	£75	£58	£46	**£38**
55	£29	£22	£17	**£14**	£69	£53	£42	£35
65	£29	£22	£17	£14	£79	£61	£49	£40
75	£37	£28	£22	£18	£111	£86	£69	£57
Female								
45	£36	£28	£23	£19	£99	£77	£63	£53
55	£38	£30	£24	£20	**£128**	£101	£83	£70
65	£38	£30	£24	£20	£119	£94	£77	£64
75	**£43**	£33	£27	£22	£121	£94	£77	£64

Lowest ICER in bold text and highest in shaded text.

6.3.4 Discussion of results

Summary of key results

The effectiveness rate of adding ezetimibe to ongoing statin treatment is assumed to be constant irrespective of the baseline statin treatment and is derived from a meta-analysis of data pooled from ezetimibe RCTs comparing treatment strategies involving different statins at various doses. The effectiveness rate for either switching to a more potent statin or titrating the current statin to a higher dose is assumed to be constant irrespective of baseline statin treatment based on published evidence. There is currently insufficient data to determine if the percentage reduction in LDL-c differs between alternative regimens involving ezetimibe co-administered with a statin. There is also insufficient data to determine if the incremental percentage reduction in LDL-c differs according to the treatment strategies being compared. Consequently, the results of the economic evaluation are entirely dependent on the incremental cost of the treatment strategies being compared.

For patients who can tolerate statins, when comparing ezetimibe plus current statin treatment with current statin treatment titrated by one dose (scenario 1), the probabilistic analyses suggest none of the results are cost effective when using a threshold of £30k per QALY irrespective of age, gender or CVD history. When using the results of the meta-analyses of the six week ezetimibe data as opposed to the 12 week ezetimibe data, the ICERs are halved but remain above a £30k per

QALY threshold. Using a threshold of £30k per QALY, the results of the probabilistic analyses suggest that ezetimibe plus generic simvastatin versus atorvastatin monotherapy (scenario 3) is cost effective for all cohorts irrespective of age, gender or CVD history. Using the 6 week ezetimibe data as opposed to the 12 week data, these results are cost effective using a £20k per QALY threshold.

The only difference between Scenario 1 and Scenario 3 is the treatment costs. Scenario 1 compares ezetimibe plus weighted current statin (annual cost = £493) with weighted current statin titrated by one dose (annual cost = £226) while Scenario 3 compares ezetimibe plus generic simvastatin (annual cost = £386) with atorvastatin (annual cost = £344). The total incremental discounted costs for Scenario 1 are approximately £3,000k (£2,000k) higher than those for Scenario 3 for cohorts aged 45 (75) years.

For individuals who do not tolerate statin treatment, using a threshold of £30k per QALY, none of the results of the probabilistic analyses for the treatment regimen ezetimibe monotherapy versus no treatment are cost effective.

The univariate sensitivity analyses suggest that the results are most sensitive to changes in the parameters used to represent the effectiveness of ezetimibe plus statin treatment and the evidence used to link reductions in LDL-c to events avoided. The results are also sensitive to changes in utility measures used, and when using a constant utility of one for all ages as opposed to utility adjusted for age, the ICERs are reduced by approximately 25%. The results for the older aged cohorts are sensitive to changes in the delay for benefits of treatment. All the results are robust to changes in the costs assigned to the health states.

The results for cohorts with no history of CVD are more cost effective than the results for cohorts with a history of CVD. While this appears to be counter-intuitive, the difference in the results is caused because all individuals in the cohorts with a history of CVD commence the analyses in a health state which incurs ongoing costs and disutilities while cohorts with no history of CVD commence the analyses in an event free health state and thus only incur treatment costs. Consequently, if a primary event is saved this accrues greater benefits in terms of the costs saved and the QALY gained from the event than a similar secondary event. Similarly, the ICERs using a life time horizon decrease as the starting age increases as the potential to accrue costs and benefits decreases.

When treatment is stopped and additional benefits from treatment are truncated at 2 (5 or 10) years while accruing costs and benefits from events avoided during the treatment period over a 20 year time horizon, the marginal costs and QALYs gained tend towards the basecase scenario. These analyses demonstrate the cost effectiveness of ezetimibe treatment if the choice to treat is not viewed as a lifetime decision but rather a short term option to be revisited in light of external and lifestyle changes.

For diabetic populations, using a threshold of £30k per QALY none of the results are cost effective when comparing ezetimibe plus current statin treatment versus current statin treatment titrated by one dose. For diabetic patients who cannot tolerate statin treatment, when comparing ezetimibe monotherapy versus no treatment the ICERs are estimated to be approximately £30k per QALY for individuals with no history of a CVD event. However, a large proportion of individuals with diabetes receive additional lipid lowering treatments. As their lipid profile is generally very different from non diabetics they frequently require multi-drug regimens to lower TG levels in addition the LDL-c. This has not been included in the cost effectiveness analyses due to lack of effectiveness evidence on the multi-treatment strategies.

The ICERs for individuals with HeFH, with no history of CVD, range from approximately £18k per QALY for those with a baseline LDL-c of 7.0 mmol/L to approximately £35k per QALY for those with a baseline LDL-c of 4.0 mmol/L. Using a threshold of £30k per QALY none of the ICERs for the individuals with HeFH with a history of CVD are cost effective.

Validity of results

The economic evaluation is based on very short term effectiveness evidence of reductions in surrogate outcomes. There is uncertainty associated with the validity of utilizing the link between reductions in LDL-c to predict reductions in CV events. There is currently no evidence available to support the assumption that the relationship between statin induced changes in LDL-c and reductions in CV events is generalisable to ezetimibe induced changes in LDLc.

There is no statistically significant evidence which suggests that ezetimibe is more effective in reducing lipids in any particular subgroup. The analyses for the individuals with very high baseline LDL-c are based on a non-significant difference in the effectiveness rates. In addition

the baseline LDL-c values used are outside the range of values used to establish the link between LDL-c and reductions in CVD events.

Limitations of analysis

There are several major limitations associated with the economic evaluation. First, the lack of robust clinical effectiveness evidence derived from patients who fail to achieve lipid goals on optimal statin treatment or patients who are intolerant of statins increases the uncertainty associated with ezetimibe treatment. Second, 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. 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, long-term adverse event data associated with ezetimibe monotherapy or ezetimibe combination treatment is not available and could have a large impact on the cost effectiveness results. The direction / magnitude of the impact on the results is not known.

7. ASSESSMENT OF FACTORS RELEVANT TO THE NHS AND OTHER PARTIES

7.1 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, i.e. those with clinical evidence of CHD, those with diabetes and those with a 10 year CVD risk greater or equal to 20%.

Number of patients currently treated with ezetimibe

Based on published prescribing data[200] in the year 2003, 3,854 patients were prescribed with ezetimibe when it was made available in England and Wales (Table 53). In 2004, the number of patients prescribed with ezetimibe was 24,651, representing an increase of 20,797 patients. An additional 32,309 patients received ezetimibe in the year 2005. This 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 patients). A similar increment is assumed for the year 2007, bringing the total number of patients to 157,346.

Table 53: Use and total annual cost of ezetimibe in England and Wales[44,45]

Ezetimibe	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

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% to 30%) of ezetimibe prescriptions are for monotherapy and 80% of prescriptions are for co-administration with a statin *(Personal Communication, Professor P Durrington, Professor of Medicine, Department of Medicine, University of Manchester, 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 to the estimated ezetimibe prescription cost of 2006 (£37.0 million). As mentioned above, it is assumed that an additional 50,193 (this is a conservative estimate) patients 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 53 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, the weighted annual cost of statins is calculated as £150, and the total 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 while 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.

Table 54: Cost associated with ezetimibe prescriptions for the additional 50,193 patients

	Number of patients	Treatment annual cost/patient	Total annual cost (£m)	Total gross budget cost for ezetimibe (£m)	Total net budget cost for ezetimibe (£m)
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	

Reduction in the number of CVD events

The Health Survey for England 2003 data contains records with sufficient information to calculate a CVD risk level.[177] Table 55 shows the mean LDL-c values obtained from the HSE in individuals with greater or equal to 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 was used to calculate the reduction in number of CVD events when the three treatment strategies mentioned above are applied.

Table 55: LDL-c mean values by age and gender[201]

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

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

- 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%[68]
- The reduction of 1 mmol/L in LDL-c is equivalent to a reduction of 21% in the number of CVD events[79]

Table 56 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 and female patients aged 65-74. 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 cardiovascular events, there is a large potential for these costs to be offset by the number of events avoided (Table 56).

Table 56: Estimated percentage reduction in CVD events by treatment strategy

	ezetimibe co-administration		ezetimibe monotherapy		statin titration	
Age	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%

7.2.1 Other major issues impacting on the NHS impact

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 an 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 cardiovascular 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 this may have on specific treatment regimens is unknown and may vary by region.

It has been estimated that 2.8 million individuals were prescribed statins in England and Wales in 2005.[44] Kirby *et al.* reported (based on data from QoF) that 72% of individuals who receive statin treatment achieve targets.[46] Hence it can be assumed that 784,000 (28%) patients may be eligible for ezetimibe treatment. Any changes in lipid goals could impact on the proportion of individuals not at target and thus the number of patients eligible for ezetimibe. Whilst 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 (Qualtity and Outcomes Framework, 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 General Medical Services (GMS) contract

While 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

While 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 cost effectiveness ratios 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 cardiovascular events, then the benefits to individual patients, particularly those who are intolerant of statins and those in whom statins are contra-indicated is potentially large. However, this must be weighed against the unknown long term safety profile of ezetimibe both as a monotherapy or 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 to 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 CVD 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 CVD 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) patients who will contribute to costs of medication through prescription charges. The cost of an additional medication prescribed for life maybe 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 continue to take ezetimibe with more affluent classes being more likely to adhere to treatments.

8. DISCUSSION

8.1 Statement of principle findings

Clinical effectiveness

There is evidence from fourteen short term RCTs that suggests that for patients whose condition is not adequately controlled with a statin alone, the combination treatment of ezetimibe with statin provides significantly more benefit by reducing LDL-c level by 13.94% compared to statin monotherapy. In addition, for patients in whom a statin is considered inappropriate, or is not tolerated, ezetimibe monotherapy is associated with a significant decrease of LDL-c concentration of 18.56% compared to 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 time 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 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 is unknown. Effects on cardiovascular morbidity and mortality are also unknown.

Cost effectiveness

Given the lack of effectiveness data there is a great deal of uncertainty in the cost effectiveness of ezetimibe. The results range from being highly cost effective to highly not cost effective. Further research is urgently required to allow more precise estimates of cost effectiveness to be calculated.

For patients who can tolerate statins, when comparing ezetimibe plus current statin treatment with current statin treatment titrated by one dose, the probabilistic analyses suggest none of the results are cost effective when using a threshold of £30k per QALY irrespective of age, gender or CVD history. Using a threshold of £30k per QALY, the results of the probabilistic analyses suggest that ezetimibe plus generic simvastatin versus atorvastatin monotherapy is cost effective for all

cohorts irrespective of age, gender or CVD history. The core difference between the two sets of analyses are the costs assigned to the treatment regimens modelled. Due to lack of detailed evidence, different efficacy data are not applied to the two treatment strategies. For individuals who do not tolerate statin treatment, using a threshold of £30k per QALY, none of the results of the probabilistic analyses for the treatment regimen ezetimibe monotherapy versus no treatment are cost effective.

The results generated are sensitive to changes in the parameters used to represent the effectiveness of ezetimibe plus statin treatment and the evidence used to link reductions in LDL-c to events avoided. The results are also sensitive to changes in utility measures used, and when using a constant utility of one for all ages as opposed to utility adjusted for age, the ICERs are reduced by approximately 25%. The results for the older aged cohorts are sensitive to changes in the delay for benefits of treatment. All the results are robust to changes in the costs assigned to the health states.

The results for cohorts with no history of CVD are more cost effective than the results for cohorts with a history of CVD. While this appears to be counter-intuitive, the difference in the results is caused because all individuals in the cohorts with a history of CVD commence the analyses in a health state which incurs ongoing costs and disutilities while cohorts with no history of CVD commence the analyses in an event free health state and thus only incur treatment costs. Consequently, if a primary event is saved this accrues greater benefits in terms of the costs saved and the QALY gained from the event than a similar secondary event. Similarly, the ICERs using a life time horizon decrease as the starting age increases as the potential to accrue costs and benefits decreases.

For diabetic populations, using a threshold of £30k per QALY none of the results are cost effective when comparing ezetimibe plus current statin treatment versus current statin treatment titrated by one dose. For diabetic patients who cannot tolerate statin treatment, when comparing ezetimibe monotherapy versus no treatment the ICERs are estimated to be approximately £30k per QALY for individuals with no history of a CVD event. However, a large proportion of individuals with diabetes receive additional lipid lowering treatments as dyslipidaemia which requires multi-drug treatment strategies is common in diabetics.

The ICERs for individuals with HeFH, with no history of CVD, range from approximately £18k per QALY for those with a baseline LDL-c of 7.0 mmol/L to approximately £35k per QALY for those with a baseline LDL-c of 4.0 mmol/L. Using a threshold of £30k per QALY none of the ICERs for the individuals with HeFH with a history of CVD are cost effective. However, robust efficacy data for this subgroup is not available and the results generated should be treated with caution.

The uncertainty associated with extrapolating very short term data over a lifetime is increased by the need to translate surrogate endpoints to hard clinical events and results for shorter time horizons have been presented. The results for both the primary and secondary analyses show that the ICERs are lower for younger aged cohorts. This is not unexpected as when treatment is commenced at a younger age there is a greater period of time over which to accrue the benefits of treatments. However, it should be noted that there is a larger uncertainty associated with the data used and consequently the results for the younger ages. For instance the data used for incidence, prevalence and natural increase by age, all have smaller numbers of patients in the younger age bands.

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 bringing the estimated gross cost of ezetimibe to approximately £54.3 million in 2007.

8.2 Strengths and limitations of the assessment

Clinical effectiveness

The clinical effectiveness has several limitations, and the foremost is 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 baing multicentre, 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 or 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. Particularly, 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.

Based on the meta-analysis (Appendix 11) it was evident that the short term studies (<12 weeks) are unlikely to adequately inform of sustainable effect over time, in terms of lipid lowering (incremental LDL-c of ezetimibe was -22% and -14% in the 6-week and 12-week studies, respectively).

Cost effectiveness

Given the lack of effectiveness data there is a great deal of uncertainty in the cost effectiveness of ezetimibe. The results range from being highly cost effective to highly not cost effective. Further research is urgently required to allow more precise estimates of cost effectiveness to be calculated.

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

The main areas of uncertainty are the use of the published link between reductions in LDL-c and the RR of cardiovascular events; the uncertainty in the effectiveness of ezetimibe in reducing LDL-c translating to corresponding reductions in cardiovascular events, extrapolating

effectiveness rates well beyond RCT evidence and the generalisability of the short term RCT effectiveness data into long term effectiveness in reducing cardiovascular 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.

A major limitation of the evaluations performed is the lack of robust evidence which could be used to estimate cost effectiveness results for subgroups who may potential gain more benefit from ezetimibe treatment such as those with higher than the norm baseline risk which could include diabetics, 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 the results generated by the Cook model are robust due to technical errors in the programming, several assumptions used in the modelling methodology and errors with the costing data used. 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 cardiovascular 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.

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 utilizing 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.

8.3 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 cardiovascular 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 is 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 is also unknown. 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 cardiovascular 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.

8.4 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. While guidelines for initiation of statin therapy recommend 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.[46] Minor changes in this contract are anticipated, such as an increase in the expected percentage of patients to target (current = 60%). However, the expected restructuring of general practice organization and Primary Care Trusts could have a larger impact on the prescribing rates as it is anticipated that GPs will be encouraged to take responsibility for their total budget.[46] In addition, if blanket treatment policies are used, it has been suggested this could breach government agendas on patient choice and involvement.[46]

9. CONCLUSIONS

9.1 Implications for service provision

The growth rate on prescribing data for ezetimibe is increasing. Assuming 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 is no published data which suggests 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 to that for other therapies until long term data on ezetimibe emerges. However, if the observed reductions in LDL-c translate to reductions in CVD events, the number of individuals requiring hospitalization and specialist treatments should decrease.

9.2 Suggested research priorities

Clinical effectiveness

The most urgent need is for further research into the clinical effectiveness of ezetimibe in reducing cardiovascular events. There are currently three ongoing studies which should emerge in 2-4 years which will provide this data. Additional research into subgroup analyses in populations who are potentially more likely to benefit from the treatment are diabetics, patients 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 followings:

- 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 haven't 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 cardiovascular events, robust evidence is required on the safety and adverse event profile of ezetimibe both as monotherapy and combination therapy with both statins and other lipid lowering treatments. If ezetimibe reacts

unfavorably with any of the lipid lowering treatments currently prescribed, the costs and disutilities associated with the adverse events could alter the cost effectiveness ratios, particularly if the events are severe. Conversely, ezetimibe treatment 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 cardiovascular 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, diabetics, individuals with high baseline lipids and those with higher than normal risk by age such as South Asian would be particularly useful to inform future economic evaluations. In addition, studies recruiting individuals who are representative of the target populations i.e. individuals who do not achieve target levels on optimal statin treatment, and individuals in whom statins are contra-indicated and those in whom statins are not tolerated would also be beneficial. Research on the attitudes of GPs to prescribe 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 increases 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 cardiovascular 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, i.e. those not at target on current therapies are also required as is evidence of differential effectiveness in different sub-group 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 and cost effectiveness review will require updating as and when further evidence from clinical studies and clinical practice emerges.

10. APPENDICES

Appendix 1: Clinical effectiveness: Literature Search Strategies

This appendix contains information on the sources searches and keyword strategies for the systematic review of clinical effectiveness.

The following electronic databases were searched

Table 57: Electronic databases

• 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 Review 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 United States National Library of Medicine's premier bibliographic database
• MEDLINE In-Process & Other Non-Indexed Citations	The National Library of Medicine's (NLM) in-process database for Ovid MEDLINE
• SCI & SSCI	Science and Social Sciences Citation Indexes

The following resources were consulted via the internet:

Table 58: Other Sources

• CCOHTA	Canadian Agency for Drugs and Technologies in Health
• CCT	Current Controlled Trials register
• NRR	National Research Register
• NCCHTA	National Co-ordinating 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 to 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 to 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 to 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 (approx. 1994-2006)

CRD website version

Search undertaken between April to 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 to 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 to 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 & Other Non-Indexed Citations

Ovid Online version

Search undertaken between April to 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

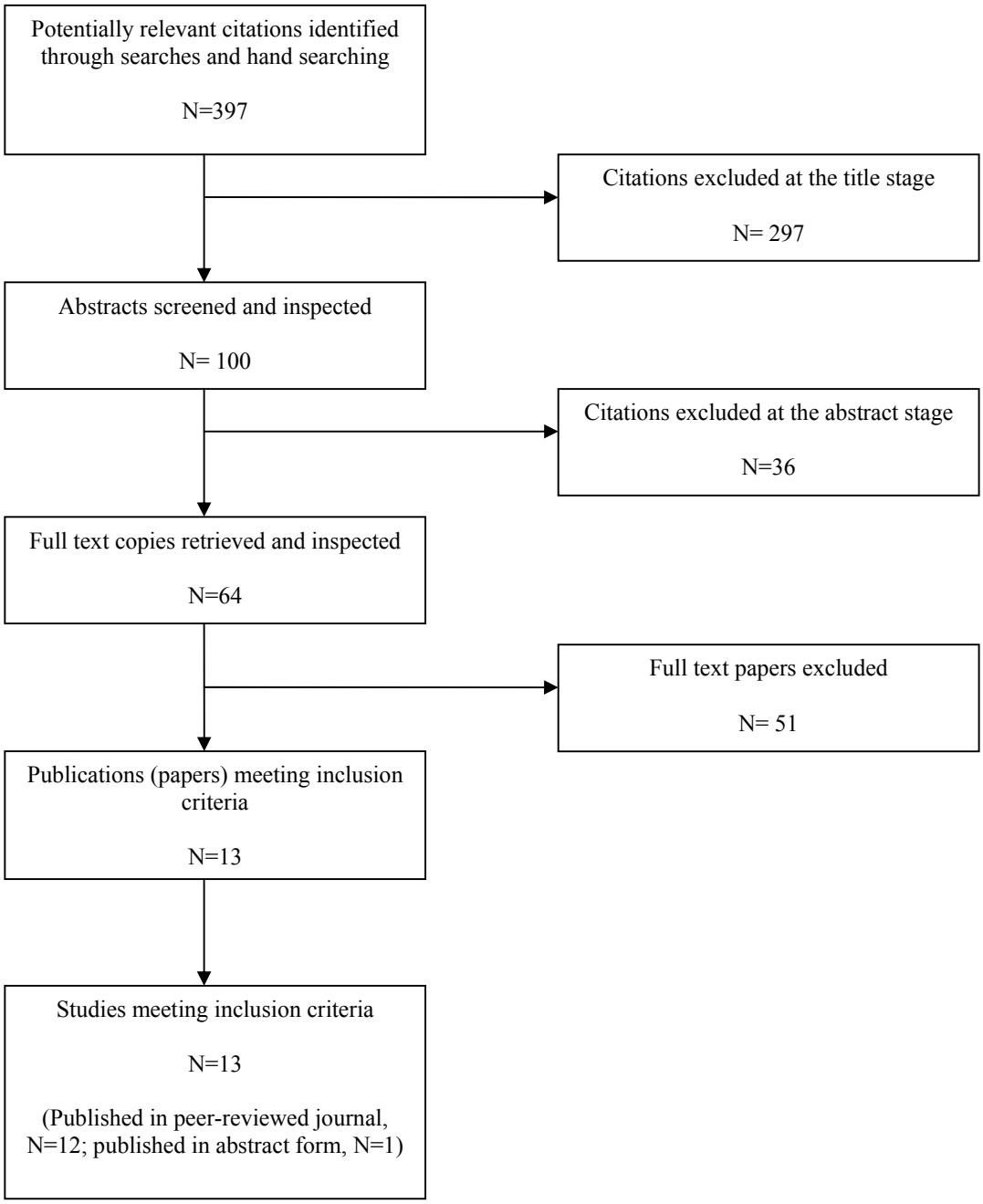
1900-2006

Web of Knowledge version

Search undertaken between April to 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 2: Clinical effectiveness: QUOROM trial flow chart



Appendix 3: Summary of excluded studies with rationale (clinical effectiveness)

REFERENCE	REASON FOR EXCLUSION
Anon. 2001[202]	Letter/comment/editorial/report
Anon. 2002[203]	German (Letter/comment/editorial/ report)
Anon. 2002[204]	German (Letter/comment/editorial/ report)
Anon. 2002[205]	German (Letter/comment/editorial/ report)
Anon. 2003[206]	German (Letter/comment/editorial/ report)
Anon. 2003[207]	German (Letter/comment/editorial/ report)
Anon. 2004[208]	6-week study
Anon. 2004[209]	Letter/comment/editorial/report
Anon. 2004[210]	Letter/comment/editorial/report
Anon. 2005[211]	German (Letter/comment/editorial/ report)
Anon. 2005[212]	German (Letter/comment/Editorial/report)
Baigent *et al.* 2003[127]	Ongoing trial
Ballantyne *et al.* 2005[213]	6-week study
Ballantyne *et al.* 2006[214] [abstract]	6-week study
Ballantyne *et al.* 2006[215] [abstract]	Same study as Ballantyne 2006 6-week
Barrios *et al.* 2005[216]	6-week study
Brohet *et al.* 2005[217]	6-week study
Cruz-Fernandez *et al.* 2005[218]	6-week study
Davidson *et al.* 2004[133]	Meta-analysis
Davidson *et al.* 2006[219] [abstract]	6-week study
Davidson *et al.* 2006[220] [abstract]	6-week study
Davidson *et al.* 2006[134]	Wrong intervention/comparator/outcome
Descamps *et al.* 2006[221] [abstract]	7-day
Dvorakova *et al.* 2006[222] [abstract]	Non-RCT
Esteban-Salan *et al.* 2006[223] [abstract]	Non-RCT
Farnier *et al.* 2005[123]	Population with mixed hyperlipidaemia
Farnier *et al.* 2005[224]	6-week study
Feldman *et al.* 2004[124]	Results only for the first 5 weeks
Gagne *et al.* 2002[176]	8-week study
Goldman-Levine *et al.* 2005[225]	Review – not systematic
Jakulj *et al.* 2005[226]	Wrong intervention/comparator/outcome
Jang-Whan Bae *et al.* 2005[227]	The libraries were unable to trace this paper
Kastelein *et al.* 2004[228]	Ongoing
Kastelein *et al.* 2005[229]	Ongoing
Leibovitz *et al.* 2006[230] [abstract]	Non-RCT
Madigosky *et al.* 2003[231]	Letter/comment/editorial
Maeder *et al.* 2005[232]	Observational programme
McKenney *et al.* 2006[233]	Mixed hyperlipidaemia. Part of Farnier *et al.* 2005 [123]
Melani *et al.* 2003[234]	Abstract, full results published by Melani *et al.*[115]
Ose *et al.* 2005[235]	Single arm
Pearson *et al.* 2005[236]	Sub-group analysis (6-week study)
Pearson *et al.* 2005[237]	6-week study
Pisciotta *et al.* 2006[238] [abstract]	Non-RCT
Rossebo *et al.* 2003[125]	Ongoing trial
Rossebo *et al.* 2005[126]	Ongoing trial. Part of [125]
Schering-Plough, www.clinicaltrials.gov (Identifier NCT00202878) Accessed 31 October 2006[239]	Ongoing trial
Shepherd *et al.* 2003[240]	Letter/comment/editorial
Simons *et al.* 2004[241]	Post-hoc analysis of Gagne *et al.* [32] (8-week study)
Stein *et al.* 2005[242]	Single arm study
Sudhop *et al.* 2002[243]	2-week study

Sudhop *et al.* 2003[244]	German (Letter/comment/editorial)
Van Heyningen *et al.* 2006[245] [abstract]	Non-RCT
Veltri *et al.* 2006[246] [abstract]	review
Vermaak *et al.* 2002[247]	Abstract, no useful data. Email to authors
Wierzbicki *et al.* 2005[248]	Non-RCT

Appendix 4: Clinical effectiveness: Quality assessment

	Ballantyne *et al.* 2003[114]87	Ballantyne *et al.* 2004a [116]93	Ballantyne *et al.* 2004b[118]94	Bays *et al.* 2004 [110]88	Davidson *et al.* 2002 [111]89	Dujovne *et al.* 2002[121]98	Goldberg *et al.* 2004[112]91	Knopp *et al.* 2003[122]99	Masana *et al.* 2005[119]95	McKenney *et al.* 2006[120]00	Melani *et al.* 2003[115]92	Rodney *et al.* 2006[113]97	Stein *et al.* 2004[117]96
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 intention-to-treat analysis included?	Y	Y	N	Y*	Y	Y	Y*	Y	Y	?	Y	Y*	N

Y – item addressed; N – no; ? – not enough information or not clear; NA –not applicable; CR-Central randomisation; CG-Single computer generated; * Modified ITT

Appendix 5: Patient demographics and baseline characteristics

STUDY	PATIENT CHARACTERISTICS								
	Mean age (Range)	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[114]	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 1 or strict diet	NR	Mixed population of pts with family history of CHD (41%), history of hypertension (35%), diabetes mellitus (4%) and CHD including CHD risk factors (9%)
Ballantyne *et al.* 2004a[116]	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 1 or strict diet	NR	Mixed population of pts with history of hypertension (38%), diabetes mellitus (4.5%), CHD including CHD risk factors (12.5%) and peripheral vascular disease (2.5%)
Ballantyne *et al.* 2004b[118]	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	Pts with established CHD or its risk equivalent conferring a 10-year risk of >20% for CHD (Framingham score)
Bays *et al.* 2004[110]	T1: 55.5 T2: 56.4 T3: 54.9 T4: 56.0 ≥65 years: T1: 22.8% T2: 23%	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	Cholesterol-lowering diet	NR	Includes pts with stable/controlled CVD, hypertension, or diabetes mellitus

STUDY	PATIENT CHARACTERISTICS								
	Mean age (Range)	Male (%)	BMI (kg/m^2) Mean (Range)	Physically active (%)	Smoker (%)	Ethnicity (%)	Lifestyle intervention	Concomitant therapy	History/ risk factors/ presence of CVD
	T3: 21.1% T4: 24%					T3: 2.7; T4: 1.4 Other: T1: 5.4; T2: 6.9 T3: 6.9; T4: 6.1			
Davidson *et al.* 2002[111]	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 pts with family history of CHD (45%), history of hypertension (30%), diabetes mellitus (6%) and CHD including CHD risk factors (6.5%)
Dujovne *et al.* 2002[121]	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	NCEP Step 1 or strict diet	CVD drugs and aspirin (≤325 mg/d) was permitted	1/3 of pts had a known family history of CAD and 1/3 had some degree of hypertension. Other CVD risk factors were less frequent (</=12% in either treatment group)
Goldberg *et al.* 2004[112]	Age <65: T1: 79% T2: 75% T3: 77%	T1: 38 T2: 48 T3: 49 T4: 41	NR	NR	NR	White T1: 77; T2: 83 T3: 79; T4: 81 Black	The NCEP Step 1 or strict diet		Pts with hypertension, diabetes, and CHD

STUDY	PATIENT CHARACTERISTICS								
	Mean age (Range)	Male (%)	BMI (kg/m^2) Mean (Range)	Physically active (%)	Smoker (%)	Ethnicity (%)	Lifestyle intervention	Concomitant therapy	History/ risk factors/ presence of CVD
	T4: 71% Age ≥65: T1: 21% T2: 25% T3: 23% T4: 29%					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			
Knopp *et al.* 2003[122]	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/d) were permitted.	1/3 of pts had a known family history of CAD and 1/3 had some degree of hypertension
Masana *et al.* 2005[119]	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	Pts with established but stable CHD and CHD-equivalents, including diabetes mellitus
McKenney *et al.* 2006[120]	NR	50% women	NR	NR	NR	NR	NR	NR	NR
Melani *et al.* 2003[115]	T1: 52.0 (26-75) T2: 56.9	T1: 36 T2: 41 T3: 49	NR	T1: 52 T2: 62 T3: 52	T1: 23 T2: 11 T3: 15	Caucasian T1: 94; T2: 86 T3: 85; T4: 80	NR	NR	40% of pts had a known family history of CHD, 29% had a history of hypertension,

STUDY	PATIENT CHARACTERISTICS								
	Mean age (Range)	Male (%)	BMI (kg/m^2) Mean (Range)	Physically active (%)	Smoker (%)	Ethnicity (%)	Lifestyle intervention	Concomitant therapy	History/ risk factors/ presence of CVD
	(20-86) T3: 55.1 (23-84) T4: 53.4 (32-76) ≥65 years: T1: 16% T2: 25% T3: 26% T4: 17%	T4: 48		T4: 58	T4: 15	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			4.2% had a diabetes mellitus, 5.5 had history of CHD, and 1.3% had a peripheral vascular disease
Rodney *et al.* 2006[113]	T1: 55.2 T2: 53.7	T1: 39 T2: 38	T1: 31.3 T2: 31.0			All pts were African-Americans	The NCEP Step 1 diet	NR	21% in the ezetimibe+ simvastatin arm and 16% in the simvastatin arm had diabetes mellitus. Pts with CHD were10% vs. 11% and CV risk ≥2 were 49% vs. 54%
Stein *et al.* 2004[117]	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 diabetes mellitus (6.5%)

Appendix 6: Data abstraction tables

Table 59: 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[114]																
Baseline	*255*	*4.65*	0.64	4.57; 4.73	*65*	*4.53*	0.56	4.39; 4.67	*248*	*4.65*	0.63	4.57; 4.73	*60*	*4.60*	0.54	4.46; 4.74
Mean % change	*255*	*-54.5*	15.01	-56.34; -52.66	*65*	*-18.4*	14.92	-22.03; -14.77	*248*	*-42.4*	14.96	-44.26; -40.54	*60*	*5.9*	14.87	2.14; 9.66
Bays *et al.* 2004[110]																
Baseline	*609*	*4.58*	0.64	4.53; 4.63	*149*	*4.68*	0.60	4.58; 4.78	*622*	*4.62*	0.66	4.57; 4.67	*148*	*4.63*	0.59	4.53; 4.73
Mean % change	*604*	*-53.0*	14.75	-54.18;-51.82	*148*	*-18.9*	14.60	-21.25; -16.55	*612*	*-39.0*	14.84	-40.18; -37.82	*146*	*-2.2*	14.50	-4.55; 0.15
Davidson *et al.* 2002[111]																
Baseline	*274*	*4.58*	*0.52*	4.52; 4.64	*61*	*4.71*	*0.60*	4.56; 4.86	*263*	*4.64*	*0.52*	4.54; 4.68	*70*	*4.61*	*0.56*	4.48; 4.74
Mean % change	*274*	*-49.9*	14.90	-51.66; -48.14	*61*	*-18.1*	14.84	-21.82; -14.38	*263*	*-36.1*	14.60	-37.86; -34.34	*70*	*-1.3*	14.22	-4.63; 2.03
Dujovne *et al.* 2002[121]																
Baseline					*666*	*4.36*	NR	NA					*226*	*4.37*	NR	NA
Mean % change					*666*	*-16.86*	14.19	-17.94; -15.78					*226*	*0.36*	12.48	-1.27; 1.99
Goldberg *et al.* 2004[112]																
Baseline	*353*	*4.55*	*0.68*	4.48; 4.62	*92*	*4.58*	*0.68*	4.44; 4.72	*349*	*4.55*	*0.65*	4.48; 4.62	*93*	*4.52*	*0.73*	4.37; 4.67
Mean % change	*353*	*-53.2*	*17.2*	-54.99; -51.41	*89*	*-19.8*	*10.5*	-21.98; -17.62	*345*	*-38.5*	*14.2*	-40.00; -37.00	*92*	*2.7*	*13.3*	-0.02; 5.42
Knopp *et al.* 2003[122]																
Baseline					*622*	*4.27*	NR	NA					*205*	*4.25*	NR	NA
Mean % change					*621*	*-17.69*	14.70	-18.85; -16.53					*204*	*0.79*	12.43	-0.92; 2.50
Melani *et al.* 2003[115]																
Baseline	*204*	*4.6*	0.5	4.53; 4.67	*64*	*4.6*	0.6	4.45; 4.75	*205*	*4.6*	0.6	4.52; 4.68	*65*	*4.6*	0.5	4.48; 4.72
Mean % change	*204*	*-37.7*	12.85	-39.46; -35.94	*64*	*-18.7*	12.80	-21.84; -15.56	*205*	*-24.3*	12.89	-26.06; -22.54	*65*	*1.3*	12.90	-1.84 ; 4.44
Rodney *et al.* 2006[113]																
Baseline	*124*	*4.59*	*0.60*						*123*	*4.54*	*0.61*					

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
Mean % change	*124*	*-45.6*	15.8	-48.53; -42.97					*123*	*-28.3*	15.7	-31.12; -25.56				
Stein *et al.* 2004[249]																
Baseline	*305*	*4.87*	1.22	4.73; 5.0					*316*	*4.84*	1.24	4.70; 4.98				
Mean % change	*293*	*-33.2*	11.98	-34.57; -31.83					*303*	*-20.30*	15.67	-22.06 ; -18.5				
23-48 week studies																
Ballantyne *et al.* 2004a[116]																
Baseline	*201*	*4.7*	*0.6*	4.62; 4.78					*45*	*4.8*	*0.6*	4.62; 4.98				
Mean % change	*201*	*-48.4*	*18.8*	-51.00; -45.80					*45*	*-38.6*	*12.4*	-42.22; -34.98				
Masana *et al.* 2005[119]																
Baseline	*355*	*3.55*	1.23	3.42; 3.68					*78*	*3.42*	1.19	3.15; 3.69				
Mean % change	*350*	*-23.7*	33.67	-27.23; -20.17					*78*	*3.3*	22.96	-1.80; 8.40				

To convert mg/dl of HDL or LDL cholesterol to mmol/L, multiplied by 0.02586; To convert mg/dl of triglycerides to mmol/L, multiplied by 0.01129
NA-Not applicable; NR –not reported; Data in *Italics* -reported data, others –calculated data;

Forced titration

STUDY	N	Mean	SD	95 % CI	N	Mean	SD	95 % CI	N	Mean	SD	95 % CI
Ballantyne *et al.* 2004b[118]												
	EZETIMIBE+ STATIN 10/10 (T1)				EZETIMIBE+ STATIN 10/20 (T2)				ATORVASTATIN 10 (T3)			
Baseline	*263*	*4.68*	1.07	4.55; 4.81	*263*	*4.66*	1.08	4.53; 4.79	*262*	*4.70*	1.19	4.56; 4.84
Mean % change at 6 weeks	*263*	*-46.1*	12.97	-47.67; -44.53	*263*	*-50.3*	12.97	-51.87; -48.73	*262*	*-37.2*	12.95	-38.77; -35.63
Mean % change at	EZETIMIBE+ STATIN 10/20				EZETIMIBE+ STATIN 10/40				ATORVASTATIN 20			
12 weeks	*250*	*-50.2*	12.65	-51.77; -48.63	*252*	*-54.3*	12.70	-55.87; -52.73	*246*	*-44.3*	14.12	-46.06; -42.54
Mean % change at	EZETIMIBE+ STATIN 10/40				EZETIMIBE+ STATIN 10/40				ATORVASTATIN 40			
18 weeks	*242*	*-55.6*	9.31	-56.78; -54.42	*240*	-55.6*	9.31*	-56.78; -54.42*	*237*	*-49.1*	13.86	-50.86; -47.34
Mean % change at	EZETIMIBE+ STATIN 10/80				EZETIMIBE+ STATIN 10/80				ATORVASTATIN 80			
24 weeks (Endpoint)	*232*	*-59.4*	10.62	-60.77; -58.03	*227*	-59.4*	10.62*	-60.77; -58.03*	*228*	*-52.5*	15.10	-54.46; -50.54

To convert mg/dl of HDL or LDL cholesterol to mmol/L, multiplied by 0.02586; To convert mg/dl of triglycerides to mmol/L, multiplied by 0.01129
*Data pooled for common doses of ezetimibe+simvastatin at weeks 18 and 24 (based on the mean sample size of the 2 arms)
Data in *Italics* -reported data, others -calculated data

Table 60: 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[114]																
Baseline	*255*	*6.91*	0.64	6.83; 6.99	*65*	*6.70*	0.73	6.52; 6.88	*248*	*6.95*	0.63	6.87; 7.03	*60*	*6.77*	0.70	6.59; 6.95
Mean % change	*255*	*-41.1*	11.82	-42.55;-39.65	*65*	*-13.5*	12.34	-16,50;-10.50	*248*	*-32.1*	11.81	-33.57; -30.63	*60*	*3.5*	11.85	0.50; 6.50
Bays *et al.* 2004[110]																
Baseline	*609*	*6.78*	0.73	6.72; 6.84	*149*	*6.88*	0.68	6.77; 6.99	*622*	*6.80*	0.75	6.74; 6.86	*148*	*6.80*	0.74	6.68; 6.92
Mean % change	*604*	*-37.6*	12.29	-38.58; -36.62	*148*	*-13.3*	10.95	-15.06; -11.54	*612*	*-27.7*	12.37	-28.68; -26.72	*146*	*-1.4*	10.87	-3.16; 0.36
Davidson *et al.* 2002[111]																
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; -35.23	*61*	*-13.3*	11.72	-16.24; -10.36	*263*	*-25.8*	11.35	-27.17; -24.43	*70*	*-0.6*	11.71	-3.34; 2.14
Dujovne *et al.* 2002[121]																
Baseline					*666*	*6.57*	NR	NA					*226*	*6.62*	NR	NA
Mean % change					*666*	*12.48*	9.81	11.74; 13.22					*226*	*0.84*	8.42	-0.26; 1.94
Goldberg *et al.* 2004[112]																
Baseline	*353*	*6.76*	*0.78*	6.68; 6.84	*92*	*6.81*	*0.78*	6.65; 6.97	*349*	*6.73*	*0.78*	6.65; 6.81	*93*	*6.71*	*0.83*	6.54; 6.88
Mean % change	*353*	*-37.7*	*13.3*	-39.09; -36.31	*90*	*-13.7*	*7.9*	-15.33; -12.07	*345*	*-26.4*	*11.3*	-27.59; -25.21	*92*	*2.2*	*9.9*	0.18; 4.22
Knopp *et al.* 2003[122]																
Baseline					*621*	*6.44*	NR	NA					*204*	*6.43*	NR	NA
Mean % change					*621*	*-12.40*	9.47	-13.14; -11.66					*204*	*0.57*	8.57	-0.61; 1.75
Melani *et al.* 2003[115]																
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; -25.92	*64*	*-13.2*	9.60	-15.55; -10.85	*205*	*-17.2*	8.59	-18.38; -16.02	*65*	*0.2*	9.67	-2.15; 2.55
Rodney *et al.* 2006[113]																
Baseline	*124*	*6.66*	*0.70*						*123*	*6.59*	*0.70*					
Mean %	*124*	*-33*	9.0	-35.19; -32.02					*123*	*21*	8.9	-22.44; -19.26				

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
change																
Stein *et al.* 2004[249]																
Baseline	*305*	*6.81*	1.22	6.67; 6.95					*316*	*6.87*	1.24	6.73; 7.00				
Mean % change	*293*	*-26.1*	11.98	-27.47; -24.73					*303*	*-16*	12.18	-17.37; -14.63				
23-48-week studies																
Ballantyne *et al.* 2004a[116]																
Baseline	*201*	*6.9*	*0.7*	6.80; 7.00					*45*	*7.0*	*0.7*	6.80; 7.20				
Mean % change	*201*	*-35.4*	*14.0*	-37.34; -33.46					*45*	*-27.5*	*10.4*	-30.54; -24.46				
Masana *et al.* 2005[119]																
Baseline	*355*	*5.62*	1.27	5.49; 5.75					*78*	*5.49*	1.26	5.21; 5.77				
Mean % change	*350*	*-15.9*	22.45	-18.25; -13.55					*78*	*2.5*	15.90	-1.03; 6.03				

To convert mg/dl of HDL or LDL cholesterol to mmol/L, multiplied by 0.02586; To convert mg/dl of triglycerides to mmol/L, multiplied by 0.01129
NA-Not applicable; NR –not reported; Data in *Italics*-reported data, others -calculated data

Forced titration

STUDY	N	Mean	SD	95 % CI	N	Mean	SD	95 % CI	N	Mean	SD	95 % CI
Ballantyne *et al.* 2004b[118]												
Baseline	EZETIMIBE+ STATIN 10/10				EZETIMIBE+ STATIN 10/20				ATORVASTATIN 10			
	263	*6.90*	1.19	6.76; 7.04	*263*	*6.86*	1.14	6.72; 6.99	*262*	*6.93*	1.29	6.77; 7.09
Mean % change at 6 weeks	*263*	*-33.9*	9.73	-35.08; -32.72	*263*	*-36.2*	9.73	-37.38; -35.02	*262*	*-28.1*	9.71	-29.28; -26.92
Mean % change	EZETIMIBE+ STATIN 10/20				EZETIMIBE+ STATIN 10/40				ATORVASTATIN 20			
at 12 weeks	*250*	*-36.5*	9.49	-37.68; -35.32	*252*	*-39.2*	9.52	-40.38; -38.02	*246*	*-33.1*	9.41	-34.28; -31.92
Mean % change	EZETIMIBE+ STATIN 10/40				EZETIMIBE+ STATIN 10/40				ATORVASTATIN 40			
at 18 weeks	*242*	*-40.5*	7.76	-41.48; -39.52	*240*	*-40.5**	7.76*	-41.48; -39.52*	*237*	*-37.0*	10.78	-38.37; -35.63
Mean % change	EZETIMIBE+ STATIN 10/80				EZETIMIBE+ STATIN 10/80				ATORVASTATIN 80			
at 24 weeks (Endpoint)	*232*	*-43.3*	7.58	-44.28; -42.32	*227*	*-43.3**	7.58*	-44.28; -42.32*	*228*	*-40.2*	10.57	-41.57; -38.83

To convert mg/dl of HDL or LDL cholesterol to mmol/L, multiplied by 0.02586

To convert mg/dl of triglycerides to mmol/L, multiplied by 0.01129

*Data pooled for common doses of ezetimibe+simvastatin at weeks 18 and 24 (based on the mean sample size of the 2 arms)

Data in *Italics* -reported data, others -calculated data

Table 61: 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[114]																
Baseline	*255*	*1.31*	0.32	1.27; 1.35	*65*	*1.31*	0.32	1.23; 1.39	248	1.39	0.32	1.35; 1.43	*60*	*1.30*	0.31	1.22; 1.38
Mean % change	*255*	*7.3*	11.66	5.87; 8.73	*62*	*4.2*	11.53	1.40; 7.0	248	4.3	11.65	2.85; 5.75	*60*	*3.7*	11.54	0.78; 6.62
Bays *et al.* 2004[110]																
Baseline	*609*	*1.35*	0.34	1.32; 1.38	*149*	*1.36*	0.33	1.31; 1.41	*622*	*1.33*	0.32	1.30; 1.36	*148*	*1.38*	0.34	1.32; 1.44
Mean % change	*604*	*7.2*	12.29	6.22; 8.18	*148*	*5.0*	13.38	2.84; 7.16	*612*	*6.8*	12.37	5.82; 7.78	*146*	*-0.3*	13.29	-2.46; 1.86
Davidson *et al.* 2002[111]																
Baseline	*274*	*1.31*	*0.32*	1.27; 1.35	*61*	*1.33*	*0.30*	1.25; 1.41	*263*	*1.33*	*0.28*	1.32; 1.40	*70*	*1.36*	*0.31*	1.29; 1.43
Mean % change	*274*	*9.3*	13.24	7.73; 10.87	*61*	*5.1*	12.50	1.96; 8.24	*263*	*6.9*	12.97	5.33; 8.47	*70*	*0.9*	12.55	-2.04; 3.84
Dujovne *et al.* 2002[121]																
Baseline					*666*	*1.35*	NR	NA					*226*	*1.36*	NR	NA
Mean % change					*666*	*1.31*	12.65	0.35; 2.27					*226*	*-1.60*	10.97	-3.03; -0.17
Goldberg *et al.* 2004[112]																
Baseline	*353*	*1.33*	*0.34*	1.29; 1.37	*92*	*1.33*	*0.34*	1.26; 1.40	*349*	*1.27*	*0.31*	1.24; 1.30	*93*	*1.30*	*0.31*	1.24; 1.36
Mean % change	*353*	*8.2*	*13.1*	6.83; 9.57	*90*	*7.0*	*12.6*	4.40; 9.60	*345*	*7.6*	*11.9*	6.34; 8.86	*92*	*2.3*	*10.8*	0.09; 4.51
Knopp *et al.* 2003[122]																
Baseline					*621*	*1.35*	NR	NA					*204*	*1.32*	NR	NA
Mean % change					*621*	*1.01*	12.46	0.03; 1.99					*204*	*-1.26*	11.14	-2.79; 0.27
Melani *et al.* 2003[115]																
Baseline	*204*	*1.3*	0.3	1.26; 1.34	*64*	*1.3*	0.3	1.23; 1.38	*205*	*1.3*	0.3	1.26; 1.34	*65*	*1.3*	0.3	1.23; 1.37
Mean % change	*204*	*8.1*	11.43	6.53; 9.67	*64*	*4.1*	12.0	1.16; 7.04	*205*	*6.7*	11.45	5.13; 8.27	*65*	*2.0*	12.09	-0.94; 4.94
Rodney *et al.* 2006[113]																
Baseline	*124*	*1.38*	*0.35*						*123*	*1.31*	*0.35*					
Mean % change	*124*	*1.0*	-11.27	3.40; -0.57					*123*	*2.0*	-8.9	3.81; 0.64				
Stein *et al.* 2004[249]																

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																
Baseline	*305*	*3.7*	11.98	2.33; 5.07					*316*	*1.0*	12.18	-0.37; 2.37				
Mean % change	*293*	*2.1*	10.27	0.92; 3.28					*303*	*1.3*	10.44	0.12; 2.48				
23-48-week studies																
Ballantyne *et al.* 2004a[116]																
Baseline	*201*	*1.4*	*0.4*	1.34; 1.46					*45*	*1.3*	*0.3*	1.21; 1.39				
Mean % change	*201*	*6.3*	*13.4*	4.45; 8.15					*45*	*5.4*	*3.13*	4.49; 6.31				
Masana *et al.* 2005[119]																
Baseline	*355*	*1.30*	0.31	1.27; 1.33					*78*	*1.33*	0.35	1.25; 1.41				
Mean % change	*350*	*2.0*	20.58	-0.16; 4.16					*78*	*-0.6*	14.13	-3.74; 2.54				

To convert mg/dl of HDL or LDL cholesterol to mmol/L, multiplied by 0.02586; To convert mg/dl of triglycerides to mmol/L, multiplied by 0.01129
NA- Not applicable; NR –not reported; Data in *Italics*-reported data, others -calculated data

Forced titration

STUDY	N	Mean	SD	95 % CI	N	Mean	SD	95 % CI	N	Mean	SD	95 % CI
Ballantyne *et al.* 2004b[118]												
	EZETIMIBE+ STATIN 10/10 (T1)				EZETIMIBE+ STATIN 10/20 (T2)				ATORVASTATIN 10 (T3)			
Baseline	*263*	*1.21*	0.32	1.17; 1.25	*263*	*1.22*	0.28	1.19; 1.25	*262*	*1.22*	0.30	1.18; 1.26
Mean % change at 6 weeks	*263*	*8.0*	12.97	6.43; 9.57	*263*	*9.5*	12.97	7.93; 11.07	*262*	*5.1*	12.95	3.53; 6.67
Mean % change at 12 weeks	EZETIMIBE+ STATIN 10/20				EZETIMIBE+ STATIN 10/40				ATORVASTATIN 20			
	250	*9.0*	14.23	7.24; 10.76	*252*	*12.4*	14.29	10.64; 14.16	*246*	*6.9*	14.12	5.14; 8.66
Mean % change at 18 weeks	EZETIMIBE+ STATIN 10/40				EZETIMIBE+ STATIN 10/40				ATORVASTATIN 40			
	242	*11.4*	10.87	10.03; 12.77	*240*	*11.4**	10.87*	10.03; 12.77*	*237*	*7.8*	15.39	5.84; 9.76
Mean % change at 24 weeks (Endpoint)	EZETIMIBE+ STATIN 10/80				EZETIMIBE+ STATIN 10/80				ATORVASTATIN 80			
	232	*12.3*	10.62	10.93; 13.67	*227*	*12.3**	10.62*	10.93; 13.67*	*228*	*6.5*	15.10	4.54; 8.46

To convert mg/dl of HDL or LDL cholesterol to mmol/L, multiplied by 0.02586
To convert mg/dl of triglycerides to mmol/L, multiplied by 0.01129
*Data pooled for common doses of ezetimibe+simvastatin at weeks 18 and 24 (based on the mean sample size of the 2 arms)
Data in *Italics* -reported data, others -calculated data

Table 62: TG (mmol/L)

STUDY	PLACEBO				EZETIMIBE				POOLED STATIN				POOLED EZETIMIBE+ STATIN			
	N	Median	SD	95 % CI	N	Median	SD	95 % CI	N	Median	SD	95 % CI	N	Median	SD	95 % CI
12-week studies																
Ballantyne *et al.* 2003[114]																
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[110]			**(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[111]			**(mean)**													
Baseline	*274*	*1.97*	*0.72*	1.88; 2.06	*61*	*2.09*	*0.75*	1.90; 2.28	*263*	*1.86*	*0.66*	1.79; 1.97	*70*	*1.88*	*0.75*	1.70; 2.06
Mean % change	*274*	*-24.1*	23.17	-26.84; -21.36	*61*	*-8.3*	23.43	-14.18; -2.42	*263*	*-16.6*	22.70	-19.34; -13.86	*70*	*2.4*	23.43	-3.09; 7.89
Dujovne *et al.* 2002[121]				**(mean)**												
Baseline					*666*	*1.86*	NA	NA					*226*	*1.92*	NA	NA
Mean % change					*666*	*-5.65*	33.81	-8.22; -3.08					*226*	*5.74*	29.62	1.88; 9.60
Goldberg *et al.* 2004[112]																
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[122]				**(mean)**												
Baseline					*621*	*1.84*	NA	NA					*204*	*1.93*	NA	NA
Mean % change					*621*	*-1.71*	35.64	-4.51; -68.42					*204*	*2.43*	31.99	-1.96; -60.47
Melani *et al.* 2003[115]			**(mean)**													
Baseline	*204*	*2.0*	0.7	1.90; 2.10	*64*	*2.0*	0.7	1.83; 2.17	*205*	*2.0*	0.7	1.90; 2.10	*65*	*1.8*	0.7	1.63; 1.97
Mean % change	*204*	*-17.6*	29.99	-21.72; -13.48	*64*	*-2.1*	30.40	-9.55; -55.78	*205*	*-7.6*	30.07	-11.72; -3.48	*65*	*2.0*	30.64	-5.45; -56.25

STUDY	PLACEBO				EZETIMIBE				POOLED STATIN				POOLED EZETIMIBE+ STATIN			
	N	Median	SD	95 % CI	N	Median	SD	95 % CI	N	Median	SD	95 % CI	N	Median	SD	95 % CI
12-week studies																
Rodney *et al.* 2006[113]																
Baseline	*124*	*1.37*	*0.11*						*123*	*1.38*	*0.64*					
Median % change	*124*	*-22*							*123*	*-15*						
Stein *et al.* 2004[249]																
			(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				
23-48-week studies																
Ballantyne *et al.* 2004a[116]																
Baseline	*201*	*1.8*	NA	*1.4; 2.4*					*45*	*1.8*	NA	*1.3; 2.3*				
Median % change	*201*	*-29.6*	NR	NR					*45*	*-16.9*	NR	NR				
Masana *et al.* 2005[119]																
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				

To convert mg/dl of HDL or LDL cholesterol to mmol/L, multiplied by 0.02586; To convert mg/dl of triglycerides to mmol/L, multiplied by 0.01129
NA- Not applicable; NR –not reported; Data in *Italics*-reported data, others -calculated data
Data in *Italics* -reported data, others -calculated data

Forced titration

STUDY	N	Median	IQR/1.075	N	Median	IQR/1.075	N	Median	IQR/1.075
Ballantyne *et al.* 2004b[118]									
	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*
Median % change at	EZETIMIBE+ STATIN 10/20			EZETIMIBE+ STATIN 10/40			ATORVASTATIN 20		
12 weeks	*250*	*-27.7*	*1.9*	*252*	*-30.8*	*1.7*	*246*	*-28.4*	*1.7*
Median % change at	EZETIMIBE+ STATIN 10/40			EZETIMIBE+ STATIN 10/40			ATORVASTATIN 40		
18 weeks	*242*	*-32.0*	*1.3*	*240*	*-32.0**	*1.3**	*237*	*-31.2*	*1.8*
Median % change at	EZETIMIBE+ STATIN 10/80			EZETIMIBE+ STATIN 10/80			ATORVASTATIN 80		
24 weeks (Endpoint)	*232*	*-35.3*	*1.2*	*227*	*-35.3**	*1.2**	*228*	*-34.8*	*1.9*

To convert mg/dl of HDL or LDL cholesterol to mmol/L, multiplied by 0.02586
To convert mg/dl of triglycerides to mmol/L, multiplied by 0.01129
*Data pooled for common doses of ezetimibe+simvastatin at weeks 18 and 24 (based on the mean sample size of the 2 arms)

Appendix 7: Meta-analyses

Figure 25: For patients whose condition is not adequately controlled with a statin alone: Fixed dose studies

Review: Ezetimibe
Comparison: 01 Ezetimibe + Statin versus Statin alone
Outcome: 03 High density lipoprotein cholesterol (HDL-c) non-titrated 12 week studies

Study or sub-category	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	604	7.20(12.29)	612	6.80(12.37)		35.69	0.40 [-0.99, 1.79]
Davidson	274	9.30(13.24)	263	6.90(12.97)		13.95	2.40 [0.18, 4.62]
Goldberg	353	8.20(13.10)	345	7.60(11.90)		19.90	0.60 [-1.26, 2.46]
Subtotal (95% CI)	1231		1220			69.54	0.86 [-0.13, 1.85]
Test for heterogeneity: Chi² = 2.35, df = 2 (P = 0.31), I² = 15.0%							
Test for overall effect: Z = 1.69 (P = 0.09)							
02 Ezetimibe + Atorvastatin versus Atorvastatin							
Ballantyne	255	7.30(11.66)	248	4.30(11.65)		16.52	3.00 [0.96, 5.04]
Subtotal (95% CI)	255		248			16.52	3.00 [0.96, 5.04]
Test for heterogeneity: not applicable							
Test for overall effect: Z = 2.89 (P = 0.004)							
03 Ezetimibe + Pravastatin versus Pravastatin							
Melani	204	8.10(11.43)	205	6.70(11.45)		13.94	1.40 [-0.82, 3.62]
Subtotal (95% CI)	204		205			13.94	1.40 [-0.82, 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, 2.12]
Test for heterogeneity: Chi² = 5.79, df = 4 (P = 0.22), I² = 31.0%							
Test for overall effect: Z = 3.05 (P = 0.002)							

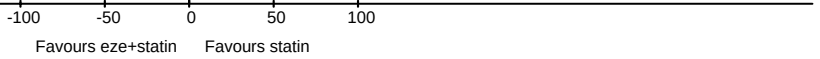


Figure 26: For patients whose condition is not adequately controlled with a statin alone: Fixed dose studies:

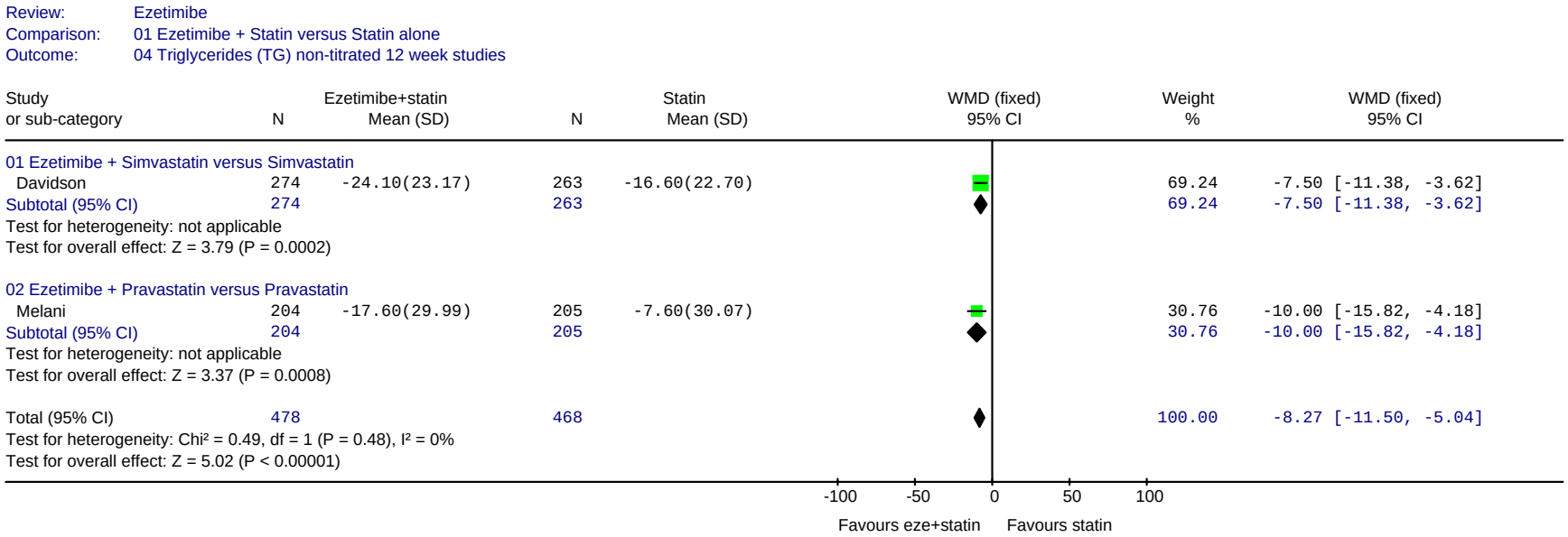


Table 63: For patients whose condition is not adequately controlled with a statin alone: Summary of titrated studies

Unit (mmol/L), total N	Endpoint mean % change (SD)		
	EZETIMIBE + POOLED STATIN	POOLED STATIN	P-value
HDL-c			
Ballantyne *et al.* 2004a[116]	6.3 (13.4)	5.4 (3.13)	NS
Ballantyne *et al.* 2004b[118]	12.3 (10.62)	6.5 (15.10)	≤0.05
Masana et al, 2005[119]	2.0 (20.58)	-0.6 (14.13)	0.07
Stein et al 2004[117]	2.1 (10.27)	1.3 (10.44)	NS
TG (median)			
Ballantyne *et al.* 2004a[116]	-29.6 (NR)	-16.9 (NR)	<0.01
Ballantyne *et al.* 2004b[118]	-35.3 (NR)	-34.8 (NR)	NS
Masana et al, 2005[119]	-8.2 (1.7)	5.4 (3.4)	<0.001
Stein et al 2004[117]	-9.3 (NR)	-3.9 (NR)	<0.01

Figure 27: For patients in whom a statin is considered inappropriate, or is not tolerated:

Review: Ezetimibe
Comparison: 02 Ezetimibe versus Placebo
Outcome: 03 High Density Lipoprotein cholesterol (LDL-c) 12-week studies

Study or sub-category	N	Ezetimibe Mean (SD)	N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
Dujovne	666	1.31(12.65)	226	-1.60(10.97)		33.47	2.91 [1.19, 4.63]
Ballantyne	65	4.20(11.53)	60	3.70(11.54)		6.06	0.50 [-3.55, 4.55]
Knopp	621	1.01(12.46)	204	-1.26(11.14)		30.13	2.27 [0.45, 4.09]
Melani	64	4.10(12.00)	65	2.00(12.09)		5.75	2.10 [-2.06, 6.26]
Bays	148	5.00(13.38)	146	-0.30(13.29)		10.69	5.30 [2.25, 8.35]
Davidson	61	5.10(12.50)	70	0.90(12.55)		5.37	4.20 [-0.10, 8.50]
Goldberg	90	7.00(12.60)	92	2.30(10.80)		8.53	4.70 [1.29, 8.11]
Total (95% CI)	1715		863			100.00	3.00 [2.01, 4.00]

Test for heterogeneity: Chi² = 5.72, df = 6 (P = 0.46), I² = 0%
Test for overall effect: Z = 5.90 (P < 0.00001)

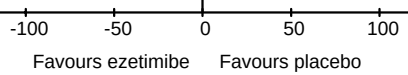
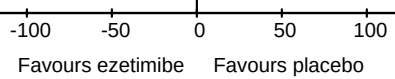


Figure 28: For patients in whom a statin is considered inappropriate, or is not tolerated:

Review: Ezetimibe
Comparison: 02 Ezetimibe versus Placebo
Outcome: 04 Triglycerides (TG)

Study or sub-category	N	Ezetimibe Mean (SD)	N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
Dujovne	666	-5.65(33.81)	226	5.74(29.62)		43.12	-11.39 [-16.03, -6.75]
Knopp	621	-1.71(35.64)	204	2.43(31.99)		34.19	-4.14 [-9.35, 1.07]
Melani	64	-2.10(30.40)	65	2.00(30.64)		8.36	-4.10 [-14.63, 6.43]
Davidson	61	-8.30(23.43)	70	2.40(23.43)		14.33	-10.70 [-18.74, -2.66]
Total (95% CI)	1412		565			100.00	-8.20 [-11.25, -5.16]

Test for heterogeneity: Chi² = 5.10, df = 3 (P = 0.16), I² = 41.2%
Test for overall effect: Z = 5.28 (P < 0.00001)

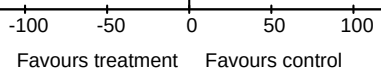


Appendix 8: Clinical effectiveness: LDL-c reduction in HeFH vs. non-HeFH group of patients (mmol/L) (Stein *et al.* 2004) [117]

Review: WMD
Comparison: 01 HeFH
Outcome: 01 LDL-c

Study or sub-category	N	Eze+Atorva Mean (SD)	N	Atorva 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, -11.17]
Non-genetic group	124	-31.10(15.59)	135	-20.50(15.10)		44.10	-10.60 [-14.34, -6.86]
Total (95% CI)	305		316			100.00	-12.78 [-15.27, -10.29]

Test for heterogeneity: Chi² = 2.33, df = 1 (P = 0.13), I² = 57.1%
Test for overall effect: Z = 10.07 (P < 0.00001)



Appendix 9: Changes in plasma lipid/lipoprotein concentrations in HeFH vs. non-HeFH patients after addition of ezetimibe to atorvastatin 10 mg/d or doubling the dose of atorvastatin to 20 mg/d (Stein *et al.* 2004) [117] *Data obtained by personal communication from Dr Evan Stein, Director of the Metabolic and Atherosclerosis Research Center, Cincinnati, Ohio, USA (30.10.06)*

		HeFH group						Non-HeFH group					
		Ezetimibe 10 mg + atorvastatin 10/20/40 mg (n=181)		Atorvastatin 20/40/80 mg (n=181)				Ezetimibe 10 mg + atorvastatin 10/20/40 mg (n=124)		Atorvastatin 20/40/80mg (n=135)			
		Absolute change (mmol/l)	Mean % change (SD)	Absolute change (mmol/l)	Mean % change (SD)	Between group % change	P-value	Absolute change (mmol/l)	Mean % change (SD)	Absolute change (mmol/l)	Mean % change (SD)	Between group % change	P-value
Week 4/5	LDL-c	- 1.21	-23.6 (12.11)	-0.39	-7.4 (13.45)	-16.2	<.01	-0.93	-21.5 (13.36)	-0.45	-10.0 (12.78)	-11.5	<.01
	Total-c	- 1.28	-18.1 (9.42)	-0.40	-5.5 (9.42)	-12.6	<.01	-1.04	-16.2 (10.02)	-0.45	-6.8 (9.30)	-9.3	<.01
	HDL-c	0.02	1.9 (9.42)	0.01	0.8 (10.76)	1.2	N.S.	0.03	2.5 (10.02)	0.02	1.9 (10.46)	0.6	N.S.
	TG (median)	- 0.09	-9.3	-0.05	-3.8	-5.5	.01	-0.15	-9.3	-0.06	-3.9	-5.4	.02
Week 9/10	LDL-c	- 1.55	-30.1 (14.80)	-0.75	-14.7 (14.80)	-15.4	<.01	-1.25	-28.7 (14.48)	-0.69	-14.9 (13.94)	-13.9	<.01
	Total-c	-1.65	-23.1 (12.11)	-0.82	-11.6 (12.11)	-11.5	<.01	-1.41	-22.0 (11.14)	-0.74	-11.0 (10.46)	-11.1	<.01
	HDL-c	0.03	2.3 (10.76)	-0.01	-0.4 (10.76)	2.7	.02	0.02	2.5 (11.14)	0.01	1.3 (10.46)	1.2	N.S.
	TG (median)	-0.11	-10.2	-0.07	-6.4	-3.8	.02	-0.20	-14.0	-0.11	-9.1	-5.0	.03
Week 14	LDL-c	-1.78	-34.6 (16.14)	-1.04	-20.1 (16.14)	-14.5	<.01	-1.39	-31.1 (15.59)	-0.94	-20.5 (15.10)	-10.5	<.01
	Total-c	-1.93	-27.0 (12.11)	-1.15	-16.2 (13.45)	-10.8	<.01	-1.61	-24.7 (11.14)	-1.04	-15.7 (10.46)	-9.0	<.01
	HDL-c	0.04	3.5 (12.11)	-0.01	-0.3 (12.11)	3.8	<.01	0.04	4.1 (13.36)	0.03	2.8 (12.78)	1.3	N.S.
	TG (median)	-0.18	-16.3	-0.12	-11.2	-5.1	.04	-0.38	-23.7	-0.22	-13.1	-10.6	<.01

Appendix 10: Adverse events

Tab1e 64: Placebo and Ezetimibe arms

	PLACEBO (%)							EZETIMIBE (%)						
	Ballantyne *et al.* 2003[114]	Bays *et al.* 2004[110]	Davidson *et al.* 2002[111]	Dujovne *et al.* 2002[121]	Goldberg *et al.* 2004[112]	Knopp *et al.* 2003[122]	Melani *et al.* 2003[115]	Ballantyne *et al.* 2003[114]	Bays *et al.* 2004[110]	Davidson *et al.* 2002[111]	Dujovne *et al.* 2002[121]	Goldberg *et al.* 2004[112]	Knopp *et al.* 2003[122]	Melani *et al.* 2003[115]
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 >/=3x 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>/=10xULN	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

Knopp *et al.* 2003 -1 pt died (drowned) in the ezetimibe arm- investigators considered not related to treatment

Table 65: Statin and Ezetimibe + Statin arms

	POOLED STATIN (%)									EZETIMIBE+POOLED STATIN (%)								
	Ballantyne *et al.* 2003[114]	Ballantyne *et al.* 2004a[116]	Bays *et al.* 2004[110]	Davidson *et al.* 2002[111]	Goldberg *et al.* 2004[112]	Masana *et al.* 2005[119]	Melani *et al.* 2003[115]	Rodney *et al.* 2006[113]	Stein *et al.* 2004[117]	Ballantyne *et al.* 2003[114]	Ballantyne *et al.* 2004a[116]	Bays *et al.* 2004[110]	Davidson *et al.* 2002[111]	Goldberg *et al.* 2004[112]	Masana *et al.* 2005[119]	Melani *et al.* 2003[115]	Rodney *et al.* 2006[113]	Stein *et al.* 2004[117]
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 >/=3x 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>/=10xULN	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

Bays *et al.* 2004 -1 pt died of cardiac arrest- (ezetimibe/simvastatin) – investigators considered not related to treatment
Davidson *et al.* 2002 - 1pt died of respiratory failure (ezetimibe/simvastatin) - investigators considered not related to treatment
Masana *et al.* 2005-1pt died of motor vehicle accident - investigators considered not related to treatment (not clear in which arm)
Stein *et al.* 2004-1 pt in statin group died of MI- investigators considered not related to treatment

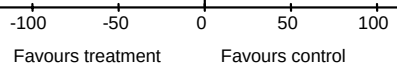
Table 65 (cont): Statin and Ezetimibe+Statin arms

	STATIN (%)		STATIN+ EZETIMIBE (%)				
	Balantyne *et al.* 2004b[118]	Feldman *et al.* 2004[124]	Balantyne *et al.* 2004b[118]		Feldman *et al.* 2004[124]		
	Atorva	Simva 20	Eze + Simva10	Eze + Simva 20	Eze+ Simva10	Eze+ Simva20	Eze+Simva40
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 >/=3x 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>/=10xULN	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 11: Meta-analysis of 6-week and 12-week studies: LDL-c

Review: Ezetimibe
Comparison: 07 Ezetimibe+ Statin versus Statin alone (LDL-c) 6-wk and 12-wk studies
Outcome: 01 Low density lipoprotein cholesterol (LDL-c)

Study or sub-category	Ezetimibe+Statin N	Ezetimibe+Statin Mean (SD)	Statin N	Statin Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 6-8-week studies							
Gagne	379	-25.00(13.63)	390	-3.70(13.82)		13.11	-21.30 [-23.24, -19.36]
Barrios	217	-32.80(17.68)	210	-20.30(17.39)		4.46	-12.50 [-15.83, -9.17]
Brohet	208	-27.10(15.45)	210	-4.10(14.78)		5.87	-23.00 [-25.90, -20.10]
Cruz-Fernandez	219	-31.10(15.50)	225	-4.20(15.60)		5.90	-26.90 [-29.79, -24.01]
Farnier	178	-25.20(15.25)	186	-0.90(18.28)		4.14	-24.30 [-27.75, -20.85]
Pearson	2020	-25.80(35.24)	1010	-2.70(18.67)		13.39	-23.10 [-25.02, -21.18]
Subtotal (95% CI)	3221		2231			46.87	-22.16 [-23.19, -21.13]
Test for heterogeneity: Chi² = 46.18, df = 5 (P < 0.00001), I² = 89.2%							
Test for overall effect: Z = 42.32 (P < 0.00001)							
02 12-week studies							
Ballantyne	255	-54.50(15.01)	248	-42.40(14.96)		7.19	-12.10 [-14.72, -9.48]
Melani	204	-37.70(12.85)	205	-24.30(12.89)		7.93	-13.40 [-15.89, -10.91]
Bays	604	-53.00(14.75)	612	-39.00(14.84)		17.84	-14.00 [-15.66, -12.34]
Davidson	274	-49.90(14.90)	263	-36.10(14.60)		7.93	-13.80 [-16.30, -11.30]
Goldberg	353	-53.20(17.20)	345	-38.50(14.20)		9.03	-14.70 [-17.04, -12.36]
Rodney	124	-45.60(15.78)	123	-28.30(15.72)		3.20	-17.30 [-21.23, -13.37]
Subtotal (95% CI)	1814		1796			53.13	-13.94 [-14.90, -12.98]
Test for heterogeneity: Chi² = 5.31, df = 5 (P = 0.38), I² = 5.8%							
Test for overall effect: Z = 28.35 (P < 0.00001)							
Total (95% CI)	5035		4027			100.00	-17.79 [-18.50, -17.09]
Test for heterogeneity: Chi² = 182.39, df = 11 (P<0.00001), I² = 94.0%							
Test for overall effect: Z = 49.64 (P<0.00001)							



Appendix 12: 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".[252] It allows a decision to be reached in real time for problems where strategic decisions are complexly interconnected, whilst 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.

SCA is seen as strategic decision making, considering problems of a short and long term nature but essentially 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. SCA considers each area of uncertainty, the potential outcomes and the information required to make this area less uncertain. SCA aid 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.[253] SODA II uses a similar methodology and the main difference is that the whole group work 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 problems structuring methods

A brief summary of the full report[89] of the PSM methods 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 cardiovascular events. Of the 634 papers identified, 25 were retained from the titles and abstracts and six were reviewed in more detail:
Framingham Anderson[77], Framingham D'Agostino[87], UKPDS,[86] WOSCOPS,[104] Lancet[79] and PROCAM.[254]
The assumptions required for each of the methods are provided in Table 67 below:

Table 66, The assumptions necessary if the papers' methodology were to be incorporated to the ezetimibe treatment.

Paper	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 hypercholesterolemia.
WOSCOPS	Predictions of events for mixed hypercholesterolemic middle aged men will be equal or close to primary, mixed age and sex hypercholesterolemic patients.
Lancet	That 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.

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 67:

Table 67, The options associated with each decision area.

Methodology	Options	Abbreviation
Fram And	Don't use Primary prediction	0 1
Fram D'Ag	Don't use Subsequent Predictions	0 2
UKPDS	Don't use Primary predictions	0 1
WOSCOPS	Don't use Primary Predictions	0 1
Lancet	Don't use Primary predictions Subsequent Predictions	0 1 2
PROCAM	Don't use Subsequent Predictions	0 2

Options graph:

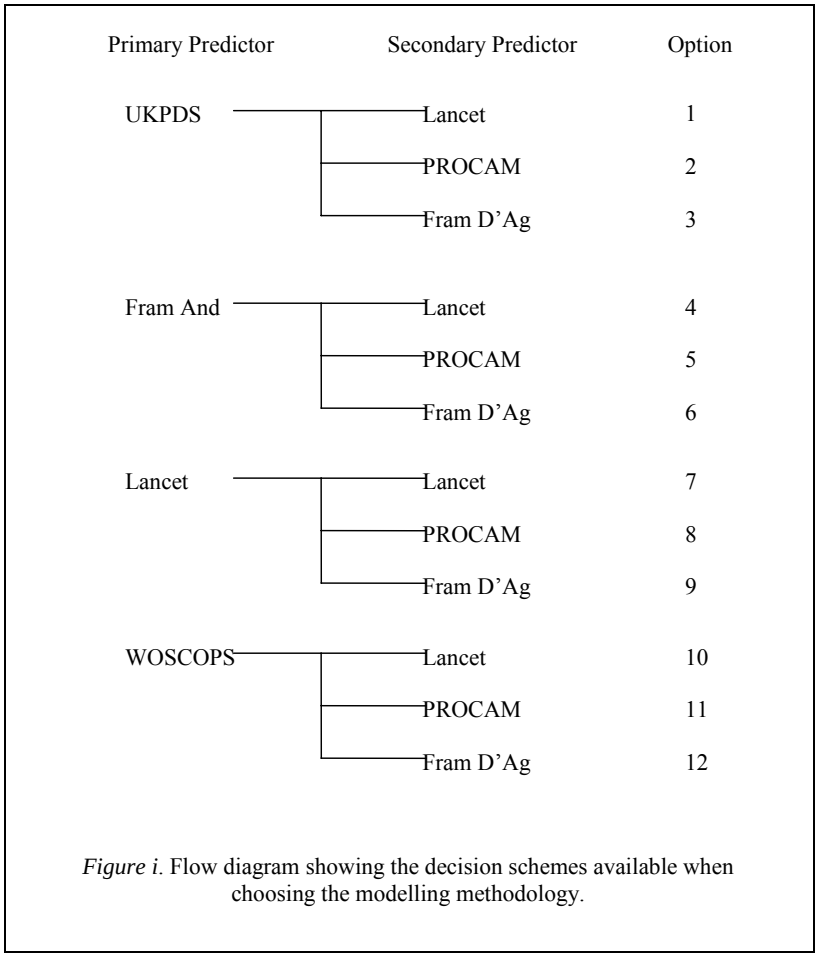


Figure i. Flow diagram showing the decision schemes available when choosing the modelling methodology.

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 hypercholesterolemic?

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 time 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?

f Will the methods, data and results be readily understood and accepted by the key decision-makers?

g Size of study

h Prediction time period

3) Rate the comparison areas against the decision schemes using a binary highest/lowest to grade each comparison area with each decision scheme. This is used to highlight dominant decision schemes

Table 68, to show the results of the decision schemes when compared to 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

Where
H represents the highest result in the comparison area and
L the lowest

4) Implement the comparisons in a cyclic format until all aspects under considerations have been applied

Table 69, 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	-

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), Uncertainties about choices on related agendas (UR) groups:

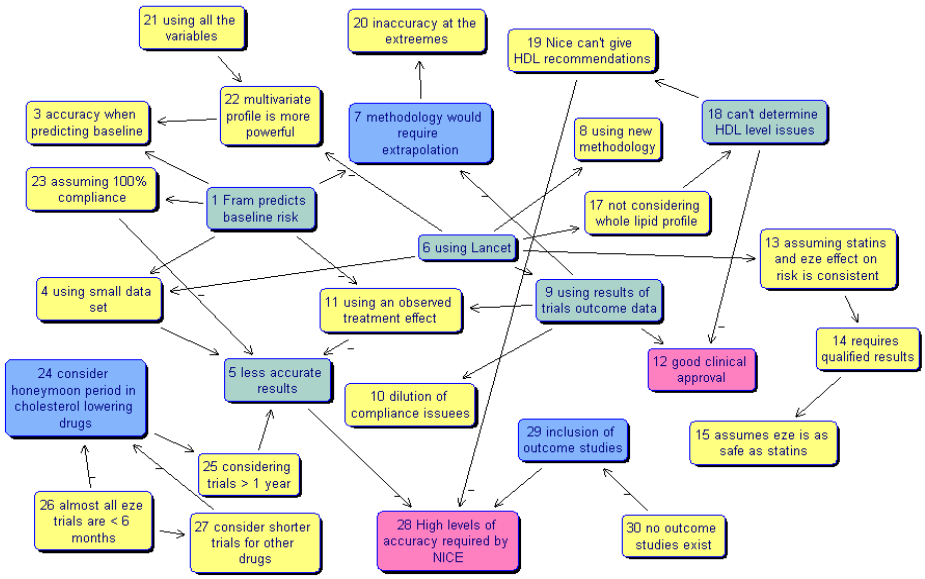
Table70, Classifications of uncertainties.

Uncertainty	Classification
Confidence in using the methodology	UV
No. of events within a time horizon	UE
Methodology's acceptance within the clinical community	UV
Adaptability of the methodology to ezetimibe	UV

7) cognitive mapping was used to explore the remaining uncertainties in the two optimal strategies identified from the earlier stages

Figure 29: Cognitive Map of Miss R. Ara of the issues surrounding the use of Framingham or Lancet as the key methodology

Figure 30: Cognitive Map of Dr. Wilf Yeo of the issues surrounding the use of Framingham or Lancet as the key methodology



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 TC and HDL-c lipids (Framingham method)

The CTTC method uses the published RR of events: non-fatal MI = 0.74, non-fatal stroke = 0.83, and fatal CHD = 0.81 for each 1 mmol/L reduction in LDL-c.

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 *et al.* 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 stroke).

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 compared with the numbers and proportions reported in the CTTC article.

Over a 5 year period, the CTTCs model over predicts the number of primary events in both the treatment and comparator arm. However, the difference in the proportion of events predicted for the

treatment and comparator arm using the CTTC model is very close (predicted: non fatal MI = 1.03% v 1.24%; non fatal stroke = 0.53% v 0.45% ; fatal CHD = 0.40% v 0.37% and all CHD events = 1.42% v 1.62%).

Over a 5 year period, the Framingham model under predicts the number of primary events in both the treatment and comparator arm. The difference in the proportion of events predicted for the treatment and comparator arm using the Framingham model is also less accurate (predicted: non fatal MI = 0.81% v 1.24%; non fatal stroke = 0.21% v 0.45% ; fatal CHD = 0.21% v 0.37% and all CHD events = 1.01% v 1.62%).

Table 71: Comparing the number of primary events predicted by the CTTC and Framingham models compared with the number observed in the CTTC data

	Treatment Arm				Comparator arm				Difference			
	Non Fatal MI	Non Fatal Stroke	Fatal CHD	All CHD events	Non Fatal MI	Non Fatal Stroke	Fatal CHD	All CHD events	Non Fatal MI	Non Fatal Stroke	Fatal CHD	All CHD events
Observed	656	656	432	1088	950	761	519	1469				
	2.73%	**2.74%**	**1.80%**	**4.54%**	**3.97%**	**3.19%**	**2.17%**	**6.16%**	**1.24%**	**0.45%**	**0.37%**	**1.62%**
CTTCs	787	705	477	1264	1031	829	571	1602				
	3.27%	**2.93%**	**1.98%**	**5.26%**	**4.30%**	**3.46%**	**2.38%**	**6.68%**	**1.03%**	**0.53%**	**0.40%**	**1.42%**
Framingham	513	347	138	652	704	396	187	891				
	2.13%	**1.44%**	**0.57%**	**2.71%**	**2.94%**	**1.65%**	**0.78%**	**3.72%**	**0.81%**	**0.21%**	**0.21%**	**1.01%**

For the secondary events, 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 *et al*.

Over a 5 year period, the CTTC model over-predicts the number of secondary events in both the treatment and comparator arm. However, the difference in the proportion of events predicted for the treatment and comparator arm using the CTTC model is slightly under-predicted (predicted: non fatal MI = 1.90% v 1.84%; non fatal stroke = 0.72% v 0.86% ; fatal CHD = 1.23% v 1.58% and all CHD events = 3.09% v 3.42%).

Over a 5 year period, the Framingham model over predicts the number of secondary events in both the treatment and comparator arm. The difference in the proportion of events predicted for the treatment and comparator arm using the Framingham model is also less accurate (predicted: non fatal MI = 1.32% v 1.84%; non fatal stroke = 1.00% v 0.86% ; fatal CHD = 0.35% v 1.58% and all CHD events = 1.67% v 3.42%).

Table 72: Comparing the number of secondary events predicted by the CTTC and Framingham models compared with the number observed in the CTTC data

Methodology	Treatment Arm				Comparator arm				Difference			
	Non Fatal MI	Non Fatal Stroke	Fatal CHD	All CHD events	Non Fatal MI	Non Fatal Stroke	Fatal CHD	All CHD events	Non Fatal MI	Non Fatal Stroke	Fatal CHD	All CHD events
Observed	1133	684	1116	2249	1510	856	1441	2951				
	5.51%	**3.45%**	**5.40%**	**10.98%**	**7.35%**	**4.31%**	**6.98%**	**14.4%**	**1.84%**	**0.86%**	**1.58%**	**3.42%**
CTTCs	1203	765	1237	2440	1594	910	1491	3086				
	5.82%	**3.86%**	**5.99%**	**11.81%**	**7.72%**	**4.58%**	**7.22%**	**14.9%**	**1.90%**	**0.72%**	**1.23%**	**3.09%**
Framingham	1516	2003	425	1941	1778	2203	496	2274				
	7.34%	**10.10%**	**2.06%**	**9.40%**	**8.66%**	**11.10%**	**2.41%**	**11.07%**	**1.32%**	**1.00%**	**0.35%**	**1.67%**

APPENDIX 13: Eddy/BMJ check lists for the published cost effectiveness studies

Table 73: Eddy/BMJ checklist for quality of studies

	Cook *et al*	Kohli *et al*
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 (eg. 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 basecase 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 basecase is not defined in terms of age and gender	Y
The results derived from applying the model for the basecase;	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

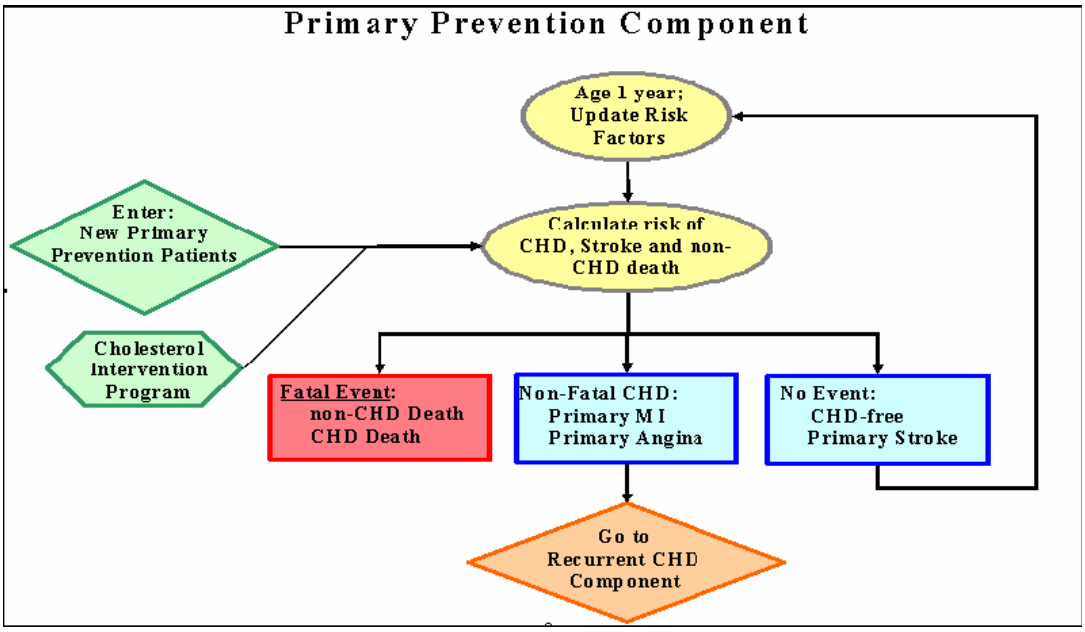
Y – yes; N – no; NA – not applicable

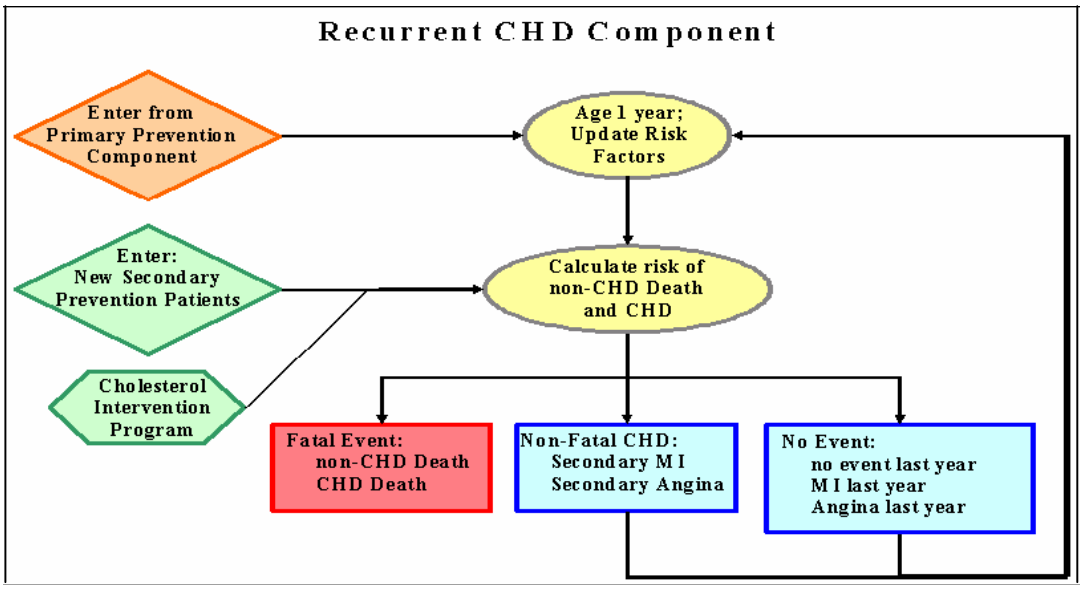
Table 74: Eddy/BMJ checklist for modelling assessment

	MSD
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 to 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 (eg. 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 basecase 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 basecase	Y The basecase (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

Y – yes; N – no; NA – not applicable

Appendix 14: Schematic models of primary and secondary prevention from the Merck Sharp & Dohme Limited and Schering -Plough Limited submission





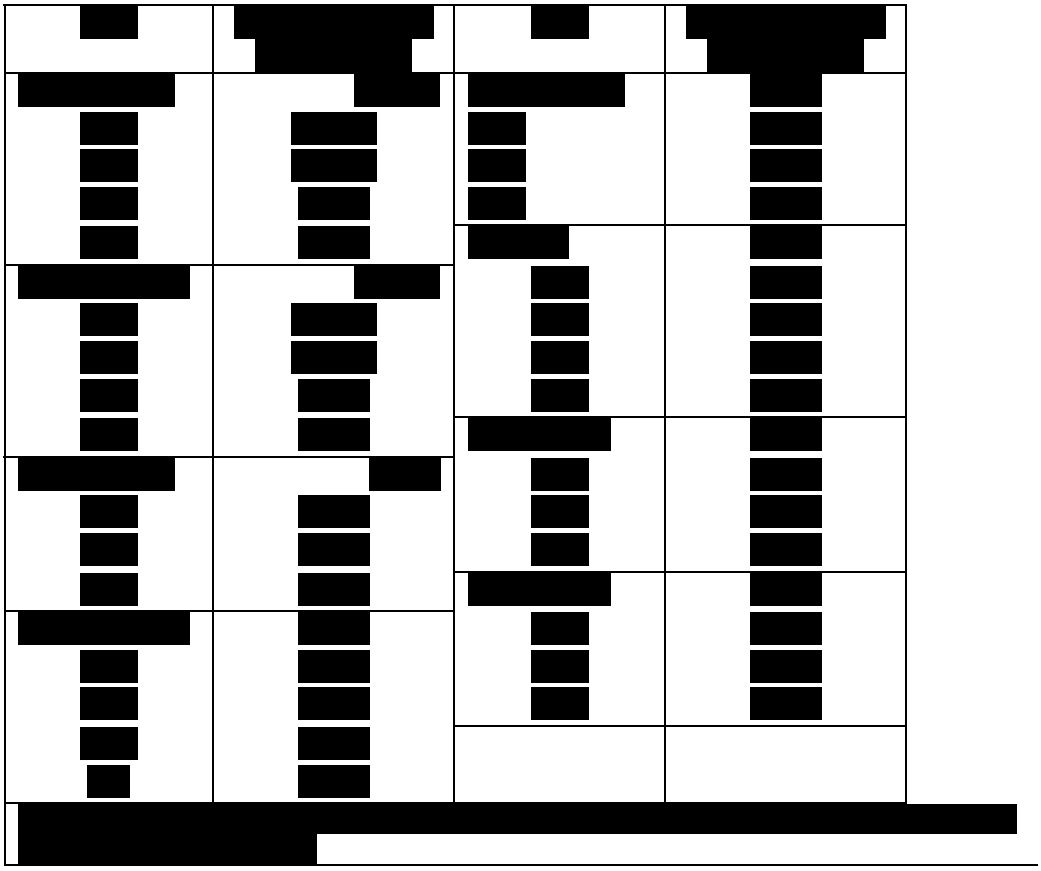
APPENDIX 15: Costs of treatments used in the MSD/SP Cook evaluation

Table 75: Cost per pack of 28 tablets of treatments used in MSD/SP

Drug	Drug Tariff Price*	Drug	Drug Tariff Price*
Simvastatin		Fluvastatin	
20mg	£1.89	40mg	£13.99
40mg	£4.17	80mg	£17.60
10mg	£1.97	20mg	£13.99
80mg	£26.42	ZOCOR ®	
Atorvastatin		20mg	£29.69
10mg	£18.03	40mg	£29.69
20mg	£24.64	10mg	£18.03
40mg	£28.21	80mg	£29.69
80mg	£28.21	LIPOSTAT ®	
Pravastatin		40mg	£27.61
40mg	£4.57	20mg	£27.61
20mg	£2.94	10mg	£15.05
10mg	£2.49	SIMVADOR ®	
Rosuvastatin		40mg	£4.17
10mg	£18.03	20mg	£1.89
20mg	£29.69	10mg	£1.97
40mg	£29.69	Ezetimibe	
5mg	£18.03	10mg	£26.31
* Based on eMIMs July 2006			

APPENDIX 16: Prescribing data used in the MSD/SP submission

[redacted]



APPENDIX 17: Meta-Analyses percentage change in TC and HDL-c

Effectiveness data for ezetimibe + statin combination treatment used in MSD/SP cost effectiveness model

Effectiveness data for ezetimibe + statin combination treatment used in MSD/SP cost effectiveness model

Effectiveness data for ezetimibe monotherapy treatment used in MSD/SP cost effectiveness model

Effectiveness data for ezetimibe monotherapy treatment used in MSD/SP cost effectiveness model

APPENDIX 18: Summary of results from the MSD/SP Cook model

Table 77: Summary of MSD/SP cost effectiveness results from the Cook model

Population	Patient profile	Disc ICER (£,000)	MSD/SP report/ appendix
	M/F[a], age, Total-c	min (max)	M
Basecase (a): Ezetimibe plus current statin vs current statin titration			
Males with history of CVD	M, 50, 6.5	15.8	3.11 pg 45
	M, 80, 4.5	(31.3)	3.11 pg 45
Females with history of CVD	F, 60, 6.5	26.3	26.1 pg 226
	F, 80, 4.5	(45.2)	26.1 pg 226
Result used to evaluate the impact of univariate Sa	M, 70, 5.5	21.4	3.15 pg 49
Sa: baseline utility = 1 plus 10% on health state utility	M, 70, 5.5	14.	3.35 pg 49
Sa: discount costs and benefits at 6%	M, 70, 5.5	24.2	3.35 pg 49
Male diabetics with no history of CVD	M, 70, 6.5	11.3	3.12 pg 46
	M, 50, 4.5	(18.5)	3.12 pg 46
Female diabetics with no history of CVD	F, 70, 6.5	15.5	26.4 pg 228
	F, 50, 4.5	(26.9)	26.4 pg 228
Result used to evaluate the impact of univariate Sa	M, 70, 5.5	13.1	3.15 pg 49
Sa: baseline utility = 1 minus 1% on HS utility	M, 70, 5.5	9.3	3.15 pg 49
Sa: 5 year time frame	M, 70, 5.5	18.4	3.15 pg 49
Males with no history of CVD	M, 60, 6.5	11.9	3.13 pg 46
	M, 50, 4.5	(18.5)	3.13 pg 46
Females with no history of CVD	F, 50, 6.5	33.7	26.7 pg 229
	F, 80, 4.5	(121.9)	26.7 pg 229
Result used to evaluate the impact of univariate Sa	M, 70, 5.5	13.6	3.15 pg 49
Sa: baseline utility = 1 minus 1% on HS utility	M, 70, 5.5	9.4	3.15 pg 49
Sa: Brindle's correction	M, 70, 5.5	17.3	3.15 pg 49
South Asians males at high risk	M, 60, 6.5	8.8	3.14 pg 47
	M, 50, 4.5	(12.9)	3.14 pg 47
South Asians females at high risk	F, 50, 6.5	21.5	26.1 pg 231
	F, 80, 4.5	(81.2)	26.1 pg 231
Basecase result (provided for comparison only) S.a not reported for this population	M, 70, 5.5	1.	3.14 pg 47
Basecase (b): Ezetimibe plus current statin vs current statin without titration (range is presented for male and female combined for brevity)			
History of CVD	M, 50, 6.5	14.1	26.2 pg 227
	F, 80, 4.5	(41.3)	26.3 pg 227
Diabetes no history of CVD	M. 70, 6.5	1.1	26.5 pg 228
	F, 50, 4.5	(23.7)	26.6 pg 229
No history of CVD	M, 60, 6.5	1.6	26.8 pg 23
	F, 80, 4.5	(11.)	26.9 pg 23
South Asians at high risk	M, 60, 6.5	7.9	26.11 pg 231
	F, 80, 4.5	73.2	26.12 pg 232

Ezetimibe monotherapy vs no treatment (range is presented for male and female combined for brevity)			
History of CVD	M, 50, 6.5	17.4	3.17 pg 51
	F, 80, 4.5	(5.6)	26.13 pg 233
Diabetes no history of CVD	M, 70, 6.5	12.4	3.18 pg 52
	F, 50, 4.5	(28.)	26.14 pg 233
No history of CVD	M, 60, 6.5	13.2	3.19 pg 52
	F, 80, 4.5	(131.1)	26.15 pg 234
South Asians at high risk	M, 60, 6.5	9.9	3.2 pg 53
	F, 80, 4.5	(87.3)	26.16 pg 234
Alt scenario 1: ezetimibe plus low cost statin vs switch to more potent high cost statin (range is presented for male and female combined for brevity)			
History of CVD	M, 50, 6.5	2.5	26.17 pg 235
	F, 80, 4.5	(6.4)	26.2 pg 236
Diabetes no history of CVD	M, 70, 6.5	1.5	26.18 pg 235
	F, 50, 4.5	(3.7)	26.21 pg 237
No history of CVD	M, 80, 6.5	1.	26.19 pg 236
	F, 80, 4.5	(15.6)	26.22 pg 237
Alt scenario 2: titrate high cost statin vs switch to low cost statin plus ezetimibe (range is presented for male and female combined for brevity)			
History of CVD	M, 50, 6.5	2.4	26.23 pg 238
	F, 80, 4.5	(6.1)	26.26 pg 239
Diabetes no history of CVD	M, 80, 6.5	1.4	26.24 pg 238
	F, 50, 4.5	(3.6)	26.27 pg 24
No history of CVD	M, 80, 6.5	1.	26.25 pg 239
	F, 80, 4.5	(14.9)	26.28 pg 24

[a] M=male, F=female

APPENDIX 19: ScHARR's initial queries on the MSD/SP economic evaluation and the responses received

1) In the cost effectiveness section of the main report the alternative scenarios 1 and 2 are described (page 40) as follows:

For scenario 1 the current therapy is assumed to be:
50% on simva 20mg & 50% on simva 40mg

The addition of Ezetimibe to this therapy is then compared to switching to atorva of the same dose.

Hence the comparators modelled are:
Treat1: (50% simva 20mg & 50% simva 40mg) plus Ezetimibe 10mg
Treat2: (50% atorva 20mg & 50% atorva 40mg)

For scenario 2 the therapy is assumed to be:
50% on atorva 10mg & 50% on atorva 20mg

The analysis compares titrating atorva by one dose (i.e. from atorva 10mg to 20mg or from atorva 20mg to 40mg) with switching to equipotent simva (i.e. from atorva 10mg to simva 20mg or from atorva 20mg to simva 40mg) plus Ezetimibe 10mg

Hence the comparators modelled are:
Treat1: (50% atorva 20mg & 50% atorva 40mg)
Treat2: (50% simva 20mg & 50% simva 40mg) plus Ezetimibe 10mg

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 below provides the range of discounted ICERs with the corresponding table and page numbers from the MSD Appendices.

Table 1: Extract from results tables for Alternative scenarios 1 and 2

Table	Pg	Sex	CVD	range disc ICER for Alt 1
26.17	235	male	Sec	£2.5 (TC 6.5, Age 50) to £4.3 (TC 4.5, Age 80)
26.19	236	male	Prim	£1.0 (TC 6.5, Age 80) to £2.1 (TC 4.5, Age 50)
26.20	236	female	Sec	£3.9 (TC 6.5, Age 60) to £6.4 (TC 4.5, Age 80)
26.22	237	female	Prim	£4.1 (TC 6.5, Age 50) to £15.6 (TC 4.5, Age 80)
Table	Pg	Sex	CVD	range disc ICER for Alt 2
26.23	238	male	Sec	£2.4 (TC 6.5, Age 50) to £4.1 (TC 4.5, Age 80)
26.25	239	male	Prim	£1.0 (TC 6.5, Age 80) to £2.0 (TC 4.5, Age 50)
26.26	239	female	Sec	£3.8 (TC 6.5, Age 60) to £6.1 (TC 4.5, Age 80)
26.28	240	female	Prim	£3.9 (TC 6.5, Age 50) to £14.9 (TC 4.5, Age 80)

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; tables 26.19 & 26.25; tables 26.20 & 26.26; tables 26.22 & 26.28 (table 26.17 and 26.23 from the appendix are copied below), are the same for the two scenarios since, these alternative scenarios have similar efficacy. However, the incremental costs are slightly different (undiscounted £10 to £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 scenario's and not in the other i.e. in alternative scenario 1 the average cost of statin titration used was £0.94, while, in alternative scenario 2 the average cost of titration used was £0.9438. We realized this lack of rounding in one of the scenarios towards the end of the submission process. In Table 1 on page 11 of the user guide we did provide cost of Statin Dose 2 = 0.94 (for Alternate Scenario 1) and Statin Dose 2 = 0.9438 (for Alternate Scenario 2) so that one could replicate the results. The use of rounding in alternative scenario 1 does not have a substantial impact of the overall ICERs and is slightly conservative in that it increases the incremental daily cost of ezetimibe arm.

Response Table 1: *Copy of Appendix Table 26.17 (Ezetimibe co-administration with simvastatin vs. switch to atorvastatin in 1,000 men with history of CVD who are not appropriately controlled with statin alone)*

		Undiscounted			*Discounted*		
Total Cholesterol	*Age*	*Incremental Cost*	*Incremental QALY*	*Incremental cost/QALY*	*Incremental Cost*	*Incremental QALY*	*Incremental cost/QALY*
4.5	*50*	*£1,072)*	*417*	*£2.6*	*£605*	*191*	*£3.2*
mmol/L	*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*	*£1,077*	*469*	*£2.3*	*£606*	*220*	*£2.8*
mmol/L	*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*	*£1,078*	*508*	*£2.1*	*£607*	*243*	*£2.5*
mmol/L	*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 1,000 men with history of CVD who are not appropriately controlled with atorvastatin alone)*

		Undiscounted			*Discounted*		
Total Cholesterol	*Age*	*Incremental Cost*	*Incremental QALY*	*Incremental cost/QALY*	*Incremental Cost*	*Incremental QALY*	*Incremental cost/QALY*
4.5	*50*	*£1,037*	*417*	*£2.5*	*£582*	*191*	*£3.0*
mmol/L	*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*	*£1,044*	*469*	*£2.2*	*£585*	*220*	*£2.7*
mmol/L	*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*	*£1,047*	*508*	*£2.1*	*£586*	*243*	*£2.4*
mmol/L	*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*

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 due 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, page 44 main MSD report) lists ICERs as high as £122k, £110k and £131k per QALY for females. Conversely, the highest equivalents for the males are £31k, £29k and £36k per QALY.

The model used in the industry submission was previously used to evaluate the cost effectiveness of Ezetimibe in Canada (Kohli, 2006) and 3 European countries (Cook, 2004). Looking at Table VI in the study by Kohli *et al.* the ICERs for males and females are very similar for diabetics (male diabetic: $Can 25k to 27k and female diabetic $Can 25k to 24k) and secondary CVD analyses (male approx $Can 21k; female approx $Can 25k). For male primary CVD analyses the ICERs reported range from $Can 19k to 20k. 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 page 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 *et al.* 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 male and female 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 ICER's for male and female diabetic as well as CVD patients in the Kohli et al are similar because the risk predicted by the model in that analysis were recalibrated as stated in the manuscript. In addition on page 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 3 times those for men (94,732 vs 30,055 at a baseline LDL-C level of 4.14 mmol/L). In our submission for ezetimibe co-administration vs statin titration the increase in ICER's for females compared to male CVD patients are 40% to 100% greater and for female diabetic patients compared to male the ICERs are 30% to 45% greater. For female patients with a 10 year risk of 20% or greater the increase in ICERs range from 3.4 to 6.7 times compared to male patients.

To confirm that the gender differences in the ICER is 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 as well as total CHD for male patients is greater compared to female patients – the largest differences 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 vs statin titration is greater for male patients compared to female patients as represented by the greater delta for male patients compared to females – again, the largest differences between men and women in risk reduction are seen in the non CVD, non diabetic patients (i.e., 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 to 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	*Baseline risk*		*Statin Titration*		*Delta (Difference between ezetimibe co-administration and statin titration)*	
Fatal CHD Event Rate						
	Males	*Females*	*Males*	*Females*	*Males*	*Females*
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 **nonCVD Diabetic group** (cholesterol level 5.5 mmol)*

Age	*Baseline risk*		*Statin Titration*		*Deltas (Difference between ezetimibe co-administration and statin titration)*	
Fatal CHD Event Rate						
	Males	*Females*	*Males*	*Females*	*Males*	*Females*
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 nonfatal CHD Event Rates for **nonCVD nonDiabetic group with 20% or greater 20 year risk of developing CVD** (cholesterol level 5.5 mmol)*

Age	*Baseline risk*		*Statin Titration*		*Deltas (Difference between ezetimibe co-administration and statin titration)*	
Fatal CHD Event Rate						
	Males	*Females*	*Males*	*Females*	*Males*	*Females*
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*

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 stroke. 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 traces 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.

4) Some of the CEAC plots (eg Fig 3.4 page 47; Fig 3.4 page 48 and Fig 3.5 page 49 and Fig 3.8 page 55 (please note there are 2 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 scale on the x-axes are different for the different plots.

Fig 1.1. Ezetimibe co-administration with Statin vs Statin titration in females with Clinical Evidence of CVD – Probability of Cost effective by Threshold

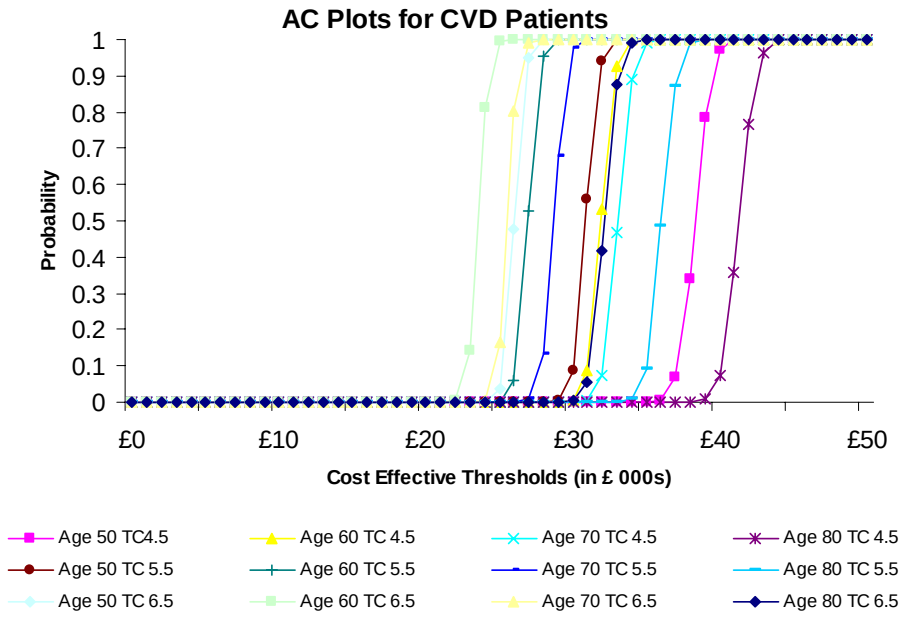


Fig 1.2. ***Ezetimibe co-administration with Statin vs Statin titration in females with diabetes but no CVD – Probability of Cost effective by Threshold***

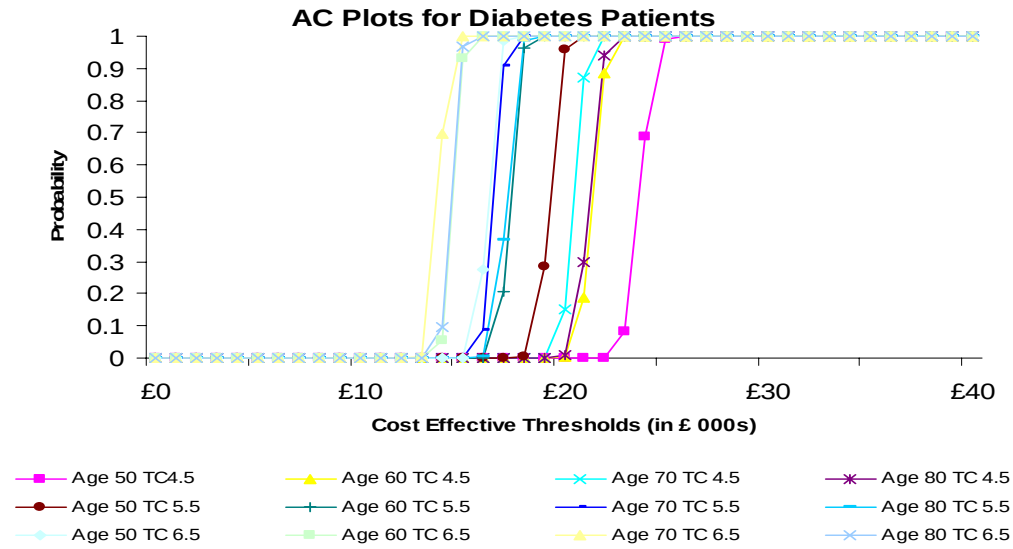


Fig 1.3 Ezetimibe co-administration with Statin vs Statin titration in females who have a 20% or Greater 10-year Risk of Developing CVD – Probability of Cost effective by Threshold

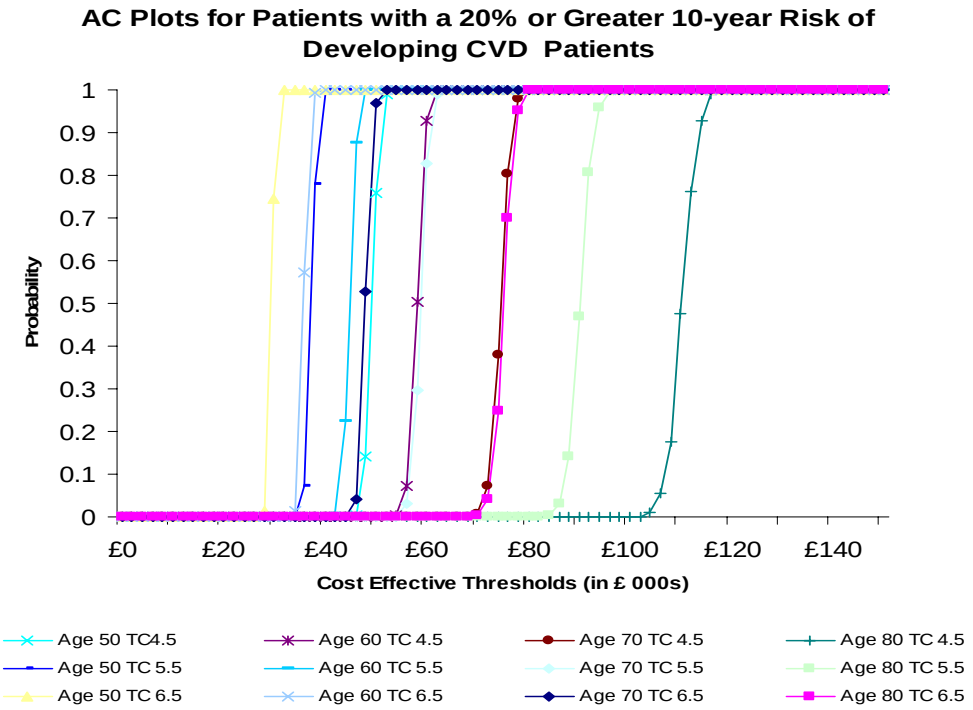


Fig 1.4 Ezetimibe Monotherapy in females with Clinical Evidence of CVD – Probability of Cost effective by Threshold

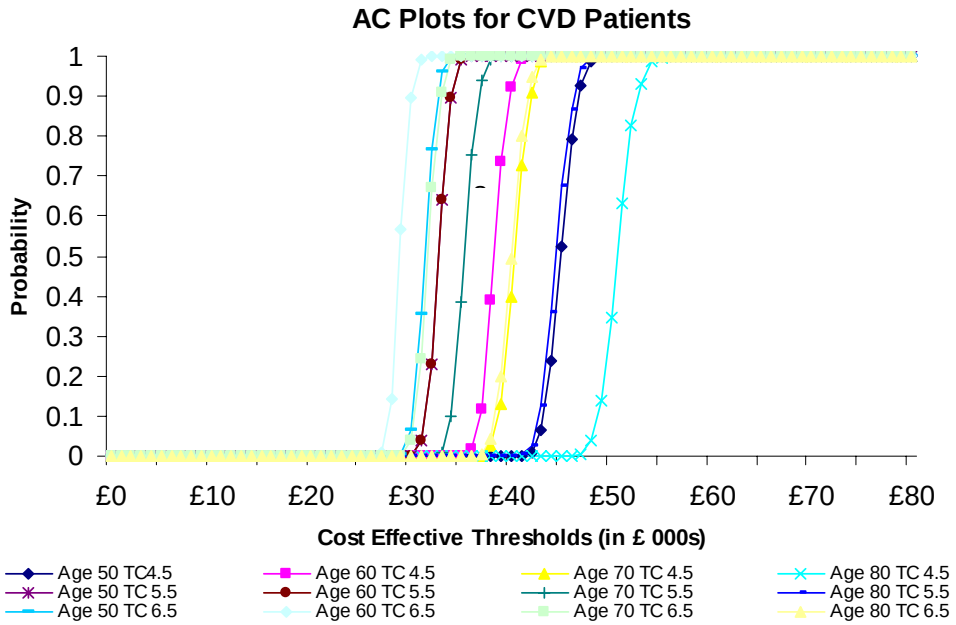


Fig 1.5 Ezetimibe Monotherapy in females with diabetes but no CVD – Probability of Cost effective by Threshold

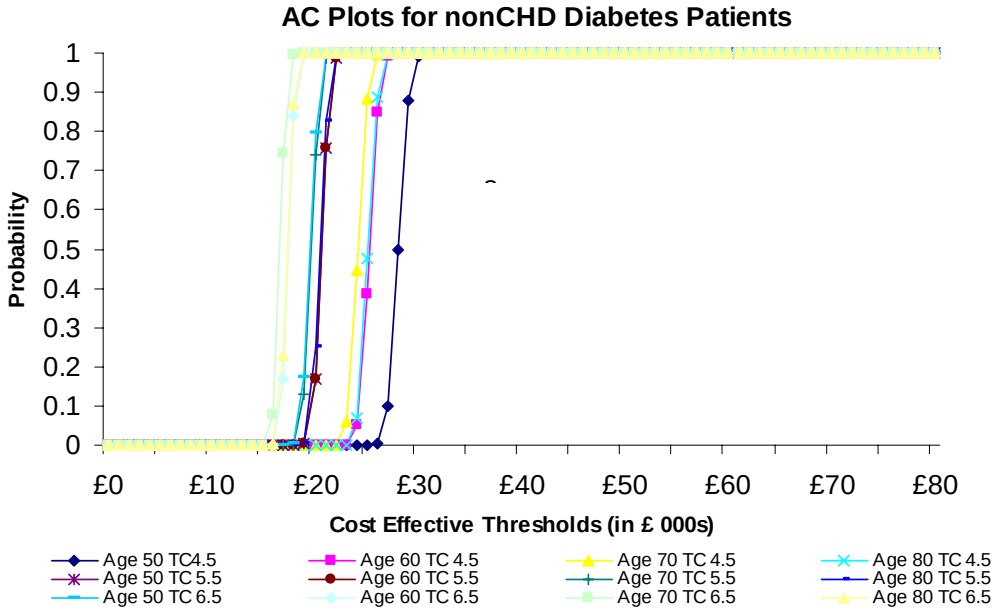
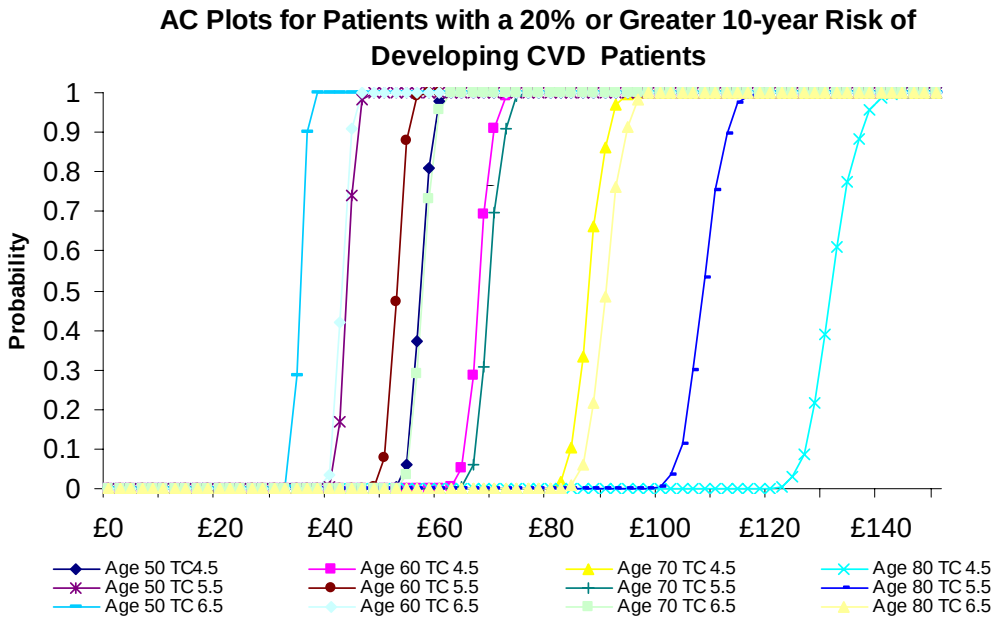


Fig 1.6 Ezetimibe Monotherapy in females who have a 20% or Greater 10-year Risk of Developing CVD – Probability of Cost effective by Threshold



Appendix 20: 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:

a) 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
b) the authors of a review on methods for predicting future events in economic models concluded the algorithms from the Framingham study was the most appropriate methodology

It is acknowledged that the US NCEP ATP III[250] recommend 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 Grieves *et al*.[90] presents a systematic and robust process for choosing a method of predicting events in economic models concentrating on the cardiovascular 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 cardiovascular events.[79] This evidence was utilised in the alternative Basic model presented by MSD/SP demonstrating that the MSD/SP analysts consider the methodology is 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" (page 43, main report).

Reported, predicted and modelled CHD risks

The MSD/SP analysts used the patient profiles in the primary CVD analyses to generate 1 year risks using the Anderson primary CHD algorithms (results tables 3.13 and 26.7 of the MSD/SP report). As the d'Agostino algorithms are used to predict annual risks in the model, it is unclear why the Anderson risks were reported here. Presumably they were used to

demonstrate that the 1 year baseline CVD risk modelled was greater than 2% as is recommended for lipid lowering treatment.[39] The analysts have assumed that a 15% 1 year risk is equivalent to a 2% 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],[251] More importantly, the 1 year Anderson risks are not consistent with either the values calculated using the MSD/SP programming code for the d'Agostino algorithms or the actual risks modelled.

The reviewers used the MSD/SP code which represents the d'Agostino algorithms and the patient profiles to generate baseline risks (columns 6:7, Table 78) for the no treatment arm. The model was then run for each individual patient profile. The number of primary angina, CHD death and MI events in the first year were summed from the corresponding Markov traces to derive the 1st year annual risk modelled (columns 8:9, Table 78) for individuals with no treatment.

As can be seen in Table 78, the risks derived from the Markov traces (columns 8:9) are consistently higher than those predicted using the d'Agostino code (columns 6:7). It is not clear why these risks are different as the risk predicted using the code should equal the modelled risk. It is thought the inconsistency may be caused by the method used to distribute risk across events. While the differences are small in the first year the errors presumably occur annually each time the risk is recalculated. As a consequence, the cumulative number of events avoided and thus the benefits from treatment are overestimated.

The majority of the reported Anderson CHD risks (columns 2:3) increase with age as would be expected. With the exception of the individuals aged 80 years, the male predicted (column 2) and modelled (column 8) risks are comparable with the annual rate estimated from the 1 year Anderson risks (column 4). For the males aged 80 years, the modelled annual risks are much higher than the corresponding Anderson 1st year rates.

For females, the one year CHD risks derived from the Anderson algorithm (column 3) show a trend which illustrates a gradual increase in CHD risk. This is not seen in the first year risks calculated using the MSD/SP code (column 7) or the estimates from the Markov traces (column 9). The MSD/SP code used to calculate the female primary CHD risks is clearly incorrect.

Table 78: Comparison of reported, predicted and modelled first year CHD risk used in the MSD/SP economic evaluation

	Reported[a] 1 year risk		Annual rate[b] (estimated)		First year risk[c] (d'Agostino)		First year risk[d] (modelled)	
Age	M	F	M	F	M	F	M	F
Total-c=4.5 mmol/L (HDL=1. mmol/L, SBP[e]=16 mgHg; Alcohol=5.67 fl.oz)								
50	15.8%	11.2%	1.71%	1.18%	1.39%	.78%	1.44%	.81%
60	23.%	15.5%	2.58%	1.67%	2.33%	.69%	2.4%	.71%
70	3.1%	17.4%	3.52%	1.89%	3.89%	.61%	4.%	.63%
80	36.7%	17.2%	4.47%	1.87%	6.47%	.53%	6.68%	.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%	1.77%	1.%	1.82%	1.3%
60	27.4%	19.2%	3.15%	2.11%	2.97%	.88%	3.5%	.9%
70	34.9%	21.2%	4.2%	2.35%	4.95%	.77%	5.1%	.79%
80	41.6%	21.1%	5.24%	2.34%	8.19%	.68%	8.4%	.7%
Total-c=6.5 mmol/L (HDL=1. mmol/L, SBP=16 mgHg; Alcohol=5.67 fl.oz)								
50	22.9%	17.%	2.57%	1.85%	2.17%	1.22%	2.22%	1.25%
60	31.3%	22.5%	3.68%	2.52%	3.63%	1.8%	3.71%	1.1%
70	38.9%	24.7%	4.81%	2.8%	6.3%	.95%	6.17%	.97%
80	45.7%	24.6%	5.92%	2.78%	9.95%	.83%	1.2%	.85%

[a]1 year CHD risks reported in Table 3.13 (pg 46) and Table 26.7 (pg 229) which are calculated using Anderson *et al.* [b]annual CHD rate estimated using formula: annual rate = 1–(1-p(10 yr))^(1/10); [c]annual CHD risk predicted using the visual basic programming code in the MSD/SP excel model; [d]actual annual CHD risk modelled in each MSD/SP analysis using the 1st year primary non fatal Angina and MI and fatal CHD events in the no treatment Markov traces; [e]SBP=systolic blood pressure

Distribution of predicted risk across event type

The d'Agostino algorithms predict a risk for CHD events which consists of MI and CHD death plus angina pectoris and coronary insufficiency.[87] The MSD/SP analysts use the Anderson equation for an MI event and the equation for death from CHD to apportion the predicted risk across the primary event types. The difference between these summed probabilities and the overall d'Agostino CHD risk is then used to apportion the number of events that are unstable angina. The secondary d'Agostino risk is apportioned using a

combination of the above methodology and the distribution of secondary events observed in the Framingham cohort (Table II d'Agostino[87]).

This methodology is flawed (see initial queries and responses above) as the summed probabilities from the individual Anderson equations are frequently larger than the predicted overall CHD risk. The MSD/SP analysts employ a mechanism in the program code in an attempt to address these inconsistencies. However, when applying this section of the code, individuals receiving statin monotherapy have more angina events than those not receiving any treatment while those receiving ezetimibe plus statin treatment have more angina events than either of the other treatment regimens. In reality this means that while the treatment regimens may reduce the risk of MIs and fatal CHD events, they increase the number of cases of angina. This is not what is reported in lipid lowering studies. The methodology biases the results in favour of ezetimibe as the cost offsets and benefits from reducing the number of MIs and fatal events is larger than those accrued from reducing the incidence and prevalence of angina.

Data used to populate the MSD/SP models

The MSD/SP analysts relied heavily on the NICE statin HTA report[39] to populate the model with UK specific data. 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. The health state costs used in the Statin HTA appraisal[39] were inflated using an incorrect unreferenced inflation rate. If the correct method had been used these costs would have been higher and the cost offsets due to events avoided greater.[154] The monitoring costs taken from the Statin HTA appraisal were not updated and an error has since been found in the cost allocated for the blood and liver tests. If the monitoring costs had been updated from source this mistake would have been noticed. The monitoring costs also appear to have been applied incorrectly with "start-up" costs for initiation of treatment applied to patients who enter the model on ongoing treatment. The monitoring costs applied in the MSD/SP evaluation are too high.

Drugs tariffs which report rates applicable to hospitals were used for the majority of treatment costs. As the target population are predominantly based in general clinical practice, the correct treatment costs are those reported in the BNF.[186] The impact of using the lower drug tariff prices is that treatment costs are underestimated in all the evaluations.

Appendix 21: 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 below (Table 79). Individual sources identified within these key categories are listed in Table 79.

Table 79 Key sources of evidence used to inform model

Review of clinical effectiveness	Assessment of clinical effectiveness of ezetimibe presented in earlier section of current report
Economic analysis previously undertaken by authors	Assessment of statin treatment undertaken to inform NICE statin guidance[135]
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 1
Ad hoc searches	
Evidence known to authors	
Expert opinion	
Reference sources (e.g. BNF)	

Individual sources of evidence

The individual sources which make up the key categories of evidence a listed below with details of how each source was identified and how each source was used in the model.

Table 80 Individual sources of evidence used to inform model development

Source	Use(s) in the model	Process of identification (originating key source)
Anderson, 1991[77]	Informing the approach to modelling surrogate to clinical endpoints Support assumptions relating to HeFH population Support assumptions relating to baseline CVD risk	Searches undertaken to inform model development
Atherosclerosis, 1999	Support assumptions relating to HeFH population	Ad hoc searches
Baigent, 2005[79]	Informing the approach to modelling surrogate to clinical endpoints Translate changes in LDL-c (surrogate endpoint) to reductions in CVD events (clinical endpoint)	Searches undertaken to inform model development

	Support assumption relating to no impact of treatment on fatal stroke	
Bamford et al., 1988[180]	Support assumptions relating to baseline CVD risk distribution	Economic analysis previously undertaken by authors[135]
BARI, 1991[192]	Provide stable angina HRQoL utility estimate	Economic analysis previously undertaken by authors[135]
Bates, 1989[170]	Support modelling search methods	Evidence known to authors
Betteridge *et al.,* 2003[42]	Inform choice of treatment comparators	Searches undertaken for review of clinical-effectiveness
BNF, 2006[38]	Provide medication cost estimates	Reference source
Bradley et al., 2000[194]	Inform MI HRQoL utility estimate	Economic analysis previously undertaken by authors[135]
Brindle *et al.* 2003[93]	Informing the approach to modelling surrogate to clinical endpoints	Searches undertaken to inform model development
Brindle *et al.* 2005[98]	Informing the approach to modelling surrogate to clinical endpoints	Searches undertaken to inform model development
Brindle *et al.* 2006[92]	Informing the approach to modelling surrogate to clinical endpoints	Searches undertaken to inform model development
Chen, 1991[81]	Informing the approach to modelling surrogate to clinical endpoints	??

Clarke, 2003[156]	Provide fatal MI cost estimate	Economic analysis previously undertaken by authors[135]
Colhoun, 2004[103]	Informing the approach to modelling surrogate to clinical endpoints	Searches undertaken to inform model development
Cooper *et al.*, 2005[88]	Informing the approach to modelling surrogate to clinical endpoints	Searches undertaken to inform model development
Curtis, 2005[187]	Provide GP contact cost estimates Provide Practice Nurse cost estimates	Reference source
Curtis, 2006[155]	Adjust cost estimates to 2006	Reference source
D'Agostino *et al.*, 2000[87]	Informing the approach to modelling surrogate to clinical endpoints Support assumptions relating to baseline CVD risk	Economic analysis previously undertaken by authors[135]
De Sauvage Nolting, 2003[256]	Support assumptions relating to HeFH population	Searches undertaken to inform model development
Dennis et al, 1993[179]	Support assumptions relating to baseline CVD risk distribution	Economic analysis previously undertaken by authors[135]

Empana *et al.* 2003[94]	Informing the approach to modelling surrogate to clinical endpoints	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	Advisers to current analysis
German, 2006[257]	Informing the approach to modelling surrogate to clinical endpoints	Undertaken as part of current analysis
Glick, 1995[258]	Informing the approach to modelling surrogate to clinical endpoints	Economic analysis previously undertaken by authors[135]
Goodacre et al., 2004[193]	Provide unstable angina HRQoL utility estimate Provide MI HRQoL utility estimate	Economic analysis previously undertaken by authors[135]
Gould,1998[84]	Informing the approach to modelling surrogate to clinical endpoints	Searches undertaken to inform model development
Government Actuary Life Tables	Inform assumptions relating to non-vascular mortality	Reference source

Grieve *et al.*, 2003[90]	Informing the approach to modelling surrogate to clinical endpoints	Searches undertaken to inform model development
Grundy, 2004[82]	Informing the approach to modelling surrogate to clinical endpoints	Searches undertaken to inform model development
Health Survey for England 2003[182]	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 endpoints	Searches undertaken to inform model development
Jurgensen, 2006	Informing the approach to modelling surrogate to clinical endpoints	??
Kind and Dolan, 1998[195]	Provide TIA HRQoL utility estimate Inform HRQoL utility by age	Reference source
Kirby, 2006[46]	Inform choice of treatment comparators	Searches undertaken for review of cost effectiveness
Kirby, 2006[46]	Inform assumptions relating to compliance	Searches undertaken to inform model development
Knopp, 1999[68]	Inform choice of treatment comparators Provide evidence of clinical effectiveness of statin titration.	Searches undertaken for review of clinical-effectiveness

Law, 2003[83]	Informing the approach to modelling surrogate to clinical endpoints	Searches undertaken to inform model development
Law, 2006[105]	Informing the approach to modelling surrogate to clinical endpoints	Searches undertaken to inform model development
LRCCPPT, 1984[171]	Inform choice of treatment comparators	Searches undertaken to inform model development
Marks *et al.* 2003	Support assumptions relating to HeFH population	Ad hoc searches
Meslop, 2003[191]	Provide stable angina HRQoL utility estimate	Economic analysis previously undertaken by authors[135]
Morris, 1997[259]	Support Markov modelling approach	Searches undertaken to inform model development
Mueck, 2002[174]	Support Markov modelling approach	Evidence known to authors
Neaton *et al.* 1992[78]	Informing the approach to modelling surrogate to clinical endpoints	Economic analysis previously undertaken by authors[135]
NHS Reference Costs, 2005[190]	Provide monitoring test cost estimates	Reference source
NICE Guide to methods of technology appraisal[175]	Support model perspective Support assumptions relating to baseline CVD risk distribution	Reference source

NICE statin assessment, in press (Ward et al. *in press*[135]	Support assumption relating to event rates for diabetes population. Support assumption in modelling link between surrogate and clinical endpoints. Support assumption relating to no impact of treatment on fatal stroke 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[135]
NICE statin guidance[260]	Inform choice of treatment comparators Inform treatment regimen scenarios	Evidence known to authors

Palmer, 2002[188]	Provide non-fatal MI cost estimate	Economic analysis previously undertaken by authors[135]
Pearson, 2000[169]	Inform choice of treatment comparators	Review of clinical effectiveness
Pedersen et al., 2004[183]	Support assumption relating to no benefits from treatment in first year	Searches undertaken to inform model development
Prescription Cost Analysis 2005, 2006[44]	Inform choice of treatment comparators Inform treatment regimen scenarios Provide estimated weighted cost of statin treatment	Reference source
Prescription rates (Wales), 2005[45]	Inform treatment regimen scenarios	Reference source
Refs from statin report	Informing the approach to modelling surrogate to clinical endpoints	Economic analysis previously undertaken by authors[135]
Review of clinical effectiveness	Support assumptions relating to baseline LDL-c levels Provide clinical effectiveness evidence to populate model	Undertaken as part of current analysis

	Provide references to sources of background evidence.	
Robinson *et al.*, 2005[85]	Informing the approach to modelling surrogate to clinical endpoints	Ad hoc searches
Rothwell *et al.*, 2004[181]	Support assumptions relating to baseline CVD risk distribution	Economic analysis previously undertaken by authors[135]
Sacks *et al.*, 1996[184]	Support assumption relating to no benefits from treatment in first year	Economic analysis previously undertaken by authors[135]
Schwartz *et al.*, 2001[185]	Support assumption relating to no benefits from treatment in first year	Economic analysis previously undertaken by authors[135]
Sever, 2003[261]	Informing the approach to modelling surrogate to clinical endpoints	Searches undertaken to inform model development
Simon Broome Register, 1991[166]	Support assumptions relating to HeFH population	Expert advice
Sonnenberg, 1993[173]	Support Markov modelling approach	Evidence known to authors
Stamler, 1993[80]	Informing the approach to modelling surrogate to clinical endpoints	Searches undertaken to inform model

		development
Stein *et al.*[117]	Support assumptions relating to HeFH population	Review of clinical effectiveness
Stevens *et al.* 2001[86]	Informing the approach to modelling surrogate to clinical endpoints	Searches undertaken to inform model development
Sutcliffe *et al.*, 2003[178]	Support assumptions relating to baseline CVD risk distribution	Economic analysis previously undertaken by authors[135]
Tengs, 2003[197]	Inform stroke HRQoL utility estimate	Economic analysis previously undertaken by authors[135]
Thomsen *et al.* 2002[96]	Informing the approach to modelling surrogate to clinical endpoints	Searches undertaken to inform model development
Van Exel, 2004[196]	Inform stroke HRQoL utility estimate	Economic analysis previously undertaken by authors[135]
WOSCOPS	Informing the approach to modelling surrogate to clinical endpoints	Economic analysis previously undertaken by authors[135]
www.bris.ac.uk[262]	Informing the approach to modelling surrogate to clinical endpoints	Searches undertaken to inform model development
Youman *et al.*,	Provide stroke cost estimates	Economic analysis previously undertaken by

2003[189]	Inform stroke HRQoL utility estimate	authors[135]

Searches undertaken to inform 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)
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 / cardiovascular events
Purpose	To explore the evidence on the link between cholesterol and clinical events
Sources searched	Medline
Type of search	Berrypicking search (keyword combinations)
Results	281 refs 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)
Results	28 refs selected from search 9 full papers consulted

Chaining search

Starting ref:

Baignet 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(9493):1267-1278.

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)
Results	55 refs selected from search 25 full papers consulted

Chaining search

Starting ref

Brindle P. What are your chances of having a heart attack? *University of Bristol Research News*. 19 March 2004. [http://www.bris.ac.uk/researchreview/2004/1113903134 – accessed 7 November 2006]

Medline search

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 timelag'	
Scope	Methods papers on modelling the timelag between biomarker and event
Purpose	To explore methods for modelling surrogate outcomes where there is a timelag between the surrogate and the event
Sources searched	Medline
Type of search	Berrypicking search (keyword combinations)
Results	26 refs 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)
Results	94 refs 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)
Results	73 refs selected from search 23 full papers consulted

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)

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)

Indirect comparators – resins	
Scope	Trials of 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)
Results	67 refs selected from search 14 full papers consulted

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	Triglycerides as a predictor of coronary or cardiovascular 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)
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)

Appendix 22: Identification of studies for the review of cost effectiveness

This appendix contains information on the sources searched and keyword strategies for the systematic review of cost effectiveness.

Table 81 Electronic databases searched for the review of cost effectiveness

CINAHL
COCHRANE LIBARY
DARE-NHSEED-HTA
EMBASE
MEDLINE
OHE HEED
WOS

Sources consulted via the WWW

See table 51, appendix 1.

Database keyword strategies

CINAHL

1982-2006

OVID Online

Search undertaken July 2006-12-06

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)

COCHRANE LIBRARY (CDSR, CENTRAL, DARE, HTA)

Issue 2, 2006

Wiley version

Search undertaken between April to 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 (approx. 1994-2006)

CRD website version

Search undertaken between April to June 2006

((ezetimibe OR ezetrol OR zetia OR vytorin OR inegy) AND (hypercholesterolemia OR hypercholesterolaemia))

EMBASE

To be added

MEDLINE

To be added

OHE HEED

To be added

WOS

1900-2006

Web of Knowledge version

Search undertaken between April to June 2006

4	TS=(hypercholesterolemia OR hypercholesterolaeima) DocType=All document types; Language=All languages; Databases=SCI-EXPANDED, SSCI; Timespan=1900-2006
5	TS=(ezetimibe OR ezetrol OR zetia OR vytorin OR inegy) DocType=All document types; Language=All languages; Databases=SCI-EXPANDED, SSCI; Timespan=1900-2006
6	#1 AND #2 DocType=All document types; Language=All languages; Databases=SCI-EXPANDED, SSCI; Timespan=1900-2006

Appendix 23: Full list of the possible transitions used in the ScHARR model

Table 82: Possible transitions in SCHARR model

Event free to Primary Angina
Event free to Primary UA
Event free to Primary MI
Event free to Primary TIA
Event free to Primary Stroke
Event free to Fatal CHD event
Event free to Fatal CVD event
Event free to Death other causes
P_SA to S_(UA or 1st MI or 1st Str or FCHD or FCVD or DOC) else post SA
P_UA to S_(1st MI or 1st Str or FCHD or FCVD or DOC) else post UA
P_MI to S_(1st MI or 1st Str or FCHD or FCVD or DOC) else post MI
P_TIA to S_(1st MI or 1st Str or FCHD or FCVD or DOC) else post TIA
P_Str to S_(1st Str or FCHD or FCVD or DOC) else post Str
post P_SA to S_(UA or 1st MI or 1st Str or FCHD or FCVD or DOC) else post SA
post P_UA to S_(1st MI or 1st Str or FCHD or FCVD or DOC) else post UA
post P_MI to S_(1st MI or 1st Str or FCHD or FCVD or DOC) else post MI
post P_TIA to S_(1st MI or 1st Str or FCHD or FCVD or DOC) else post TIA
post P_St to S_(1st Str or FCHD or FCVD or DOC) else post Str
S_SA to S(UA or 2nd MI or 2nd Str or FCHD or FCVD or DOC) else post SA
S_UA to S(2nd MI or 2nd Str or FCHD or FCVD or DOC) else post UA
S_MI to S(2nd MI or 2nd Str or FCHD or FCVD or DOC) else post MI
S_TIA to S(2nd MI or 2nd Str or FCHD or FCVD or DOC) else post TIA
S_Str to S(2nd Str or FCHD or FCVD or DOC) else post Str
post S_SA to S_(UA or 2nd MI or 2nd Str or FCHD or FCVD or DOC) else post SA
post S_UA to S_(2nd MI or 2nd Str or FCHD or FCVD or DOC) else post UA
post S_MI to S_(2nd MI or 2nd Str or FCHD or FCVD or DOC) else post MI
post S_TIA to S_(2nd MI or 2nd Str or FCHD or FCVD or DOC) else post TIA
post S_St to S_(2nd Str or FCHD or FCVD or DOC) else post Str

DOC = Death other causes

Appendix 24: List of variables with probabilistic distributions used in the ScHARR model

Table 83: Probability distributions for parameters used in the ScHARR probabilistic sensitivity analyses

Variable	Distribution	mean	LCI	UCI
Baseline LDL-c (mmol/L)	Triangular	4	-10%	10%
Treatment effectiveness				
Ezetimibe monotherapy (versus placebo)	Normal	18.56	17.44	19.68
Ezetimibe plus statin (versus statin monotherapy)	Normal	22.16	21.13	23.19
RR corresponding to reduction in LDL-c of 1 mml				
Stable Angina	ExpNorminv	0.74	0.7	0.79
Unstable Angina	ExpNorminv	0.74	0.7	0.79
Non fatal MI	ExpNorminv	0.74	0.7	0.79
Fatal CHD	ExpNorminv	0.81	0.76	0.85
TIA	ExpNorminv	0.83	0.78	0.88
Stroke	ExpNorminv	0.83	0.78	0.88
Health related quality of life utilities				
Utility by age	MultiNormal	1.060	0.00084	0.00000
	MultiNormal	-0.004	-0.00001	0.00000
Stable Angina		0.808	assume correlated with UA	
Unstable Angina	Normal	0.77	0.04	
MI		0.76	assume correlated with UA	
Stroke	Normal	0.629	0.04	
Health state costs				
Stable Angina	Triangle	£201	£180.9	£221.1
Unstable Angina (1st yr)		£477	assume correlated with MI	
MI (1st year)	Normal	£4,867	£401.24	
Fatal CHD	Triangle	£1,242	£1,117.80	£1,366.20
TIA (1st year)	Normal	£1,110	£250.00	
Stroke (1st yr)	Triangle	£8,070	£7,263.00	£8,877.00
Stroke (2nd+ year)	Triangle	£2,169	£1,952.10	£2,385.90
Fatal CVD	Triangle	£7,407	£6,666.30	£8,147.70
Prevalence for health states	Beta	various		
Incidence distributions	Beta	various		
Annual CVD risks	Triangle	various	-10%	10%

Appendix 25: Regressions used to model the natural increase by age in the ScHARR model

Natural increase in risk by age

	male	female
Beta0	-0.0459	-0.0163
Beta1	0.0001	-0.0014
Beta2	0.0001	0.000075

Appendix 26: Diabetes data used in the ScHARR cost effectiveness model

Table 84: Health state utilities used in the diabetic analysis of the ScHARR cost effectiveness model

	basecase	diabetic
Stable Angina	0.808	0.724[a]
Unstable Angina	0.770	0.690[a]
1st year MI	0.760	0.681
Post MI	0.760	0.681
TIA	1.000	1.000
1st Stroke yr1	0.629	0.526
Post 1st Stroke	0.629	0.526

[a]adjusted using 1st year diabetic MI utility and basecase utilities for stable and unstable angina respectively

Table 85: Health state costs used in the diabetic analysis of the ScHARR cost effectiveness model[156]

	basecase	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
On-going costs MI	£201	£492
Fatal MI	£1,242	£1,662
TIA	£1,110	£1,612 [b]
Post TIA (on going costs)	£276	£401 [b]
1st year costs Stroke	£8,070	£11,722 [b]
On-going costs Stroke	£2,169	£3,151
Fatal Stroke	£7,407	£10,759 [b]

[a] assumed equal to on-going costs for MI
[b] costs adjusted using ongoing costs for stroke and basecase costs

Appendix 27: List of the key modelling assumptions used in the ScHARR model

Table 86: 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 & clinical advise
Population	Assume primary event rates for diabetic is two times norm by age	Clinical opinion
Population	Assume primary event rates 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 is derived from cohorts who had a wash-out prior to baseline of studies) is representative for the target population i.e. patients not at goal on statin treatment Perform sensitivity analyses using the results of the meta-analysis of 6 week RCT data derived from individuals who did not have a wash-out prior to baseline of studies	
Effectiveness data	Assume observed short term lipid changes will be maintained over a long time periods Perform sensitivity analyses where treatment effects are truncated at shorter time periods	
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	Statin titration of 1 dose provides an additional 6% reduction in LDL-c irrespective of statin	Published data[122]
Relationship LDL-c and CVD events	Assume the results of the meta-analysis which provides a relationship between reductions in LDL-c and relative risks of events (derived from statin RCT data) is generalisable to ezetimibe monotherapy and ezetimibe co-administered with a statin	
	Assume the relative risk (RR) for angina = RR for non-fatal MI Assume the RR for TIA = RR for non-fatal stroke	
	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 stroke/fatal stroke = 1	
Time horizon	Use a 20 year time horizon in basecase Perform sensitivity analyses using shorter and lifetime horizons Examine the impact of truncating treatment effects at shorter times but accruing costs and benefits over 20 years	
CVD definition	CVD event is defined as stable angina, unstable angina, non-fatal MI, CHD death, TIA, non-fatal stroke, death from TIA/CVD related causes This is based on evidence available for CVD health states	
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	
Events	Assume cannot move from a more severe health state to a less	

	severe health state	
Prevalence	Assume data for angina in the HSE is for stable angina only	HSE[255]
	Assume no individuals commence in post unstable angina	
	Assume TIA prevalence is 25% that of stroke	
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 basecase Sensitivity analyses performed using constant utility of 1 across all ages	
	Assume no disutility for TIA	
	Assume no disutility associated with treatments modelled	
Compliance	Assume full compliance to treatment	

Appendix 28: Additional results tables for the ScHARR economic evaluation

Table 87: Scenario 1, discounted 20 year incremental costs (£,000) when varying the baseline LDL-c value

	Primary prevention			Secondary prevention		
	baseline LDL-c (mmol/L)					
Age	3.0	3.5	4.0	3.0	3.5	4.0
Male						
45	£3,594	£3,567	£3,541	£3,442	£3,410	£3,376
55	£3,409	£3,382	£3,355	£3,184	£3,153	£3,121
65	£3,055	£3,029	£3,004	£2,840	£2,815	£2,790
75	£2,476	£2,459	£2,442	£2,313	£2,296	£2,280
Female						
45	£3,591	£3,576	£3,560	£3,384	£3,368	£3,352
55	£3,389	£3,373	£3,358	£3,233	£3,220	£3,207
65	£3,038	£3,022	£3,007	£2,832	£2,819	£2,806
75	£2,460	£2,448	£2,436	£2,207	£2,196	£2,185

Table 88: Scenario 1, discounted 20 year incremental QALYs when varying the baseline LDL-c value

	Primary prevention			Secondary prevention		
	baseline LDL-c (mmol/L)					
Age	3.0	3.5	4.0	3.0	3.5	4.0
Male						
45	33.9	39.6	45.4	20.8	24.4	28.0
55	35.2	41.1	47.1	20.9	24.5	28.1
65	33.4	39.0	44.7	16.5	19.3	22.1
75	20.9	24.5	28.0	9.7	11.4	13.0
Female						
45	30.2	35.2	40.3	16.3	19.0	21.8
55	28.5	33.3	38.1	12.0	14.1	16.1
65	26.4	30.9	35.3	11.2	13.2	15.1
75	18.3	21.3	24.4	8.6	10.1	11.6

Table 89: Scenario 1, 20 year discounted incremental costs (£,000) for males with baseline LDL-c of 3.5 mmol/L

	Value	Primary Prevention				Secondary Prevention			
Age		45	55	65	75	45	55	65	75
Scenario 1 basecase		£3,567	£3,382	£3,029	£2,459	£3,410	£3,153	£2,815	£2,296
Discount for costs and utilities									
	0%								
Time lag for effectiveness of treatment									
	0	£3,552	£3,366	£3,013	£2,442	£3,385	£3,129	£2,794	£2,277
	2 yr	£3,582	£3,397	£3,046	£2,474	£3,432	£3,175	£2,834	£2,313
Health state costs									
	Plus 20%	£3,528	£3,341	£2,991	£2,433	£3,362	£3,107	£2,778	£2,272
	Minus 20%	£3,607	£3,422	£3,068	£2,485	£3,458	£3,198	£2,852	£2,321
Health related QoL utilities									
Plus 10%		£3,567	£3,382	£3,029	£2,459	£3,410	£3,153	£2,815	£2,296
Minus 10%		£3,567	£3,382	£3,029	£2,459	£3,410	£3,153	£2,815	£2,296
Constant utility by age		£3,567	£3,382	£3,029	£2,459	£3,410	£3,153	£2,815	£2,296
Constant utility by age plus 10% on health state utilities		£3,567	£3,382	£3,029	£2,459	£3,410	£3,153	£2,815	£2,296
Constant utility by age minus 10% on health state utilities		£3,567	£3,382	£3,029	£2,459	£3,410	£3,153	£2,815	£2,296
Relative risk on events corresponding to reduction in LDL-c									
	LCI	£3,524	£3,338	£2,988	£2,431	£3,348	£3,095	£2,768	£2,266
	UCI	£3,614	£3,430	£3,075	£2,489	£3,474	£3,214	£2,865	£2,329
Effectiveness of ezetimibe treatment									
	LCI	£3,544	£3,358	£3,007	£2,444	£3,382	£3,126	£2,793	£2,282
	UCI	£3,590	£3,405	£3,051	£2,473	£3,438	£3,179	£2,836	£2,311
No relative risk on stroke or transient ischemic attack (TIA)									
		£3,683	£3,500	£3,144	£2,534	£3,616	£3,353	£2,978	£2,400
Baseline LDL-c (mmol/L)									
	3.0	£3,594	£3,409	£3,055	£2,476	£3,442	£3,184	£2,840	£2,313
	4.0	£3,541	£3,355	£3,004	£2,442	£3,376	£3,121	£2,790	£2,280
Using effectiveness rates from short term ezetimibe studies									
	6wks	£3,372	£3,183	£2,841	£2,333	£3,167	£2,923	£2,629	£2,173

LCI = lower confidence interval, UCI = upper confidence interval

Table 90: Scenario 1, 20 year discounted incremental QALYs for males with baseline LDL-c of 3.5 mmol/L

	Value	Primary Prevention				Secondary Prevention			
Age		45	55	65	75	45	55	65	75
Scenario 1 basecase		40	41	39	24	24	25	19	11
Discount for costs and utilities									
	0%	62	64	59	35	37	37	28	16
Time lag for effectiveness of treatment									
	0	44	46	44	29	28	28	22	14
	2 yr	36	37	34	20	21	21	16	9
Health state costs									
	Plus 20%	40	41	39	24	24	25	19	11
	Minus 20%	40	41	39	24	24	25	19	11
Health related QoL utilities									
	Plus 10%	32	35	33	21	27	27	21	13
	Minus 10%	47	48	45	28	22	22	17	10
	Constant utility by age	49	53	53	35	30	32	26	16
	Constant utility by age plus 10% on health state utilities	40	45	46	30	33	35	29	18
	Constant utility by age minus 10% on health state utilities	57	62	61	40	27	28	23	15
Relative risk on events corresponding to reduction in LDL-c									
	LCI	48	50	48	30	31	31	24	14
	UCI	31	32	30	19	19	19	15	9
Effectiveness of ezetimibe treatment									
	LCI	44	46	44	27	27	28	22	13
	UCI	35	36	34	22	21	22	17	10
No relative risk on stroke or transient ischemic attack (TIA)									
		30	32	30	19	17	18	15	9
Baseline LDL-c (mmol/L)									
	3.0	34	35	33	21	21	21	16	10
	4.0	45	47	45	28	28	28	22	13
Using effectiveness rates from short term ezetimibe studies									
	6wks	81	84	80	50	50	50	40	23

LCI = lower confidence interval, UCI = upper confidence interval

Table 91: Scenario 1; 20 year discounted ICERs (£,000) for females with baseline LDL-c of 3.5 mmol/L

	Value	Primary Prevention				Secondary Prevention			
Age		45	55	65	75	45	55	65	75
Scenario 1 basecase		£102	£101	£98	£115	£177	£229	£214	£217
Discount for costs and utilities									
	0%	£87	£87	£84	£98	£154	£198	£185	£189
Time lag for effectiveness of treatment									
	0	£90	£90	£86	£96	£156	£201	£186	£178
	2 yr	£115	£115	£113	£138	£203	£262	£249	£267
Health state costs									
	Plus 20%	£101	£101	£97	£114	£176	£228	£213	£216
	Minus 20%	£102	£102	£99	£116	£179	£231	£216	£219
Health related QoL utilities									
	Plus 10%	£126	£125	£117	£134	£160	£207	£194	£197
	Minus 10%	£85	£85	£84	£100	£199	£257	£240	£243
	Constant utility by age	£83	£78	£72	£80	£145	£178	£158	£152
	Constant utility by age plus 10% on health state utilities	£102	£96	£86	£93	£131	£160	£142	£138
	Constant utility by age minus 10% on health state utilities	£70	£66	£62	£70	£163	£199	£177	£170
Relative risk on events corresponding to reduction in LDL-c									
	LCI	£84	£83	£80	£93	£139	£180	£168	£170
	UCI	£130	£131	£127	£149	£232	£300	£281	£285
Effectiveness of ezetimibe treatment									
	LCI	£90	£90	£87	£102	£157	£204	£190	£193
	UCI	£116	£116	£112	£131	£203	£262	£245	£249
No relative risk on stroke or transient ischemic attack TIA									
		£123	£127	£125	£149	£234	£302	£280	£281
Baseline LDL-c (mmol/L)									
	3.0	£119	£119	£115	£135	£208	£269	£252	£256
	4.0	£88	£88	£85	£100	£154	£199	£186	£189
Using effectiveness rates from short term ezetimibe studies									
	6wks	£48	£48	£46	£54	£83	£109	£101	£102

LCI = lower confidence interval, UCI = upper confidence interval

Table 92: Scenario 1, 20 year discounted incremental costs (£,000) for females with baseline LDL-c of 3.5 mmol/L

	Value	Primary Prevention				Secondary Prevention			
Age		45	55	65	75	45	55	65	75
Scenario 1 basecase		£3,576	£3,373	£3,022	£2,448	£3,368	£3,220	£2,819	£2,196
Discount for costs and utilities									
	0%	£4,784	£4,469	£3,922	£3,046	£4,472	£4,241	£3,626	£2,695
Time lag for effectiveness of treatment									
	0	£3,567	£3,364	£3,012	£2,437	£3,357	£3,212	£2,810	£2,183
	2 yr	£3,584	£3,382	£3,032	£2,458	£3,378	£3,228	£2,828	£2,207
Health state costs									
	Plus 20%	£3,552	£3,349	£2,998	£2,429	£3,343	£3,200	£2,800	£2,179
	Minus 20%	£3,600	£3,398	£3,047	£2,467	£3,392	£3,240	£2,839	£2,213
Health related QoL utilities									
Plus 10%		£3,576	£3,373	£3,022	£2,448	£3,368	£3,220	£2,819	£2,196
Minus 10%		£3,576	£3,373	£3,022	£2,448	£3,368	£3,220	£2,819	£2,196
Constant utility by age		£3,576	£3,373	£3,022	£2,448	£3,368	£3,220	£2,819	£2,196
Constant utility by age plus 10% on health state utilities		£3,576	£3,373	£3,022	£2,448	£3,368	£3,220	£2,819	£2,196
Constant utility by age minus 10% on health state utilities		£3,576	£3,373	£3,022	£2,448	£3,368	£3,220	£2,819	£2,196
Relative risk on events corresponding to reduction in LDL-c									
	LCI	£3,551	£3,348	£2,997	£2,429	£3,338	£3,197	£2,796	£2,176
	UCI	£3,602	£3,401	£3,050	£2,469	£3,399	£3,245	£2,844	£2,218
Effectiveness of ezetimibe treatment									
	LCI	£3,562	£3,360	£3,009	£2,438	£3,354	£3,209	£2,808	£2,186
	UCI	£3,589	£3,387	£3,036	£2,458	£3,382	£3,231	£2,830	£2,206
No relative risk on stroke or transient ischemic attack (TIA)									
		£3,639	£3,444	£3,095	£2,502	£3,472	£3,302	£2,902	£2,267
Baseline LDL-c (mmol/L)									
	3.0	£3,591	£3,389	£3,038	£2,460	£3,384	£3,233	£2,832	£2,207
	4.0	£3,560	£3,358	£3,007	£2,436	£3,352	£3,207	£2,806	£2,185
Using effectiveness rates from short term ezetimibe studies									
	6wks	£3,461	£3,257	£2,907	£2,360	£3,249	£3,126	£2,724	£2,112

LCI = lower confidence interval, UCI = upper confidence interval

Table 93: Scenario 1, 20 year discounted incremental QALYs for females with baseline LDL-c of 3.5 mmol/L

	Value	Primary Prevention				Secondary Prevention			
Age		45	55	65	75	45	55	65	75
Scenario 1 basecase		35	33	31	21	19	14	13	10
Discount for costs and utilities									
	0%	55	51	47	31	29	21	20	14
Time lag for effectiveness of treatment									
	0	39	37	35	25	22	16	15	12
	2 yr	31	29	27	18	17	12	11	8
Health state costs									
	Plus 20%	35	33	31	21	19	14	13	10
	Minus 20%	35	33	31	21	19	14	13	10
Health related QoL utilities									
	Plus 10%	28	27	26	18	21	16	15	11
	Minus 10%	42	40	36	24	17	13	12	9
	Constant utility by age	43	43	42	31	23	18	18	14
	Constant utility by age plus 10% on health state utilities	35	35	35	26	26	20	20	16
	Constant utility by age minus 10% on health state utilities	51	51	49	35	21	16	16	13
Relative risk on events corresponding to reduction in LDL-c									
	LCI	42	40	38	26	24	18	17	13
	UCI	28	26	24	17	15	11	10	8
Effectiveness of ezetimibe treatment									
	LCI	40	37	35	24	21	16	15	11
	UCI	31	29	27	19	17	12	12	9
No relative risk on stroke or transient ischemic attack (TIA)									
		30	27	25	17	15	11	10	8
Baseline LDL-c (mmol/L)									
	3.0	30	28	26	18	16	12	11	9
	4.0	40	38	35	24	22	16	15	12
Using effectiveness rates from short term ezetimibe studies									
	6wks	72	68	63	44	39	29	27	21

LCI = lower confidence interval, UCI = upper confidence interval

Table 94: Scenario 2, discounted incremental costs (£,000) using different time horizons and a baseline LDL-c of 3.5 mmol/L

	Primary prevention			Secondary prevention		
Age	5 yr[a]	20 yr[a]	life	5 yr[a]	20 yr[a]	life
Male						
45	£1,631	£4,611	£6,082	£1,554	£4,356	£5,877
55	£1,615	£4,355	£5,252	£1,527	£4,021	£4,874
65	£1,582	£3,889	£4,267	£1,503	£3,608	£3,956
75	£1,524	£3,184	£3,243	£1,458	£2,971	£3,024
Female						
45	£1,646	£4,699	£6,148	£1,602	£4,416	£5,653
55	£1,626	£4,425	£5,334	£1,597	£4,242	£5,064
65	£1,595	£3,951	£4,337	£1,553	£3,701	£4,027
75	£1,534	£3,205	£3,265	£1,462	£2,873	£2,917

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

Table 95: Scenario 2, discounted incremental QALYs using different time horizons and a baseline LDL-c of 3.5 mmol/L

	Primary prevention			Secondary prevention		
Age	5 yr[a]	20 yr[a]	life	5 yr[a]	20 yr[a]	life
Male						
45	5.1	92.6	231.6	3.6	56.9	102.8
55	5.5	96.1	182.6	4.0	57.2	85.1
65	6.3	91.1	124.9	3.7	45.0	55.1
75	6.3	57.2	61.2	3.2	26.5	27.8
Female						
45	4.6	82.3	209.1	2.6	44.4	83.3
55	4.7	77.8	146.6	2.0	32.8	53.6
65	5.0	72.1	100.2	2.3	30.7	39.0
75	5.0	49.8	54.0	2.8	23.6	24.8

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

Table 96: Scenario 2, discounted 20 year incremental costs (£,000) when varying the baseline LDL-c value

	Primary prevention			Secondary prevention		
	baseline LDL-c (mmol/L)					
Age	3.0	3.5	4.0	3.0	3.5	4.0
Male						
45	£4,675	£4,611	£4,548	£4,436	£4,356	£4,277
55	£4,420	£4,355	£4,290	£4,096	£4,021	£3,945
65	£3,951	£3,889	£3,827	£3,669	£3,608	£3,547
75	£3,225	£3,184	£3,142	£3,012	£2,971	£2,930
Female						
45	£4,737	£4,699	£4,661	£4,455	£4,416	£4,376
55	£4,463	£4,425	£4,386	£4,273	£4,242	£4,211
65	£3,989	£3,951	£3,913	£3,733	£3,701	£3,669
75	£3,234	£3,205	£3,176	£2,901	£2,873	£2,845

Table 97: Scenario 2, discounted 20 year incremental QALYs when varying the baseline LDL-c value

	Primary prevention			Secondary prevention		
	baseline LDL-c (mmol/L)					
Age	3.0	3.5	4.0	3.0	3.5	4.0
Male						
45	79.3	92.6	105.9	48.6	56.9	65.3
55	82.2	96.1	110.0	48.8	57.2	65.6
65	78.0	91.1	104.4	38.4	45.0	51.6
75	48.9	57.2	65.4	22.7	26.5	30.4
Female						
45	70.5	82.3	94.2	38.0	44.4	50.8
55	66.6	77.8	89.0	28.1	32.8	37.6
65	61.7	72.1	82.5	26.3	30.7	35.2
75	42.7	49.8	57.0	20.2	23.6	27.0

Table 98: Scenario 2, discounted incremental costs (£,000) when truncating treatment but accruing costs and benefits over a 20 year period using a baseline LDL-c of 3.5 mmol/L

	Primary Prevention				Secondary Prevention			
Age	Basecase	2yr	5yr	10yr	Basecase	2yr	5yr	10yr
Male								
45	£4,611	£670	£1,531	£2,739	£4,356	£652	£1,467	£2,610
55	£4,355	£668	£1,515	£2,674	£4,021	£651	£1,450	£2,526
65	£3,889	£664	£1,485	£2,553	£3,608	£655	£1,444	£2,443
75	£3,184	£663	£1,452	£2,386	£2,971	£658	£1,417	£2,281
Female								
45	£4,699	£685	£1,584	£2,843	£4,416	£680	£1,558	£2,756
55	£4,425	£682	£1,566	£2,770	£4,242	£685	£1,564	£2,732
65	£3,951	£678	£1,534	£2,639	£3,701	£680	£1,520	£2,564
75	£3,205	£673	£1,482	£2,425	£2,873	£669	£1,433	£2,261

Table 99: Scenario 2, discounted incremental QALYs when truncating treatment but accruing costs and benefits over a 20 year period using a baseline LDL-c of 3.5 mmol/L

	Primary Prevention				Secondary Prevention			
Age	Basecase	2yr	5yr	10yr	Basecase	2yr	5yr	10yr
Male								
45	92.6	9.4	35.1	72.8	56.9	6.8	24.2	47.0
55	96.1	10.3	38.0	76.9	57.2	7.3	25.6	48.1
65	91.1	11.0	39.4	76.6	45.0	6.3	21.6	39.1
75	57.2	9.4	30.7	51.5	26.5	4.7	15.1	24.3
Female								
45	82.3	9.2	33.4	66.5	44.4	5.4	19.3	36.9
55	77.8	8.9	32.1	63.2	32.8	4.0	14.2	27.3
65	72.1	9.0	31.8	60.9	30.7	4.1	14.3	26.5
75	49.8	8.2	26.8	45.0	23.6	4.2	13.4	21.6

Table 100: Scenario 2, 20 year discounted incremental costs (£,000) for males with baseline LDL-c of 3.5 mmol/L

	Value	Primary Prevention				Secondary Prevention			
Age		45	55	65	75	45	55	65	75
Scenario 2 basecase		£4,611	£4,355	£3,889	£3,184	£4,356	£4,021	£3,608	£2,971
Discount for costs and utilities									
	0%	£6,139	£5,739	£5,021	£3,948	£5,803	£5,287	£4,645	£3,669
Time lag for effectiveness of treatment									
	0	£4,573	£4,316	£3,847	£3,143	£4,297	£3,962	£3,556	£2,924
	2 yr	£4,648	£4,392	£3,929	£3,221	£4,412	£4,075	£3,656	£3,013
Health state costs									
	Plus 20%	£4,519	£4,260	£3,798	£3,123	£4,244	£3,914	£3,521	£2,913
	Minus 20%	£4,703	£4,450	£3,979	£3,244	£4,469	£4,128	£3,695	£3,029
Health related QoL utilities									
Plus 10%		£4,611	£4,355	£3,889	£3,184	£4,356	£4,021	£3,608	£2,971
Minus 10%		£4,611	£4,355	£3,889	£3,184	£4,356	£4,021	£3,608	£2,971
Constant utility by age		£4,611	£4,355	£3,889	£3,184	£4,356	£4,021	£3,608	£2,971
Constant utility by age plus 10% on health state utilities		£4,611	£4,355	£3,889	£3,184	£4,356	£4,021	£3,608	£2,971
Constant utility by age minus 10% on health state utilities		£4,611	£4,355	£3,889	£3,184	£4,356	£4,021	£3,608	£2,971
Relative risk on events corresponding to reduction in LDL-c									
	LCI	£4,506	£4,248	£3,787	£3,116	£4,208	£3,881	£3,494	£2,897
	UCI	£4,724	£4,470	£3,999	£3,257	£4,511	£4,168	£3,728	£3,050
Effectiveness of ezetimibe treatment									
	LCI	£4,584	£4,327	£3,863	£3,166	£4,323	£3,989	£3,582	£2,954
	UCI	£4,638	£4,382	£3,915	£3,201	£4,390	£4,053	£3,634	£2,988
No relative risk on stroke or transient ischemic attack (TIA)									
		£4,882	£4,633	£4,157	£3,361	£4,836	£4,485	£3,987	£3,212
Baseline LDL-c (mmol/L)									
	3.0	£4,675	£4,420	£3,951	£3,225	£4,436	£4,096	£3,669	£3,012
	4.0	£4,548	£4,290	£3,827	£3,142	£4,277	£3,945	£3,547	£2,930

LCI = lower confidence interval, UCI = upper confidence interval

Table 101: Scenario 2, 20 year discounted incremental QALYs for males with baseline LDL-c of 3.5 mmol/L

	Value	Primary Prevention				Secondary Prevention			
Age		45	55	65	75	45	55	65	75
Scenario 2 basecase		93	96	91	57	57	57	45	27
Discount for costs and utilities									
	0%	144	149	138	82	87	86	66	38
Time lag for effectiveness of treatment									
	0	64	65	52	32	64	65	52	32
	2 yr	83	86	80	48	50	50	38	22
Health state costs									
	Plus 20%	93	96	91	57	57	57	45	27
	Minus 20%	93	96	91	57	57	57	45	27
Health related QoL utilities									
Plus 10%		76	81	78	49	63	63	50	29
Minus 10%		109	111	104	65	51	51	40	24
Constant utility by age		114	124	124	82	70	74	61	38
Constant utility by age plus 10% on health state utilities		93	105	107	70	77	82	68	42
Constant utility by age minus 10% on health state utilities		134	144	142	94	62	66	55	34
Relative risk on events corresponding to reduction in LDL-c									
	LCI	112	117	111	70	72	73	57	34
	UCI	72	75	71	44	43	44	35	20
Effectiveness of ezetimibe treatment									
	LCI	98	102	97	61	60	61	48	28
	UCI	87	90	86	54	53	54	42	25
No relative risk on stroke or transient ischemic attack (TIA)									
		70	74	71	45	40	42	34	20
Baseline LDL-c (mmol/L)									
	3.0	79	82	78	49	49	49	38	23
	4.0	106	110	104	65	65	66	52	30

LCI = lower confidence interval, UCI = upper confidence interval

Table 102: Scenario 2, 20 year discounted ICERs (£,000) for females with baseline LDL-c of 3.5 mmol/L

	Value	Primary Prevention				Secondary Prevention			
Age		45	55	65	75	45	55	65	75
Scenario 2 basecase		£57	£57	£55	£64	£100	£129	£121	£122
Discount for costs and utilities									
	0%	£49	£49	£47	£55	£86	£111	£104	£106
Time lag for effectiveness of treatment									
	0	£51	£50	£48	£54	£87	£113	£104	£99
	2 yr	£65	£65	£63	£78	£114	£148	£141	£151
Health state costs									
	Plus 20%	£56	£56	£54	£63	£98	£128	£119	£120
	Minus 20%	£58	£58	£56	£65	£101	£131	£122	£124
Health related QoL utilities									
	Plus 10%	£71	£70	£66	£75	£90	£117	£109	£110
	Minus 10%	£48	£48	£47	£56	£112	£145	£135	£136
	Constant utility by age	£47	£44	£40	£45	£81	£100	£89	£85
	Constant utility by age plus 10% on health state utilities	£57	£54	£48	£52	£73	£90	£80	£77
	Constant utility by age minus 10% on health state utilities	£39	£37	£35	£39	£91	£112	£99	£95
Relative risk on events corresponding to reduction in LDL-c									
	LCI	£47	£46	£44	£52	£78	£101	£94	£95
	UCI	£74	£74	£72	£84	£131	£170	£159	£161
Effectiveness data									
	LCI	£54	£53	£51	£60	£93	£121	£113	£114
	UCI	£61	£61	£59	£69	£106	£138	£129	£130
No relative risk on stroke or transient ischemic attack (TIA)									
		£70	£72	£72	£85	£134	£174	£161	£161
Baseline LDL-c (mmol/L)									
	3.0	£67	£67	£65	£76	£117	£152	£142	£144
	4.0	£50	£49	£47	£56	£86	£112	£104	£105

LCI = lower confidence interval, UCI = upper confidence interval

Table 103: Scenario 2, 20 year discounted incremental costs (£,000) for females with baseline LDL-c of 3.5 mmol/L

	Value	Primary Prevention				Secondary Prevention			
Age		45	55	65	75	45	55	65	75
Scenario 2 basecase		£4,699	£4,425	£3,951	£3,205	£4,416	£4,242	£3,701	£2,873
Discount for costs and utilities									
	0%	£6,264	£5,841	£5,108	£3,975	£5,851	£5,576	£4,750	£3,520
Time lag for effectiveness of treatment									
	0	£4,676	£4,401	£3,925	£3,176	£4,389	£4,221	£3,677	£2,841
	2 yr	£4,720	£4,448	£3,976	£3,231	£4,441	£4,262	£3,724	£2,902
Health state costs									
	Plus 20%	£4,643	£4,368	£3,894	£3,161	£4,358	£4,196	£3,655	£2,833
	Minus 20%	£4,755	£4,482	£4,008	£3,249	£4,473	£4,288	£3,747	£2,914
Health related QoL utilities									
Plus 10%		£4,699	£4,425	£3,951	£3,205	£4,416	£4,242	£3,701	£2,873
Minus 10%		£4,699	£4,425	£3,951	£3,205	£4,416	£4,242	£3,701	£2,873
Constant utility by age		£4,699	£4,425	£3,951	£3,205	£4,416	£4,242	£3,701	£2,873
Constant utility by age plus 10% on health state utilities		£4,699	£4,425	£3,951	£3,205	£4,416	£4,242	£3,701	£2,873
Constant utility by age minus 10% on health state utilities		£4,699	£4,425	£3,951	£3,205	£4,416	£4,242	£3,701	£2,873
Relative risk on events corresponding to reduction in LDL-c									
	LCI	£4,638	£4,362	£3,887	£3,157	£4,343	£4,184	£3,643	£2,823
	UCI	£4,765	£4,493	£4,020	£3,257	£4,492	£4,303	£3,762	£2,927
Effectiveness of ezetimibe treatment									
	LCI	£4,683	£4,409	£3,935	£3,193	£4,399	£4,229	£3,688	£2,862
	UCI	£4,715	£4,441	£3,967	£3,217	£4,432	£4,255	£3,714	£2,885
No relative risk on stroke or transient ischemic attack (TIA)									
		£4,848	£4,591	£4,121	£3,332	£4,657	£4,433	£3,894	£3,039
Baseline LDL-c (mmol/L)									
	3.0	£4,737	£4,463	£3,989	£3,234	£4,455	£4,273	£3,733	£2,901
	4.0	£4,661	£4,386	£3,913	£3,176	£4,376	£4,211	£3,669	£2,845

LCI = lower confidence interval, UCI = upper confidence interval

Table 104: Scenario 2, 20 year discounted incremental QALYs for females with baseline LDL-c of 3.5 mmol/L

	Value	Primary Prevention				Secondary Prevention			
Age		45	55	65	75	45	55	65	75
Scenario 2 basecase		82	78	72	50	44	33	31	24
Discount for costs and utilities									
	0%	128	120	109	72	68	50	46	33
Time lag for effectiveness of treatment									
	0	92	87	82	59	50	37	35	29
	2 yr	73	69	63	42	39	29	26	19
Health state costs									
	Plus 20%	82	78	72	50	44	33	31	24
	Minus 20%	82	78	72	50	44	33	31	24
Health related QoL utilities									
	Plus 10%	67	63	60	43	49	36	34	26
	Minus 10%	98	92	84	57	40	29	27	21
	Constant utility by age	101	101	98	72	54	42	42	34
	Constant utility by age plus 10% on health state utilities	82	82	82	61	60	47	46	37
	Constant utility by age minus 10% on health state utilities	120	119	114	82	48	38	37	30
Relative risk on events corresponding to reduction in LDL-c									
	LCI	99	94	88	61	56	41	39	30
	UCI	65	61	56	39	34	25	24	18
Effectiveness of ezetimibe treatment									
	LCI	87	83	76	53	47	35	33	25
	UCI	77	73	68	47	42	31	29	22
No relative risk on stroke or transient ischemic attack (TIA)									
		69	63	58	39	35	26	24	19
Baseline LDL-c (mmol/L)									
	3.0	70	67	62	43	38	28	26	20
	4.0	94	89	83	57	51	38	35	27

LCI = lower confidence interval, UCI = upper confidence interval

Table 105: Scenario 3, discounted 20 year incremental costs (£,000) using different time horizons and a baseline LDL-c of 3.5 mmol/L

	Primary prevention			Secondary prevention		
Age	5 yr[a]	20 yr[a]	life	5 yr[a]	20 yr[a]	life
Male						
45	£173	£390	£430	£143	£331	£457
55	£169	£358	£387	£138	£302	£374
65	£162	£312	£328	£137	£285	£315
75	£155	£275	£279	£136	£254	£259
Female						
45	£180	£457	£551	£167	£422	£530
55	£176	£425	£485	£170	£420	£493
65	£170	£371	£398	£161	£357	£387
75	£162	£304	£309	£146	£270	£274

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

Table 106: Scenario 3, discounted 20 year incremental QALYs using different time horizons and a baseline LDL-c of 3.5 mmol/L

	Primary prevention			Secondary prevention		
Age	5 yr[a]	20 yr[a]	life	5 yr[a]	20 yr[a]	life
Male						
45	2.2	39.6	99.3	1.6	24.4	44.1
55	2.4	41.1	78.3	1.7	24.5	36.5
65	2.7	39.0	53.5	1.6	19.3	23.6
75	2.7	24.5	26.2	1.4	11.4	11.9
Female						
45	2.0	35.2	89.6	1.1	19.0	35.7
55	2.0	33.3	62.8	0.8	14.1	23.0
65	2.1	30.9	42.9	1.0	13.2	16.7
75	2.1	21.3	23.1	1.2	10.1	10.6

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

Table 107: Scenario 3, discounted 20 year incremental costs (£,000) when varying the baseline LDL-c value

	Primary prevention			Secondary prevention		
	baseline LDL-c (mmol/L)					
Age	3.0	3.5	4.0	3.0	3.5	4.0
Male						
45	£417	£390	£363	£365	£331	£297
55	£385	£358	£330	£334	£302	£270
65	£338	£312	£286	£310	£285	£258
75	£293	£275	£258	£271	£254	£237
Female						
45	£473	£457	£441	£439	£422	£406
55	£441	£425	£408	£433	£420	£407
65	£387	£371	£354	£370	£357	£344
75	£317	£304	£292	£282	£270	£258

Table 108: Scenario 3, incremental 20 year discounted QALYs when varying the baseline LDL-c value

	Primary prevention			Secondary prevention		
	baseline LDL-c (mmol/L)					
Age	3.0	3.5	4.0	3.0	3.5	4.0
Male						
45	33.9	39.6	45.4	20.8	24.4	28.0
55	35.2	41.1	47.0	20.9	24.5	28.1
65	33.4	39.0	44.7	16.5	19.3	22.1
75	20.9	24.5	28.0	9.7	11.4	13.0
Female						
45	30.2	35.2	40.3	16.3	19.0	21.8
55	28.5	33.3	38.1	12.0	14.1	16.1
65	26.4	30.9	35.3	11.2	13.2	15.1
75	18.3	21.3	24.4	8.6	10.1	11.6

Table 109: Scenario 3, discounted incremental costs (£,000) when truncating treatment but accruing costs and benefits over a 20 year period using a baseline LDL-c of 3.5 mmol/L

	Primary Prevention				Secondary Prevention			
Age	Basecase	2yr	5yr	10yr	Basecase	2yr	5yr	10yr
Male								
45	£390	£65	£130	£207	£331	£57	£106	£165
55	£358	£64	£127	£196	£302	£57	£105	£161
65	£312	£63	£121	£180	£285	£60	£112	£170
75	£275	£64	£124	£192	£254	£62	£119	£182
Female								
45	£457	£71	£154	£261	£422	£70	£148	£249
55	£425	£71	£151	£251	£420	£72	£155	£260
65	£371	£69	£144	£232	£357	£70	£147	£237
75	£304	£68	£139	£219	£270	£67	£134	£204

Table 110: Scenario 3, discounted incremental QALYs when truncating treatment but accruing costs and benefits over a 20 year period using a baseline LDL-c of 3.5 mmol/L

	Primary Prevention				Secondary Prevention			
Age	Basecase	2yr	5yr	10yr	Basecase	2yr	5yr	10yr
Male								
45	39.6	4.0	15.0	32.7	24.4	2.9	10.4	21.0
55	41.1	4.4	16.2	34.5	24.5	3.1	11.0	21.4
65	39.0	4.7	16.9	34.2	19.3	2.7	9.2	17.4
75	24.5	4.0	13.1	22.7	11.4	2.0	6.4	10.7
Female								
45	35.2	4.0	14.3	29.8	19.0	2.3	8.2	16.5
55	33.3	3.8	13.8	28.3	14.1	1.7	6.1	12.2
65	30.9	3.8	13.6	27.2	13.2	1.8	6.1	11.8
75	21.3	3.5	11.5	19.8	10.1	1.8	5.7	9.5

Table 111: Scenario 3, 20 year discounted incremental costs (£,000) for males with baseline LDL-c of 3.5 mmol/L

	Value	Primary Prevention				Secondary Prevention			
Age		45	55	65	75	45	55	65	75
Scenario 3 basecase		£390	£358	£312	£275	£331	£302	£285	£254
Discount for costs and utilities									
	0%	£493	£446	£382	£330	£427	£386	£359	£309
Time lag for effectiveness of treatment									
	0	£374	£341	£294	£258	£305	£277	£262	£234
	2 yr	£405	£374	£329	£291	£354	£325	£305	£272
Health state costs									
	Plus 20%	£350	£317	£273	£250	£283	£256	£247	£229
	Minus 20%	£429	£398	£351	£301	£379	£348	£322	£279
Health related QoL utilities									
	Plus 10%	£390	£358	£312	£275	£331	£302	£285	£254
	Minus 10%	£390	£358	£312	£275	£331	£302	£285	£254
	Constant utility by age	£390	£358	£312	£275	£331	£302	£285	£254
	Constant utility by age plus 10% on health state utilities	£390	£358	£312	£275	£331	£302	£285	£254
	Constant utility by age minus 10% on health state utilities	£390	£358	£312	£275	£331	£302	£285	£254
Relative risk on events corresponding to reduction in LDL-c									
	LCI	£345	£312	£269	£247	£267	£242	£236	£222
	UCI	£438	£407	£359	£307	£397	£365	£335	£288
Effectiveness of ezetimibe treatment									
	LCI	£367	£334	£290	£261	£302	£275	£263	£240
	UCI	£413	£381	£334	£290	£359	£329	£306	£269
No relative risk on stroke or transient ischemic attack (TIA)									
		£505	£477	£427	£351	£537	£501	£447	£357
Baseline LDL-c (mmol/L)									
	3.0	£417	£385	£338	£293	£365	£334	£310	£271
	4.0	£363	£330	£286	£258	£297	£270	£258	£237
Using effectiveness rates from short term ezetimibe studies									
	6wks	£193	£157	£121	£148	£86	£70	£96	£129

LCI = lower confidence interval, UCI = upper confidence interval

Table 112: Scenario 3, 20 year discounted incremental QALYs for males with baseline LDL-c of 3.5 mmol/L

	Value	Primary Prevention				Secondary Prevention			
Age		45	55	65	75	45	55	65	75
Scenario 3 basecase		40	41	39	24	24	25	19	11
Discount for costs and utilities									
	0%	62	64	59	35	37	37	28	16
Time lag for effectiveness of treatment									
	0	44	46	44	29	28	28	22	14
	2 yr	36	37	34	20	21	21	16	9
Health state costs									
	Plus 20%	40	41	39	24	24	25	19	11
	Minus 20%	40	41	39	24	24	25	19	11
Health related QoL utilities									
	Plus 10%	32	35	33	21	27	27	21	13
	Minus 10%	47	48	45	28	22	22	17	10
	Constant utility by age	49	53	53	35	30	32	26	16
	Constant utility by age plus 10% on health state utilities	40	45	46	30	33	35	29	18
	Constant utility by age minus 10% on health state utilities	57	62	61	40	27	28	23	15
Relative risk on events corresponding to reduction in LDL-c									
	LCI	48	50	48	30	31	31	24	14
	UCI	31	32	30	19	19	19	15	9
Effectiveness of ezetimibe treatment									
	LCI	44	46	44	27	27	28	22	13
	UCI	35	36	34	22	21	22	17	10
No relative risk on stroke or transient ischemic attack (TIA)									
		30	32	30	19	17	18	15	9
Baseline LDL-c (mmol/L)									
	3.0	34	35	33	21	21	21	16	10
	4.0	45	47	45	28	28	28	22	13
Using effectiveness rates from short term ezetimibe studies									
	6wks	81	84	80	50	50	50	40	23

LCI = lower confidence interval, UCI = upper confidence interval

Table 113: Scenario 3, 20 year discounted ICERs (£,000) for females with baseline LDL-c of 3.5 mmol/L

	Value	Primary Prevention				Secondary Prevention			
Age		45	55	65	75	45	55	65	75
Scenario 3 basecase		£13	£13	£12	£14	£22	£30	£27	£27
Discount for costs and utilities									
	0%	£11	£11	£10	£12	£19	£25	£23	£23
Time lag for effectiveness of treatment									
	0	£11	£11	£10	£12	£19	£26	£23	£21
	2 yr	£15	£15	£14	£18	£26	£35	£32	£34
Health state costs									
	Plus 20%	£12	£12	£11	£13	£21	£29	£26	£25
	Minus 20%	£14	£14	£13	£15	£24	£31	£29	£29
Health related QoL utilities									
	Plus 10%	£16	£16	£14	£17	£20	£27	£25	£24
	Minus 10%	£11	£11	£10	£12	£25	£34	£30	£30
	Constant utility by age	£11	£10	£9	£10	£18	£23	£20	£19
	Constant utility by age plus 10% on health state utilities	£13	£12	£11	£12	£16	£21	£18	£17
	Constant utility by age minus 10% on health state utilities	£9	£8	£8	£9	£20	£26	£22	£21
Relative risk on events corresponding to reduction in LDL-c									
	LCI	£10	£10	£9	£11	£16	£22	£20	£20
	UCI	£18	£17	£17	£20	£31	£41	£38	£38
Effectiveness data									
	LCI	£11	£11	£10	£12	£19	£26	£23	£23
	UCI	£15	£15	£14	£17	£26	£35	£32	£32
No relative risk on stroke or transient ischemic attack (TIA)									
		£18	£18	£18	£21	£35	£46	£43	£42
Baseline LDL-c (mmol/L)									
	3.0	£16	£16	£15	£17	£27	£36	£33	£33
	4.0	£11	£11	£10	£12	£19	£25	£23	£22
Using effectiveness rates from short term ezetimibe studies									
	6wks	£5	£5	£4	£5	£8	£11	£10	£9

LCI = lower confidence interval, UCI = upper confidence interval

Table 114: Scenario 3, 20 year discounted incremental costs (£,000) for females with baseline LDL-c of 3.5 mmol/L

	Value	Primary Prevention				Secondary Prevention			
Age		45	55	65	75	45	55	65	75
Scenario 3 basecase		£457	£425	£371	£304	£422	£420	£357	£270
Discount for costs and utilities									
	0%	£595	£547	£467	£370	£552	£545	£453	£327
Time lag for effectiveness of treatment									
	0	£447	£415	£360	£292	£411	£411	£347	£257
	2 yr	£466	£434	£381	£315	£433	£428	£367	£282
Health state costs									
	Plus 20%	£433	£400	£346	£285	£398	£400	£337	£253
	Minus 20%	£481	£449	£395	£323	£447	£439	£377	£288
Health related QoL utilities									
	Plus 10%	£457	£425	£371	£304	£422	£420	£357	£270
	Minus 10%	£457	£425	£371	£304	£422	£420	£357	£270
	Constant utility by age	£457	£425	£371	£304	£422	£420	£357	£270
	Constant utility by age plus 10% on health state utilities	£457	£425	£371	£304	£422	£420	£357	£270
	Constant utility by age minus 10% on health state utilities	£457	£425	£371	£304	£422	£420	£357	£270
Relative risk on events corresponding to reduction in LDL-c									
	LCI	£431	£398	£344	£284	£392	£395	£333	£249
	UCI	£485	£454	£400	£326	£455	£446	£383	£293
Effectiveness of ezetimibe treatment									
	LCI	£443	£411	£357	£294	£408	£409	£346	£260
	UCI	£470	£438	£384	£315	£437	£431	£368	£280
No relative risk on stroke or transient ischemic attack (TIA)									
		£520	£496	£443	£359	£526	£501	£440	£341
Baseline LDL-c (mmol/L)									
	3.0	£473	£441	£387	£317	£439	£433	£370	£282
	4.0	£441	£408	£354	£292	£406	£407	£344	£258
Using effectiveness rates from short term ezetimibe studies									
	6wks	£340	£306	£253	£214	£302	£324	£260	£185

LCI = lower confidence interval, UCI = upper confidence interval

Table 115: Scenario 3, 20 year discounted incremental QALYs for females with baseline LDL-c of 3.5 mmol/L

	Value	Primary Prevention				Secondary Prevention			
Age		45	55	65	75	45	55	65	75
Scenario 3 basecase		35	33	31	21	19	14	13	10
Discount for costs and utilities									
	0%	55	51	47	31	29	21	20	14
Time lag for effectiveness of treatment									
	0	39	37	35	25	22	16	15	12
	2 yr	31	29	27	18	17	12	11	8
Health state costs									
	Plus 20%	35	33	31	21	19	14	13	10
	Minus 20%	35	33	31	21	19	14	13	10
Health related QoL utilities									
	Plus 10%	28	27	26	18	21	16	15	11
	Minus 10%	42	40	36	24	17	13	12	9
	Constant utility by age	43	43	42	31	23	18	18	14
	Constant utility by age plus 10% on health state utilities	35	35	35	26	26	20	20	16
	Constant utility by age minus 10% on health state utilities	51	51	49	35	21	16	16	13
Relative risk on events corresponding to reduction in LDL-c									
	LCI	42	40	38	26	24	18	17	13
	UCI	28	26	24	17	15	11	10	8
Effectiveness of ezetimibe treatment									
	LCI	40	37	35	24	21	16	15	11
	UCI	31	29	27	19	17	12	12	9
No relative risk on stroke or transient ischemic attack (TIA)									
		30	27	25	17	15	11	10	8
Baseline LDL-c (mmol/L)									
	3.0	30	28	26	18	16	12	11	9
	4.0	40	38	35	24	22	16	15	12
Using effectiveness rates from short term ezetimibe studies									
	6wks	72	68	63	44	39	29	27	21

LCI = lower confidence interval, UCI = upper confidence interval

Table 116: Scenario 1, discounted incremental costs (£,000) when varying the baseline LDL-c value with diabetic patients over a 20 year period

	Primary prevention			Secondary prevention		
	baseline LDL-c (mmol/L)					
Age	3.0	3.5	4.0	3.0	3.5	4.0
Male						
45	£3,337	£3,278	£3,220	£3,382	£3,339	£3,295
55	£3,118	£3,062	£3,005	£3,128	£3,087	£3,047
65	£2,752	£2,701	£2,650	£2,794	£2,761	£2,728
75	£2,237	£2,202	£2,167	£2,282	£2,260	£2,238
Female						
45	£3,354	£3,318	£3,283	£3,354	£3,334	£3,313
55	£3,113	£3,080	£3,046	£3,209	£3,192	£3,175
65	£2,738	£2,707	£2,675	£2,808	£2,791	£2,774
75	£2,207	£2,183	£2,158	£2,186	£2,172	£2,157

Table 117: Scenario 1, discounted incremental QALYs when varying the baseline LDL-c value with diabetic patients over a 20 year period

	Primary prevention			Secondary prevention		
	baseline LDL-c (mmol/L)					
Age	3.0	3.5	4.0	3.0	3.5	4.0
Male						
45	61.4	72.0	82.6	20.8	24.4	27.9
55	59.4	69.6	79.9	20.6	24.1	27.7
65	51.9	60.8	69.9	16.2	18.9	21.7
75	33.6	39.4	45.2	9.6	11.2	12.9
Female						
45	54.0	63.2	72.5	15.9	18.6	21.3
55	46.8	54.8	62.9	11.9	13.9	15.9
65	40.3	47.3	54.2	11.1	13.0	14.9
75	28.5	33.4	38.3	8.5	9.9	11.4

Table 118: Scenario 2, discounted incremental costs (£,000) when varying the baseline LDL-c value with diabetic patients over a 20 year period

	Primary prevention			Secondary prevention		
	baseline LDL-c (mmol/L)					
Age	3.0	3.5	4.0	3.0	3.5	4.0
Male						
45	£4,141	£4,002	£3,863	£4,295	£4,192	£4,088
55	£3,855	£3,720	£3,584	£3,966	£3,869	£3,771
65	£3,396	£3,274	£3,151	£3,563	£3,483	£3,404
75	£2,798	£2,714	£2,629	£2,940	£2,887	£2,834
Female						
45	£4,297	£4,211	£4,125	£4,387	£4,336	£4,285
55	£3,987	£3,906	£3,825	£4,217	£4,176	£4,136
65	£3,491	£3,415	£3,337	£3,676	£3,635	£3,594
75	£2,817	£2,757	£2,696	£2,852	£2,817	£2,780

Table 119: Scenario 2, discounted incremental QALYs when varying the baseline LDL-c value with diabetic patients over a 20 year period

	Primary prevention			Secondary prevention		
	baseline LDL-c (mmol/L)					
Age	3.0	3.5	4.0	3.0	3.5	4.0
Male						
45	143.3	167.9	192.7	48.6	56.9	65.2
55	138.5	162.3	186.3	48.1	56.3	64.6
65	121.0	141.9	163.0	37.8	44.2	50.7
75	78.4	91.9	105.5	22.4	26.2	30.0
Female						
45	125.9	147.5	169.1	37.1	43.4	49.7
55	109.1	127.8	146.7	27.8	32.5	37.2
65	94.1	110.2	126.5	25.9	30.3	34.7
75	66.5	77.9	89.3	19.8	23.2	26.6

Table 120: Scenario 4, discounted incremental costs (£,000) when varying the baseline LDL-c value over a 20 year period

	Primary Prevention				Secondary Prevention			
Age	4.0	5.0	6.0	7.0	4.0	5.0	6.0	7.0
Male								
45	£3,461	£3,330	£3,198	£3,064	£3,501	£3,390	£3,277	£3,161
55	£3,230	£3,102	£2,973	£2,843	£3,236	£3,131	£3,023	£2,914
65	£2,847	£2,732	£2,614	£2,495	£2,903	£2,818	£2,732	£2,644
75	£2,329	£2,249	£2,168	£2,086	£2,389	£2,333	£2,276	£2,218
Female								
45	£3,556	£3,481	£3,406	£3,331	£3,552	£3,499	£3,447	£3,393
55	£3,297	£3,225	£3,152	£3,078	£3,409	£3,368	£3,326	£3,284
65	£2,890	£2,821	£2,751	£2,679	£2,976	£2,934	£2,892	£2,849
75	£2,328	£2,274	£2,219	£2,163	£2,311	£2,273	£2,236	£2,198

Table 121: Scenario 4, discounted incremental QALYs when varying the baseline LDL-c value over a 20 year period

	Primary Prevention				Secondary Prevention			
Age	4.0	5.0	6.0	7.0	4.0	5.0	6.0	7.0
Male								
45	113	142	173	203	46	59	71	84
55	111	141	171	201	47	59	71	84
65	98	125	151	179	37	46	56	66
75	64	80	97	115	22	27	33	39
Female								
45	99	125	151	178	36	45	55	64
55	86	109	132	155	27	33	40	47
65	75	95	115	136	25	31	38	44
75	54	68	83	97	19	24	29	34

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