NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia (review of TA132)

This premeeting briefing presents:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Key issues for consideration

Clinical effectiveness

- The ERG considered that the search strategy developed by the company to identify relevant trials for the meta-analyses of low-density lipoprotein cholesterol (LDL-c) and total cholesterol (TC) levels of ezetimibe versus comparators may have lacked sensitivity and potentially failed to identify other relevant trial evidence.
    - ◊ Is the Committee persuaded that the company's search strategy is sufficiently robust and that it is unlikely that important information has been missed?
- The company did not undertake any meta-analyses of clinical outcomes such as mortality or cardiovascular (CV) events, which could have potentially been used to inform its economic model directly, rather than using an external meta-analysis to model indirect effects via LDL-c reduction.

  - The ERG noted that clinical outcomes were available in at least 2 of the included studies.
    - ◊ What is the Committee's view on the company's approach to analysing the clinical outcomes with ezetimibe?
- The company did not perform a network meta-analysis to examine the relationship between LDL-c levels and outcomes.
  - The ERG was of the opinion that this was feasible and could have potentially included different statin doses as separate treatments within the network, as well as other combinations of statins, placebo and lipid-regulating drugs.
    - ◊ Does the Committee consider that a network meta-analysis would be a more appropriate method of synthesising the evidence?

Cost effectiveness

- The final scope specified a population of people with primary heterozygous familial or non-familial hypercholesterolaemia: whose condition is not appropriately controlled with a statin alone or in whom a statin is considered inappropriate or is not tolerated.
  - In its model, the company used a population of primary prevention (10–30% 10-year risk of developing cardiovascular disease (CVD)) and secondary prevention (established CVD) of people with primary heterozygous familial or non-familial hypercholesterolaemia whose condition is not appropriately controlled with a statin alone or in whom a statin is considered inappropriate or is not tolerated.
    - ◊ Is the company's rationale for modelling a different population according to presence or risk of CVD appropriate?
- The final scope specified the comparator 'other lipid-regulating drugs' for people with primary heterozygous familial or non-familial hypercholesterolaemia in whom a statin is considered inappropriate or is not tolerated.
  - The company asserted that the most appropriate comparator is 'no treatment' based on recommendations in the NICE guideline on Lipid modification (CG181).

  - ◊ What is the Committee's view on the company's choice of comparator for this population?
- The company's model omitted the stable angina or transient ischaemic attack (TIA) health states from its base-case analyses, which was inconsistent with previous NICE technology appraisal guidance on ezetimibe (TA132) and the NICE guideline on lipid modification (CG181).
  - The ERG believed that it was inappropriate to assume zero risk of these events because the associated morbidity, costs and downstream risks may still influence comparisons.
    - ◊ Does the Committee consider that the stable angina and TIA states should be included in the model?
- The company used an external meta-analysis (by the Cholesterol Treatment Trialists' Collaboration: CTTC) to link LDL-c levels to clinical outcomes (CV events); this approach was also taken in previous technology appraisal guidance on ezetimibe because of a lack of clinical data.
  - The ERG noted that the company had not performed a systematic review and meta-analysis of clinical outcomes currently available for the intervention and comparators. The ERG considered that it could be appropriate to model the effect of ezetimibe in the secondary prevention population using the IMPROVE-IT results.
    - ◊ Does the Committee find the company's approach of modelling CV events using an external meta-analysis to link surrogate and clinical outcomes to be acceptable?
- The company calculated the treatment effect of ezetimibe as an add-on to a statin using the estimated additional percentage reduction in LDL-c (from baseline pre-treatment levels) achieved with ezetimibe + statin versus statin alone, rather than using a multiplicative percentage reduction in LDL-c from the post-statin LDL-c level.
  - The ERG stated that the absolute further reduction in LDL-c associated with ezetimibe as an add-on may be less when using the multiplicative approach than when using the pooled additive effect (as used in the company's base case).

  - The ERG stated that the absolute further reduction in LDL-c levels associated with ezetimibe as an add-on may be less when using the multiplicative approach than when using the pooled additive effect (as used in the company's base case).
    - ◊ What approach does the Committee think is the most appropriate to estimate treatment effect?
    - ◊ Does the Committee find it reasonable to assume a constant treatment effect over time?
- The company assigned a treatment effect of ezetimibe compared with no treatment or statin on non-CV deaths (via LDL-c level reduction).
  - The ERG stated this effect was not significant in the CTTC meta-analysis and noted this was inconsistent with previous modelling in the technology appraisal guidance on ezetimibe (TA132).
    - ◊ Does the Committee find it reasonable to include a treatment effect for ezetimibe on non-CV deaths?

1 Remit and decision problem

1.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of ezetimibe within its licensed indication for treating primary hypercholesterolaemia in adults.

1.2 The technology appraisal guidance on ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia (TA132) was reviewed in 2012. The review identified an ongoing study (IMPROVE-IT) which was thought to be important because it measured clinical outcomes (such as CV events). NICE's Guidance Executive recommended TA132 should be updated and the update was scheduled so that the results of IMPROVE-IT could be taken into account.

1.3 The final NICE scope and company's decision problem is shown in Table 1. The company provided an overview of how its approach to the guidance review differed from its original approach (Table 2).

Table 1 Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Population	People with primary heterozygous familial or non-familial hypercholesterolaemia: • whose condition is not appropriately controlled with a statin alone or • in whom a statin is considered inappropriate or is not tolerated.	People with primary heterozygous familial or non-familial hypercholesterolaemia: • Co-administered with a statin in people whose condition is not appropriately controlled with a statin alone, either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance. • As monotherapy in patients where a statin is considered inappropriate or is contraindicated or not tolerated. The following populations are considered: • Primary prevention (10-30% 10-year risk of developing CVD) • Secondary prevention (established CVD)	The monotherapy population is in line with the final NICE scope. The population co-administration with a statin considers patients not appropriately controlled with a statin alone where up-titration is inappropriate or not tolerated. The company stated that this is in line with clinical practice and NICE clinical guideline 181. The company stated that the base case-populations for primary and secondary prevention were in line with NICE guidance.	The ERG noted that the populations used in the company's base-case were different to those in the NICE final scope. However, the ERG agreed that the company's specification of the population for this appraisal was appropriate and clinically relevant.
Intervention	Ezetimibe alone or in	• Ezetimibe monotherapy	In line with final NICE scope.	The ERG stated that the

	combination with a statin	• Ezetimibe in combination with a statin		intervention addressed by the company is in line with the final scope issued by NICE.
Comparators	For people with primary heterozygous familial or non-familial hypercholesterolaemia whose condition is not appropriately controlled with a statin alone: • Optimal statin therapy For people with primary heterozygous familial or non-familial hypercholesterolaemia in whom a statin is considered inappropriate or is not tolerated: • Other lipid-regulating drugs	For people with primary heterozygous familial or non-familial hypercholesterolaemia whose condition is not appropriately controlled with a statin alone: • Optimal statin therapy (maximum tolerated dose) For people with primary heterozygous familial or non-familial hypercholesterolaemia in whom a statin is considered inappropriate or is not tolerated: • No treatment	Ezetimibe monotherapy: CG181 does not recommend the use of nicotinic acid, bile acid sequestrants or omega-3 fatty acid compounds. Additionally, it does not routinely recommend the use of fibrates, which are more applicable in treating hypertriglyceridaemia.	For people with primary heterozygous familial or non-familial hypercholesterolaemia whose condition is not appropriately controlled with a statin alone: The ERG agreed with the company's specification of using a maximum tolerated dose for the pertinent (optimum) statin therapy For people with primary heterozygous familial or non-familial hypercholesterolaemia in whom a statin is considered inappropriate or is not tolerated: The ERG noted that the NICE final scope specified other lipid-regulating drugs. It also noted that the company's justification for their choice of 'no treatment' comparator was based on the NICE guideline on lipid modification which did not recommend use of nicotinic acid, bile acid sequestrants or omega-3 fatty acid compounds,

				or routine use of fibrates.
Outcomes	The outcome measures to be considered include: • plasma lipid and lipoprotein levels, including LDL cholesterol, non-HDL cholesterol, apolipoprotein B and lipoprotein a • requirement of procedures including LDL apheresis and revascularisation • fatal and non-fatal cardiovascular events • coronary events • stroke • mortality • adverse effects of treatment • health-related quality of life.	• Mean % change in LDL-c and TC, apolipoprotein B and lipoprotein A. • Survival/mortality. • Fatal and non-fatal cardiovascular events. • Stroke. • Adverse effects of treatment. • Health-related quality of life.	• Non-HDL-c was not included because it was not routinely reported in the ezetimibe clinical trials. • Coronary events are considered under non-fatal CV events. • LDL-c apheresis is primarily used in patients with Homozygous Familial Hypercholesterolaemia (HoFH). HoFH is not relevant to this appraisal. • Revascularisation has been considered as part of the health state costs in the cost-effectiveness analysis.	The ERG noted that the NICE guideline on lipid modification recommends the measurement of non-HDL-c levels (among other measurements) both before starting lipid modification therapy and subsequently as a key marker of effectiveness of the therapy. The ERG stated that despite the lack of available trial data, non-HDL-c measures should have been considered by the company among the relevant outcomes measures for this appraisal. The ERG stated that the company did not include LDL-c apheresis as it is predominantly used in homozygous familial hypercholesterolemia and therefore not relevant to the remit of this appraisal. The ERG noted that clinical outcomes (survival/mortality, CV events, stroke and health-related quality of life) specified

				in the NICE final scope were not reported in the company's systematic review of the clinical evidence.
Subgroups	If the evidence allows, consideration will be given to the following subgroups: • Presence or risk of cardiovascular disease • People with heterozygous familial hypercholesterolaemia • People with statin intolerance • Severity of hypercholesterolaemia	Where evidence allows, analysis of subgroups will be considered in: • Primary prevention in people with diabetes • People with CKD • People with heterozygous-familial hypercholesterolaemia	• The presence or risk of CVD is considered by using the primary prevention population 10-30% 10-year CV risk. • People with statin intolerance are considered in the base-case as ezetimibe monotherapy population. • Severity of hypercholesterolaemia is considered as part of the CV risk score and baseline LDL-c values will be modelled. • Subgroups for diabetes and CKD are considered	The ERG noted that NICE final scope specified the following subgroups if evidence allowed: presence or risk of cardiovascular disease; people with heterozygous familial hypercholesterolaemia; people with statin intolerance; severity of hypercholesterolaemia. The ERG stated that the subgroups considered by the company were: primary prevention in people with diabetes; people with chronic kidney disease (CKD); people with heterozygous familial hypercholesterolaemia; the severity of hypercholesterolaemia as part of the CV risk score and baseline LDL cholesterol values. The ERG noted the company's inclusion of the diabetes and CKD subgroups following consultee feedback on the draft scope.

Table 2 Company's approach to the decision problem in TA132 and its review

TA132 approach (Nov 2007)	Approach for the review of TA132 (June 2015)	Company's rationale
Population		
• Ezetimibe plus current statin therapy versus current statin therapy titrated to the next dose (generic simvastatin) • Ezetimibe monotherapy versus no treatment • Ezetimibe plus non-proprietary simvastatin versus atorvastatin • Ezetimibe plus current statin therapy versus current statin therapy alone • Ezetimibe plus rosuvastatin versus rosuvastatin monotherapy	• Ezetimibe monotherapy versus no treatment • Ezetimibe co-administered with current statin therapy versus current statin therapy alone	• Ezetimibe plus current statin therapy versus current statin therapy titrated to the next dose (generic simvastatin) is not considered. According to clinical practice and CG181, up-titration of a statin should be investigated before adding ezetimibe. • Ezetimibe plus non-proprietary simvastatin versus atorvastatin is not considered because atorvastatin is now generic and first-line option for treatment • Ezetimibe plus rosuvastatin versus rosuvastatin monotherapy is not considered because CG181 states that atorvastatin should be considered over rosuvastatin.
Comparators		
For the co-administration with a statin population in the 2007 appraisal of ezetimibe, up-titration of the statin dose was considered a comparator.	For the co-administration with a statin population, this review will only consider patients that cannot increase their statin dose due to intolerance or contraindication.	Unlike when the original appraisal was published, there are now many low-cost statins. Therefore, the company did not consider up-titration of a statin to be a comparator because increasing the statin dose should be considered before adding ezetimibe.
Simvastatin was considered standard of care.	Atorvastatin 10–80 mg is considered standard of care depending on the population.	Atorvastatin is the first statin of choice in CG181. Since it became generic, it has replaced simvastatin as the first-line statin of choice.

Cardiovascular risk		
Clinical practice and guidelines focused on a person's 10-year risk of CVD being over/equal to 20% before starting treatment with lipid-lowering therapy.	The appraisal will consider the use of ezetimibe with 10–30% 10-year risk of CVD.	CG181, which was published after TA132, states that lipid-modifying treatment can be considered for people whose 10-year risk of developing CVD is 10% or greater. The company submission considers people whose 10-year risk of developing CVD is 10–30% to reflect the evolution of clinical practice (although ezetimibe's marketing authorisation does not consider a person's risk of CVD).
Historically, in clinical practice Framingham risk scoring has been used to estimate a person's risk of CVD.	QRISK2 will be used.	In CG181, QRISK2 is the risk scoring tool of choice to assess CVD risk for the primary prevention.

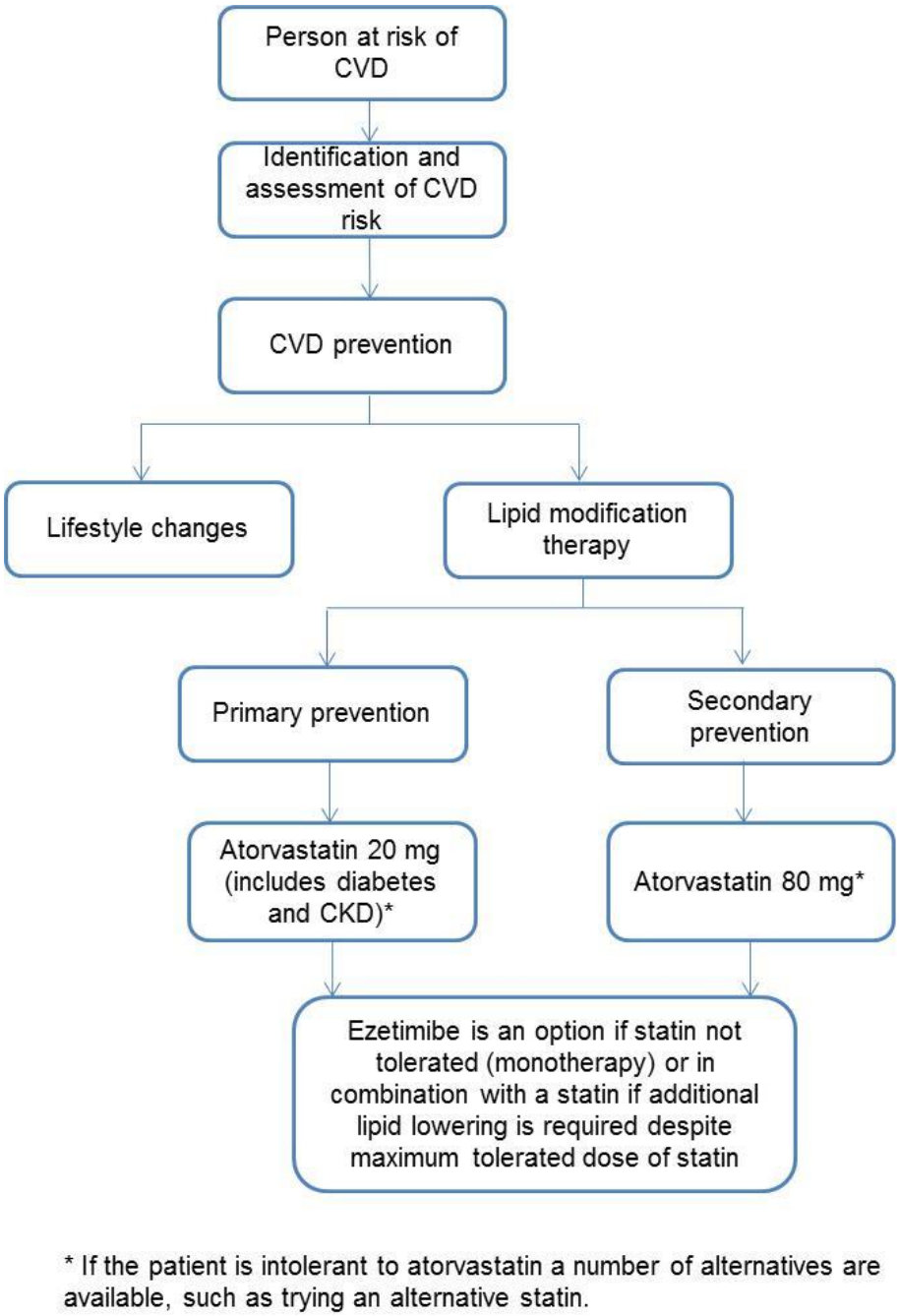
TA132, NICE technology appraisal 132: Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia; CG181, NICE clinical guideline 181: Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease

2 The technology and the treatment pathway

2.1 People with hypercholesterolaemia are at increased risk of cardiovascular disease (CVD) because long-term elevations of cholesterol accelerate the build-up of fatty deposits in the arteries (atherosclerosis). Primary non-familial hypercholesterolaemia affects about 4% of the adult population, totalling approximately 1.5 million people in England, of whom an estimated 600,000 are diagnosed and 460,000 are receiving treatment. Primary heterozygous-familial hypercholesterolaemia affects an estimated 1 in 500 people, totalling 106,000 in England (although only 15–17% are diagnosed).

2.2 Managing primary hypercholesterolaemia involves dietary and lifestyle changes (such as smoking cessation, weight loss and increased physical activity) and treatment with a lipid-regulating drug, if appropriate (see Figure 1). Starting drug treatment is generally based on an assessment of the person's cardiovascular risk.

Figure 1 Treatment pathway



Source: figure 2, page 38 of the company submission

2.3 Statins are usually the first-choice drugs. The NICE guideline on lipid modification (CG181) recommends that when a decision is made to prescribe a statin, a statin of high intensity and low acquisition cost should be used. It recommends atorvastatin 20 mg for the primary prevention of

CVD in people who have a 10% or greater 10-year risk of developing CVD, as estimated using the QRISK2 assessment tool.

2.4 NICE technology appraisal 132 recommends ezetimibe as an option for treating primary (heterozygous familial or non-familial) hypercholesterolaemia, as a monotherapy when statins are contraindicated or not tolerated and in combination with statins when initial statin therapy does not provide appropriate control of LDL-cholesterol. It was determined that technology appraisal guidance on ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia was unsuitable for updating in the NICE guideline on lipid modification. Instead, a technology appraisal review was scheduled to allow new data to be taken into account.

Table 3 Technologies

	Ezetimibe	Statins
Marketing authorisation	Ezetimibe, co-administered with an HMG-CoA reductase inhibitor (statin) is indicated as adjunctive therapy to diet for use in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia who are not appropriately controlled with a statin alone. Ezetrol monotherapy is indicated as adjunctive therapy to diet for use in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia in whom a statin is considered inappropriate or is not tolerated.	Atorvastatin is indicated as an adjunct to diet for reduction of elevated total cholesterol (total-C), LDL-cholesterol (LDL-C), apolipoprotein B, and triglycerides in adults, adolescents and children aged 10 years or older with primary hypercholesterolaemia including familial hypercholesterolaemia (heterozygous variant) or combined (mixed) hyperlipidaemia (Corresponding to Types IIa and IIb of the Fredrickson classification) when response to diet and other nonpharmacological measures is inadequate. Atorvastatin is also indicated to reduce total-C and LDL-C in adults with homozygous familial hypercholesterolaemia as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are unavailable. Prevention of cardiovascular events in adult patients estimated to have a high risk for a first cardiovascular event, as an adjunct to correction of other risk factors. Details of the marketing authorisations for other statins can be found here.
Administration method	Oral	Oral
Cost information	A 28-tab pack of ezetimibe 10 mg costs £26.31 (BNF, accessed July 2015).	A 28-tab pack of atorvastatin costs £1.18 for 10-mg tablets, £1.59 for 40 mg tablets and £2.71 for 80-mg tablets (BNF, accessed July 2015). See the BNF for prices of the other statins.

See summary of product characteristics for details on adverse reactions and contraindications.

3 Comments from consultees

3.1 The patient organisations stated that hypercholesterolaemia can be managed using medication (such as statins) and with lifestyle changes (such as exercise and diet). The professional organisations noted that certain lipid-regulating alternatives to ezetimibe (such as fibrates and fish oils) are no longer recommended in recent guidelines such as the NICE guideline on lipid modification, but considered bile acid sequestrants as a possible appropriate comparator for familial hypercholesterolaemia. The patient organisations stated that ezetimibe is easier to use than bile acid sequestrants and is less invasive than procedures such as apheresis.

3.2 Patient and professional organisations highlighted that ezetimibe is currently available and widely used in clinical practice, but described regional variation in its use because of differing interpretations of the available data.

3.3 The professional organisations were aware of recent evidence on CV outcomes from the IMPROVE-IT and SHARP trials, but highlighted the lack of clear trial evidence demonstrating reductions in CV risks for primary prevention of hypercholesterolaemia, familial hypercholesterolaemia and for people with diabetes. It was noted that LDL-c may be an appropriate surrogate outcome for long-term CV outcomes. One professional organisation also stated that there are differences in opinion about whether LDL-c targets should be set.

3.4 The professional organisations considered that people with a high risk of CVD or familial hypercholesterolaemia may have greater benefit from ezetimibe when used with an add-on to a statin. They stated that people with diabetes and CKD may react differently to those without the conditions.

4 Clinical-effectiveness evidence

4.1 The company performed a systematic literature review to identify RCTs of ezetimibe (monotherapy and in combination with a statin) for treating primary hypercholesterolemia that were greater than 12 weeks in duration. The evidence base for evidence synthesis described 24 RCTs, plus the IMPROVE-IT clinical trial report (see table 15 on page 66 of the company submission and section A7 of the company's clarification response for details of the included trials).

4.2 The company provided a narrative summary of 3 clinical outcome trials. Since the publication of technology appraisal guidance on ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia (TA132), SHARP, IMPROVE-IT and SEAS have examined the effectiveness of ezetimibe in reducing CV events.

Overview of the clinical trials

4.3 SHARP was a randomised, double-blind, placebo-controlled study in 9270 patients with chronic kidney disease and unknown history of myocardial infarction or coronary revascularisation. Patients were randomised in a 4:4:1 ratio to either ezetimibe 10 mg plus simvastatin 20 mg once daily, placebo once daily, or simvastatin 20 mg for 1 year. After 1 year, the simvastatin arm was re-randomised to either ezetimibe 10 mg plus simvastatin 20 mg once daily or placebo once daily. At a median follow-up of 4.9 years, ezetimibe plus simvastatin produced a 17% proportional reduction in the primary efficacy endpoint composite of CHD death, non-fatal MI, revascularization, or non-fatal non-haemorrhagic stroke compared with placebo (RR 0.83, 95% CI 0.74 to 0.94; p=0.0021). The reduction in non-fatal myocardial infarction or coronary death (RR 0.92, 95% CI 0.76 to 1.11) was not statistically significant, but the trial was not powered to assess the major atherosclerotic events separately. Mean reduction in LDL-c at 26–31 months was 0.85 mmol/L with ezetimibe plus simvastatin compared with placebo (a relative reduction of 61%).

4.4 IMPROVE-IT was a randomised, double-blind, active-controlled study in 18,144 patients with stabilised acute coronary syndrome. Patients were randomised in a 1:1 ratio to either ezetimibe 10 mg plus simvastatin 40 mg once daily or simvastatin 40 mg once daily. At a median follow-up of 6 years, ezetimibe plus simvastatin produced a 6.4% relative risk reduction in the primary efficacy endpoint composite of CV death, major coronary event, or non-fatal stroke compared with treatment with simvastatin alone (HR 0.936 [95% CI 0.89 to 0.99], p=0.016). There was a further reduction in LDL-c at 1 year of 0.43 mmol/L with ezetimibe plus simvastatin compared with simvastatin alone (a relative reduction of 24%).

4.5 SEAS was a randomised, double-blind, placebo-controlled study in 1873 patients with mild-to-moderate, asymptomatic aortic stenosis. Patients were randomised 1:1 to receive either ezetimibe 10 mg plus simvastatin 40 mg once daily or placebo once daily. Median follow-up was 52.2 months. The primary composite efficacy endpoint outcome measured major cardiovascular events, including death from CV causes, aortic-valve replacement, non-fatal MI, hospitalisation for unstable angina pectoris, heart failure, coronary-artery bypass grafting, percutaneous coronary intervention, and non-haemorrhagic stroke. The outcome occurred in 333 patients (35.3%) patients receiving ezetimibe plus simvastatin and in 355 patients (38.2%) receiving placebo (HR 0.96 [95% CI 0.83 to 1.12], p=0.59).

Study	Population	Intervention	Comparator	Median duration	Primary outcome
SHARP	Patients aged ≥40 with chronic kidney disease (n=9270)	Ezetimibe (10 mg) + simvastatin (20 mg)	Placebo	4.9 years	Reduction in major atherosclerotic events (RR 0.83, 95% CI 0.74; 0.94 p=0.0021)
IMPROVE-IT	Patients with stabilised ACS (n=18,144)	Ezetimibe (10 mg) + simvastatin (40 mg)	Simvastatin (40 mg)	6.0 years	Reduction in the composite of CV death, major coronary event, or non-fatal

					stroke (HR 0.936, 95% CI 0.887–0.988 p=0.016)
SEAS	Patients with asymptomatic, mild-to-moderate aortic-valve stenosis (n=1873)	Ezetimibe (10 mg/day) + simvastatin (40 mg/day)	Placebo	4.4 years	Composite of major cardiovascular events (HR 0.96, 95% CI 0.83–1.12 p=0.59)

ERG comments

4.6 The ERG stated the company's search strategy to identify relevant studies was broadly appropriate, but considered the search insufficiently sensitive. The ERG could not confirm that the company's approach was comprehensive in identifying relevant studies, and also noted that the company's submission did not provide any information on how ongoing studies were identified.

4.7 The ERG commented that the SEAS study would not have been retrieved by the company's search strategy. The ERG also identified 1 RCT which compared ezetimibe versus lovastatin versus ezetimibe plus lovastatin versus placebo in people with primary hypercholesterolaemia and was of the opinion that it should have been included in the systematic review. The ERG noted that the SEAS and the SHARP trials did not meet the eligibility criteria as they compare a combination of ezetimibe and simvastatin versus placebo.

4.8 The ERG noted that no attempt was made to consider revascularisation or quality of life outcomes in the company's submission even though these outcomes were specified in the NICE final scope.

4.9 The ERG considered the methods of data extraction to be appropriate. It also considered the criteria involved for quality assessment of studies to be appropriate, but identified some inconsistencies when assessing the risk of bias in trials.

Meta-analyses

4.10 The company performed meta-analyses for mean percent change from baseline in LDL-c and TC. The company compared ezetimibe 10 mg monotherapy with placebo and ezetimibe 10 mg plus statin with a matching statin dose. For each outcome, pairwise meta-analysis was performed using a random effects model. The company presented the relative treatment effect (mean difference and 95% CI) of ezetimibe vs placebo for each study, pooled mean difference and 95% CI for each subgroup. There was a large degree of heterogeneity in all analyses, as shown by a high result using the I^2 statistic. Data in the company's response to clarification superseded the original submission because some data had previously been double-counted. As reported in Table 4, the company's results showed that:

- Where ezetimibe was used as monotherapy, a meta-analysis of 12 RCTs revealed that ezetimibe provided a statistically significant 20.6% reduction in LDL-c.
- Where ezetimibe was used in combination with a statin, a meta-analysis of 17 RCTs revealed that ezetimibe provided a further statistically significant 15.6% lowering in LDL-c when combined with a statin versus statin alone.

Further details of the company's meta-analyses (for example, why certain studies were excluded) can be found in sections A6 and A7 of the company's clarification response.

Table 4 Results of the company's meta-analyses

	Mean difference in LDL-c (95% CI)	**Mean difference in TC (95% CI)**
Ezetimibe vs placebo	-20.59 (-22.13 to -19.05)	-16.07% (-17.01 to -15.13)
Ezetimibe vs matching statin dose	-15.60 (-17.05 to -14.13)	-12.17% (-12.90 to -11.45)

Source: Response to A7 in the company's clarification response

4.11 The company also identified 3 pre-planned subgroups: people with diabetes, people with CKD and people with heterozygous familial hypercholesterolaemia. In people with CKD and people with heterozygous familial hypercholesterolaemia, no meta-analyses were conducted because only 1 trial was identified in each subgroup (both trials were in combination with a statin). In people with diabetes, 1 trial using monotherapy and 3 trials in combination with a statin were identified. In patients with diabetes, the mean difference in LDL-c for ezetimibe plus statin compared with statin alone was -18.8% (95% CI -20.7 to -17.0). In patients without diabetes, the mean difference was -15.0% (95% CI -15.8 to -14.1). The estimated difference in treatment effect between patients with diabetes and those without was -3.87% (95% CI -5.85 to -1.90).

ERG comments

4.12 The ERG identified several studies included in the meta-analyses that did not meet the eligibility criteria specified in the company's submission because the patient population may not have had primary hypercholesterolaemia. In its response to clarification, the company justified the inclusion of these studies by suggesting that the patient populations were at high risk of CVD and relevant to clinical practice.

4.13 The ERG noted that the decision to exclude Asian studies may have been inconsistently applied in the company's submission. In response to clarification, the company argued that some Asian trials were not excluded because the study participants were considered similar to the demographics of the UK population. The ERG further noted that the external meta-analyses undertaken by CTTC and used to link clinical outcomes to LDL-c level included studies conducted in Asia.

4.14 The ERG stated that clinical outcomes such as mortality and cardiovascular events were not reported in the company's submission despite their eligibility for consideration as evidence. The ERG noted that a similar approach was used in technology appraisal guidance on

ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia (TA132) whereby clinical outcomes were linked to the lowering of LDL-c levels through an external meta-analysis (CTTC). The ERG was of the opinion that the approach used by the company in this appraisal was not fully justified because at least 3 trials in the company's submission assessed clinical outcomes. However, these had not been reported, and no searches for other external meta-analyses or clinical outcomes were attempted or discussed. The ERG was of the opinion that a direct meta-analysis of clinical outcomes would have provided more clinically relevant information. The ERG noted that relative effectiveness had been tested by the company in sensitivity analysis, and further investigated by the ERG in its exploratory analyses (see section 5.34).

4.15 The ERG noted high levels of statistical heterogeneity in the meta-analyses and observed that no attempt had been made to investigate the reasons for this.

4.16 The ERG believed that the company could have performed a network meta-analysis for LDL-c levels, and potentially included different statin doses as separate treatments within the network as well as other combinations of statins, placebo and lipid-regulating drugs.

Adverse effects of treatment

4.17 The company reported that no new safety concerns related to ezetimibe were raised in SHARP or IMPROVE-IT. It said that, in both of these trials, the safety findings were consistent with those described in the current summary of product characteristics for ezetimibe and simvastatin. It further stated that there were no meaningful differences between the treatment groups in clinical adverse events, including those leading to discontinuation of study drug and those reported as serious. Adverse events are summarised on pages 77–78 of the company submission.

Details of adverse events in all trials included in the evidence synthesis are given in appendix 13 of the company submission.

ERG comments

4.18 The ERG stated that the adverse events in each trial were narratively summarised in the company's systematic review. The ERG also noted when considering the rate of adverse events, there were no clear differences between groups.

5 Cost-effectiveness evidence

5.1 The company's base-case cost-effectiveness analyses included patients with primary hypercholesterolaemia in a primary prevention (without established CVD) or a secondary prevention population (with established CVD), using ezetimibe either:

- as a monotherapy in patients where a statin is considered inappropriate or is contraindicated or not tolerated;
- or, co-administered with a statin in people whose condition is not appropriately controlled with a statin alone, either after appropriate dose titration of initial statin therapy or because dose titration is inappropriate or not tolerated.

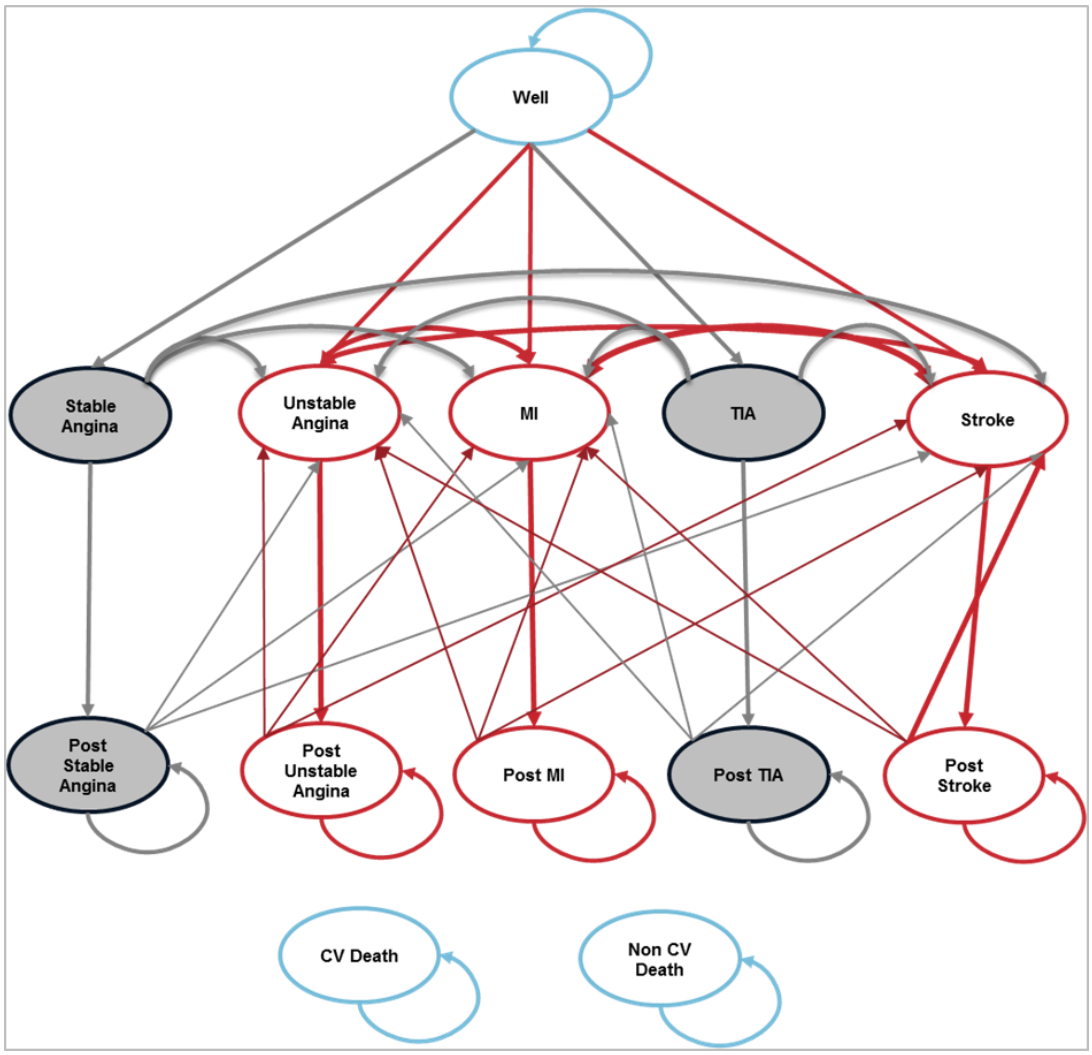
The company also discussed 3 further subgroups: primary prevention for people with diabetes, people with chronic kidney disease and people with heterozygous-familial hypercholesterolaemia.

Model structure

5.2 The company submitted a Markov model based on the modelling approaches developed for 2 previous NICE technology appraisals, Statins for the prevention of cardiovascular events (NICE technology appraisal 94) and Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia (NICE technology appraisal 132) (Figure 2). The cycle length was 1 year and a half cycle

correction was applied. An annual discount rate of 3.5% was applied to costs and health effects. The model had a lifetime time horizon and was conducted from an NHS and personal social services perspective.

Figure 2 Company's model structure



Stable angina and transient ischemic attack (TIA) health states (shown in grey) are additional health states explored in scenario analyses. All non-fatal health states can transition to the absorbing fatal health states.

Source: Figure 14 on page 104 of the company submission

5.3 For primary prevention, the baseline characteristics of the population in the model were informed by a Clinical Practice Research Datalink (CPRD) observational study which investigated statin prescribing in the primary prevention population in the UK (n=300,914). The starting age was 60 years and 46.4% of the cohort was female. All patients started in the

'well' state and were assumed not to have previously had any CV event. For the base case, the company applied a 20% 10-year risk of experiencing a CV event, as defined by the QRISK2 risk assessment tool. Patients could remain in the 'well' state, or transition to 1 of 3 major CV events health states (unstable angina, MI and stroke) or die. The effect of ezetimibe on stable angina and transient ischemic attack was explored in scenario analyses. Revascularisation was not modelled as a separate health state because it was captured in the cost data for the health states.

5.4 For secondary prevention, the baseline characteristics of the population in the model were derived from a UK retrospective observational study, with a starting age of 69 years and 34.6% of the cohort was female. People who had previously had a non-fatal CV event were categorised depending on whether they had experienced unstable angina, MI or a stroke. They could incur any of the other CV events in the next cycle or die; patients who did not experience any of these events moved into the respective post-event state.

5.5 For both primary and secondary prevention, the company modelled each non-fatal CV event in 2 stages. The first stage captured costs and impact on health-related quality of life in the first year following the event, and the second stage captured the long-term outcomes.

ERG comments

5.6 The ERG considered the structure of the economic model to be generally appropriate and generally consistent with previous models used to inform previous NICE guidance (including TA 132). However, it noted that the stable angina and TIA health states had been excluded from the company's base-case analysis.

5.7 The ERG stated that the populations modelled for primary prevention in the company's base-case analyses were generally appropriate, but noted that the model assumed that age, sex, and preventive CV risk were independent of the appropriateness, tolerance and response to statin

therapy. It further noted that the baseline characteristics for the secondary prevention population were applicable to the decision problem.

5.8 The ERG discussed the exclusion of any risk of stable angina or TIA in the company's base-case analysis. The company stated that this was due to lack of evidence for the effect of lipid lowering therapy on the incidence of stable angina and TIA. The ERG was of the opinion that it was inappropriate to assume zero risk of these events as morbidity, costs and downstream risks associated with the occurrence of stable angina and TIA may still influence comparisons. It was further noted that ezetimibe might reduce the risks of TIA and stable angina and may also influence the risk of other included events (other CV events) in the model. The ERG conducted exploratory analyses using different assumptions (see section 5.34).

Model details

Treatment

5.9 Ezetimibe was given in line with its marketing authorisation in the model. The comparator for ezetimibe monotherapy was 'no treatment' and the comparator for ezetimibe plus a statin was the maximum tolerated dose of statin alone. The company stated that using atorvastatin as the main statin in the base-case analyses reflected the NICE guideline on lipid modification and clinical practice:

- For primary prevention with ezetimibe plus a statin, atorvastatin 20 mg was used. The company explained that this was because the dose may not be up-titrated in the relevant population.
- For secondary prevention with ezetimibe plus a statin, atorvastatin 40 mg was used.
  - The company stated that although atorvastatin 80 mg is recommended in the NICE guideline on lipid modification and most

patients start on this dose post-event in clinical practice, the dose is often later reduced by GPs because of tolerability issues.

  - The company also considered that, the cholesterol of those patients that can tolerate atorvastatin 80 mg for primary or secondary prevention are likely to be appropriately controlled at this dose, and not require the add-on of ezetimibe.

- Lifetime treatment was assumed for both statins and ezetimibe (in line with each drug's summary of product characteristics).

Transition probabilities

5.10 The proportion of patients in each health state was determined by age-dependent time-variant transition matrices. In the base case, the 20% 10-year CVD risk defined by QRISK2 was converted into 1-year probabilities (that is, per cycle). The distribution of patients to primary CVD event health states and to initial health states in the secondary prevention analyses was based on Ward et al., 2007 (see tables 26 and 27 on pages 108–9 of the company submission for details). Secondary event transition probabilities were sourced from the NICE guideline on lipid modification (see table 29 on page 110 of the company submission). Time dependency was incorporated by cross-referencing age as a risk factor for mortality and increasing CV risk over time (the annual age-related increase was 0.03% for men and 0.008% for women). Mortality was incorporated by transitioning to the CV death and non-CV health states, which could occur at the end of each model cycle. Non-CV related death in the company's model was based on life tables from the Office of National Statistics.

Clinical variables and parameters

5.11 In NICE technology appraisal 132, a CTTC meta-analysis was used to model the treatment effect of ezetimibe and the comparators, linking the absolute reduction in LDL-c to the proportional reduction of CV events. Since the guidance was published, IMPROVE-IT and SHARP have investigated the effect of adding ezetimibe to statin therapy on reducing

CV events. However, the patient populations in IMPROVE-IT and SHARP were narrower than the population specified in ezetimibe's marketing authorization. The company considered that baseline characteristics, CV risk and treatment pathway for the population in the clinical trials would be different from the other populations (for example, primary prevention, high-risk primary hypercholesterolaemia patients with diabetes and those receiving ezetimibe monotherapy). Therefore, the company again chose to use the CTTC meta-analysis to model the effect of ezetimibe on CV outcomes linked to decreased LDL-c.

5.12 The Cholesterol Treatment Trialists' Collaboration (CTTC) has performed meta-analyses of statin RCTs to demonstrate the link between lowering LDL-c and reducing coronary events. The most recent CTTC meta-analysis from 2010 included 26 RCTs and showed that reducing LDL-c by 1.0 mmol/L with statin treatment reduced the risk of CV events, including death (Table 5).

Table 5 Individual endpoints from the CTTC meta-analysis

Endpoint	RR (96% CI), 1 mmol/L reduction in LDL-c
Non-fatal MI	0.74, 95% CI 0.69; 0.78 p<0.0001
Stroke	0.85, 95% CI 0.80;0.90 p<0.0001
Any CV death	0.86, 95% CI 0.82;0.90 p<0.0001
All-non CV deaths	0.97, 95% CI 0.91;1.03 p<0.0001

Source: Table 29 on page 111 of the company submission

5.13 For the comparator group in the ezetimibe monotherapy analyses, the baseline event rates were used for patients who had no treatment. For the comparator group in the ezetimibe plus add-on statin analyses, the baseline transition probabilities were adjusted to reflect the intensity of background statin therapy (that is, different maximum tolerated doses). The company then derived risk ratios to apply to the baseline risk data using RCT data with CV endpoints for the comparator arm (see table 30 on page 113 of the company submission). The company highlighted these

risk ratios focused on low, medium and high intensity groups of statins rather than specific statins and doses, leading to a simplifying assumption that different high-intensity doses of atorvastatin (20 mg, 40 mg and 80 mg) had the same relative risk reduction of CV events. The risk ratios used in the base case of the company's model are shown in Table 6. Identical risk ratios were used for primary and secondary prevention populations.

Table 6 Risk ratios for comparator arm for add-on to statin

Health state	Add-on to statin: risk ratios for high-intensity statin versus no treatment (add-on to statin)[a]
Unstable angina (non-fatal)	Same as MI (non-fatal)
MI (non-fatal)	0.46
Stroke (non-fatal)	0.80
CV death	0.72
Non-CV death	0.96
[a] Low-, medium- and high-intensity category definitions sourced from the NICE guideline on lipid modification. High-intensity statins include simvastatin 80 mg, atorvastatin 20 mg, atorvastatin 40 mg & atorvastatin 80 mg	

Source: Taken from Table 43 on page 141–2 of the company submission and the company's model

5.14 The company undertook 2 meta-analyses to estimate the relative clinical effectiveness of ezetimibe in LDL-c change from baseline:

- Ezetimibe 10 mg monotherapy versus placebo, based on 12 RCTs (n=3,094)
- Ezetimibe 10 mg plus statin versus matching statin dose, based on 17 RCTs (n=18,966).

The company incorporated the results of the meta-analyses into its economic model to estimate the LDL-c reduction with ezetimibe as monotherapy or in combination with a statin In its response to clarification, the company noted that correcting the meta-analysis values for double-counting had little impact on the mean difference values used in the economic model (see Table 7).

Table 7 Meta-analysis results used to inform reduction in LDL-c with ezetimibe

% reduction in LDL-c	Mean	N	95% confidence interval
Ezetimibe monotherapy	20.59%	3,094	[22.13 to 19.05]
Ezetimibe add on to statin	15.60%	18,966	[17.06 to 14.13]

Source: Table 1 on page 5 of the company's response for clarification

5.15 For the subgroup of patients with diabetes, the company also incorporated the results from the meta-analysis into its economic model, and assumed that ezetimibe plus a statin reduced LDL-c by an additional 18.83% (95% CI -20.66 to -17.00) compared with a statin alone.

Utility values

5.16 Baseline utility was time dependent and fell as the cohort aged. The company derived utility values for each health state from the literature (Table 8). The company stated that quality-adjusted life years for the cohort were computed for each annual cycle by multiplying the proportion of the cohort in each state by the heath state utility value weighted by corresponding age and sex related utility values for the cohort.

Table 8 Utility values used in the company's economic model

Health state	Utility value (mean)	Reference
Well	1	N/A
Unstable angina	0.77	Goodacre et al., 2004
Post-unstable angina	0.80	NCCPC 2008; Ara et al.
MI	0.76	Goodacre et al., 2004
Post-MI	0.799	MI plus Lacey et al., 2003
Stroke	0.50	Derived from Tengs et al. 2003
Post-stroke	0.628	Derived from Tengs et al. 2003
CV death	0	N/A
Non-CV death	0	N/A

Source: Table 34 on page 121 of the company submission

5.17 The company advised that it expected adverse reactions associated with ezetimibe to have minimal impact on patients' health-related quality of life and therefore did not apply any treatment-related utility decrements.

Costs

5.18 Drug acquisition costs were taken from the drug and pharmaceutical electronic market information tool (eMit) and the Monthly Index of Medical Specialities (MIMs). Monitoring costs were those used in the NICE guideline on lipid modification. Health-state costs were taken from published literature and inflated to 2013/2014 values (Table 9). Costs per cycle were summed using the same approach as was used for the QALYs. Higher monitoring and appointment costs were applied during the first year of both primary and secondary treatment than in subsequent years.

Table 9 Health-state costs in the company's economic model

Cost Inputs	Value	Reference
Well	£0.00	N/A
Stable angina	£242.38	Ara 2008
Post stable angina	£242.38	Ara 2008
Unstable angina	£575.21	Ara 2008
Post unstable angina	£245.06	NICE CG94
MI	£6,154.50	Palmer et al 2002
Post MI	£625.27	NICE CG94
TIA	£3,982.31	Luengo-Fernandez et al 2012
Post TIA	£1,386.22	Luengo-Fernandez et al 2012
Stroke	£14,151.26	Youman et al.2003
Post stroke	£3,927.73	Youman et al. 2003
CV death	£5,536.52	Ara 2008

Source: Table 38 on page 127 of the company submission

ERG comments

5.19 The ERG was concerned by the face validity of the CV risks increasing with age in the company's submission for the base-case analysis of the primary prevention population. The ERG estimated that the relative risk of any CV event in the model was 1.21 for a 10 year increase in age, alternatively using the Q-risk algorithm, the adjusted hazard ratio for a 10% increase in age was 1.66 for women and 1.59 for men (Hippisley-Cox et al, 2008). The ERG was of the opinion that the risk of primary CV events may not be increasing sharply enough with age. It suggested that

this caused counterintuitive outputs whereby the modelled ratio of CV to non-CV deaths falls by age, and that overall mortality appears low for high risk cohorts.

5.20 The ERG stated that the modelled annual increases in the risk of CV events caused by increasing age, may have been over-adjusted to account for increases in the risk of TIA and stroke which had not been included in the estimated annual risk increases. In its response for clarification, the company stated that the adjustment only occurred once. The ERG insisted that risk of CV events may have been inflated twice and had not been explained or justified by the company. The ERG explored these issues in an exploratory analysis (see section 5.34).

5.21 The ERG considered the approach to estimating treatment effect using reductions in LDL-c linked CV events for ezetimibe monotherapy and ezetimibe as an add-on to statin in the primary prevention cohort. The ERG thought the approach was justified on the grounds that no trials for ezetimibe versus placebo with CV events had been undertaken in the primary population or for the ezetimibe monotherapy in the secondary prevention population. For ezetimibe as an add-on to statin therapy in the secondary prevention cohort, the ERG were not convinced by the approach to estimate treatment effect using reductions in LDL-c linked to CV events (using the CTTC meta-analysis). The ERG stated that it could be argued that the IMPROVE-IT trial offers a more appropriate source of effectiveness data for the analysis. The ERG conducted exploratory analyses using different assumptions (see section 5.35).

5.22 The ERG stated that relationship of LDL-c reduction to non-CV events (sourced from the CTTC meta-analysis) suggested that the rate ratio was not statistically different from 1. The ERG stated that the relative effectiveness of ezetimibe versus no treatment or statin alone for the non-CV events that was included in the company's base case was inconsistent with previous modelling carried out in technology appraisal guidance on

ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia (TA132). The ERG conducted an exploratory analysis to investigate this (see section 5.34).

5.23 The ERG stated that the treatment effect of ezetimibe as an add-on to a statin compared with a statin alone was additive rather than multiplicative in the company's base-case analysis. To estimate the absolute further reduction in LDL-c associated with ezetimibe as an add-on to statin, the company had estimated the additive percentage reduction in LDL-c levels for statin plus ezetimibe compared with statin alone and had applied this to the modelled baseline (pre-treatment) LDL-c value.. The ERG noted that the company had also estimated a weighted average multiplicative percentage reduction in LDL-c levels achieved with statin plus ezetimibe compared with statin alone. When considering ezetimibe as an add-on treatment to statin therapy, the ERG stated that applying the weighted average multiplicative percentage reduction to typical LDL-c levels gave a smaller absolute further reduction than applying the additive effect to the baseline (pre-treatment) LDL-c level. The ERG conducted exploratory analyses using the multiplicative approach to estimate treatment effects in the primary and secondary population models (see section 5.35).

5.24 The ERG considered the selection of utility values for most health states to be reasonably well justified. The ERG believed that that a more appropriate baseline utility equation in the primary prevention models would have been for a non-CVD population instead of general population utility values. It noted that, for subsequent health states, the approach used to identify utility values was consistent with technology appraisal guidance on ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia (TA132). The ERG highlighted a potentially inappropriate method for combining age- and sex-specific baseline utility data with the health state utility data in the company's model. The ERG was of the opinion that the utility multipliers for the modelled CV states were not age-adjusted before they were

multiplicatively combined with the age-related baseline utility values. Furthermore, the ERG identified utility values from Ara and Brazier (2010) for people with and without CVD that it considered to be more representative and suitable. The ERG stated that alternative utility values were available for unstable angina, post unstable angina, MI and post-MI health states. The ERG conducted exploratory analyses using different assumptions (see section 5.34).

5.25 The ERG was aware that different sources of data were used for resources and costs. The ERG highlighted that the drug intervention and comparator costs were sourced from the drug and pharmaceutical electronic market information tool (eMit) or the Monthly Index of Medical Specialties (MIMS), and noted that the NICE methods guide states the preferred source for drugs prescribed predominantly in primary care is the NHS Drug Tariff. The ERG generally found the monitoring assumptions and costs to be appropriate, apart from the assumption that monitoring costs would be the same for ezetimibe and comparators in the first cycle (because people taking comparators would be continuing their current treatment). For health state costs, the ERG noted that costs associated with stroke and MI were based on old estimates inflated to the current cost year, which may lead to inaccuracy and fail to account for changes in cost driven by changes in practice over time. The ERG agreed with the company's base-case assumption that differences in adverse events are likely to be small and have little impact on the overall differences in cost between strategies.

Company's base-case results and sensitivity analysis

5.26 In its response to clarification, the company corrected an error in its model relating to the inflation of CV risk over time. This slightly increased the ICERs for the primary prevention population compared with the original submission (the error did not apply to the calculations for secondary prevention). The company's base-case results are presented in Table 10. For primary prevention, the corrected base-case ICERs were £30,129 per

QALY gained for ezetimibe monotherapy compared with no treatment and £58,473 per QALY gained for ezetimibe plus statin therapy compared with stain therapy alone. For secondary prevention, the base-case ICERs were £17,553 per QALY gained for ezetimibe monotherapy compared with no treatment and £30,940 per QALY gained for ezetimibe plus statin therapy compared with stain therapy alone.

Table 10 Company's base-case results

	Total Costs	Total QALYs	Total LYs	Incremental Costs	Incremental QALYs	ICER
Primary prevention – ezetimibe monotherapy[a]						
No treatment	£8,143	11.82	23.76	-	-	-
Ezetimibe 10mg	£13,332	11.99	24.23	£5,188	0.172	£30,129
Primary prevention – add on to statin[a]						
Atorvastatin 20mg	£8,359	12.10	24.57	-	-	-
Ezetimibe 10mg + Atorvastatin 20mg	£13,796	12.20	24.84	£5,437	0.093	£58,473
Secondary prevention – monotherapy						
No Treatment	£31,072	13.80	5.76	-	-	-
Ezetimibe 10mg	£34,957	14.49	5.98	£3,885	0.221	£17,553
Secondary prevention – add-on to statin						
Atorvastatin 40mg	£31,699	6.24	15.30	-	-	-
Ezetimibe 10mg + Atorvastatin 40mg	£35,811	6.37	15.73	£4,113	0.133	£30,940
[a] Includes age -adjusted risk fix provided in response to clarification						

Source: Tables 1–2 of the company clarification response and tables 47–48 of the company submission

5.27 The company explored parameter uncertainty in deterministic sensitivity analyses according to upper and lower bound values. For both primary and secondary prevention, the ICER was most sensitive to changes in risk

ratios for non-CV death and the discounting of costs and health benefits. The company also explored uncertainty using probabilistic sensitivity analyses (see pages 158–162 of the company submission for details). The probabilistic and deterministic ICERs for each patient population were broadly similar.

5.28 The ERG identified more recent EQ-5D utility values for the stroke and post stroke health states and in its response to clarification, the company applied these values, but this was found to have minimal impact on ICERS.

Company's subgroup results

5.29 The company also conducted subgroup analyses in people with diabetes, and people with chronic kidney disease (Table 11). For primary prevention, the corrected ICERs were £20,294 per QALY gained for ezetimibe monotherapy compared with no treatment and £31,352 per QALY gained for ezetimibe plus statin therapy compared with statin therapy alone. For secondary prevention in people with CKD, the ICER for ezetimibe plus statin therapy compared with stain therapy alone was £30,939 per QALY gained.

Table 11 Company's subgroup results for people with diabetes and CKD

	Total Costs	Total QALYs	Total LYs	Incremental costs	Incremental QALYs	ICER
Primary prevention with diabetes – monotherapy[a]						
No treatment	£8,709	9.36	18.00	-	-	-
Ezetimibe 10mg + Atorvastatin 20mg	£12,815	9.56	18.47	£4,106	0.202	£20,294
Primary prevention with diabetes – add-on to statin[a]						
Atorvastatin 20mg	£8,483	9.72	18.87	-	-	-
Ezetimibe 10mg + Atorvastatin 20mg	£12,843	9.86	19.20	£4,360	0.139	£31,352

Secondary prevention with CKD – add-on to statin						
Atorvastatin 20mg	£31,694	15.30	6.24	-	-	-
Ezetimibe 10mg + Atorvastatin 20mg	£35,807	15.73	6.37	£4,112	0.133	£30,939
[a] Includes age-adjusted risk fix provided in response to clarification						

Source: Tables 3 and 4 on page 22 of the company's clarification response and Table 83 on page 188 of the company submission

5.30 The company noted that people with heterozygous-familial hypercholesterolaemia have high LDL-c (at least 8 mmol/L) and are at significantly elevated CV risk. However, the company was unable to conduct cost-effectiveness analyses because of limited data available on the group's baseline risks. It provided a scenario analysis using the base-case population with high levels of LDL-c (see figure 41 on page 179 of the company submission).

ERG comments

5.31 The ERG was aware that the company had conducted both deterministic and probabilistic sensitivity analyses to evaluate the uncertainty around different parameters in the model. It noted a number of issues relating to the parameter distribution used for the probabilistic sensitivity analysis which resulted in a significant underestimation of uncertainty around the ICERS (see ERG report pages 99–100).

Company scenarios

5.32 The company undertook a range of scenario analyses. In the primary prevention population receiving ezetimibe monotherapy, the scenarios that had the greatest impact on the ICER (base case: £30,129 per QALY gained) were:

- Shortening the time horizon from lifetime to 10 years, which increased to £101,898 per QALY gained

- Decreasing the 10-year CV risk to 10%, which increased the ICER to £47,067 per QALY gained
- Assuming a price reduction of 75% after ezetimibe's patent expires, which decreased the ICER to £10,146 per QALY gained.

A similar pattern was seen in the scenario analyses in the primary prevention population receiving ezetimibe plus a statin, and in the secondary prevention populations receiving ezetimibe as monotherapy or in combination with a statin. A short description of the company's scenario analyses and accompanying rationale is given in Table 62 on page 164 of the company submission. Their results are presented in Tables 69–76 of the company submission (page 173 of the company submission onwards).

ERG comments

5.33 The ERG noted that the company attempted to validate the model using data from IMPROVE-IT and stated the company's model under-predicted the incidence of events such as MI, stroke and non-CV death compared with the trial. The ERG noted that no attempt was made to assess external validity of primary prevention model.

ERG exploratory analyses

5.34 The ERG undertook additional exploratory analyses (see Table 12). These were broadly undertaken in 4 steps:

- Step 1: Correction of apparent bugs in the model relating to the different half cycle correction, the annual age-related increase in the risk of CV events, the proportional distribution of first CV events by age and sex, and several distributions used in the probabilistic sensitivity analyses. The ICERs calculated by the ERG's exploratory analyses for primary and secondary prevention, monotherapy and as an add-on were modestly lower than the company's base case ICERs.
- Step 2: Including the TIA and stable angina states in the model with the relative treatment effects (for statins and ezetimibe) for these events

switched off. The ERG's exploratory analysis (after making the changes outlined in steps 1 and 2) had limited impact on the ICERs.

- Step 3: Applying age adjustment to alternative and newer health state utilities. The ERG's exploratory analysis (following the changes outlined in Steps 1, 2, 3) had a limited impact on the ICERs.
- Step 4: Assigning no effect of LDL-c reductions on non-CV related deaths, but applying relative treatment effects of ezetimibe and statins for TIA and stable angina. The ERG's exploratory analysis (following the changes outlined in Steps 1, 2, 3 and 4) showed the ICER for ezetimibe compared with no treatment was £31,939 per QALY gained and the ICER for ezetimibe as an add-on to a statin compared with a statin alone was £75,950 per QALY gained primary population. In the secondary prevention population, the ICER for ezetimibe compared with no treatment was £17,279 per QALY gained and the ICER for ezetimibe as an add-on to a statin compared with a statin alone was £36,042 per QALY gained

5.35 The ERG also conducted 2 additional scenarios:

Scenario A: Using multiplicative effects of ezetimibe (as an add-on) on post-statin LDL-c levels instead of an additive treatment effect. This models reduction in LDL-c associated with statin therapy, and then applies the estimated further multiplicative proportional reduction in LDL-c with ezetimibe from post statin LDL-c levels. The ERG exploratory analysis results outlined in Steps 1, 2 ,3 and 4 and Scenario A showed the ICERs for ezetimibe as an add-on to statin compared with the statin alone in the primary prevention population ranged from £43,230 to £116,246 per QALY gained. The ICERs for ezetimibe as an add-on to statin compared with the statin alone in the secondary prevention population ranged from £22,056 to £51,975 per QALY gained (see Table 13 for results).

Scenario B: Using the ezetimibe add-on to statin treatment effect on CV outcomes from the IMPROVE-IT trial instead of using LDL-c reduction to

link to CV outcomes (which used the CTTC meta-analysis). The ERG exploratory analysis results outlined in Steps 1, 2 ,3 and 4 and Scenario B showed the ICER for ezetimibe as an add-on to statin (using simvastatin) compared with the statin alone in the secondary prevention population was £115,354 per QALY gained (see Table 12 for results).

Table 12 ERG exploratory analyses: deterministic base-case ICERS (cost per QALY)

Scenario	Primary prevention		Secondary prevention	
	Monotherapy Ezetimibe 10mg compared with no treatment	**As an add-on to a statin** Atorvastatin 20mg compared with Ezetimibe 10mg + Atorvastatin 20mg	**Monotherapy** Ezetimibe 10mg compared with no treatment	**As an add-on to a statin** Atorvastatin 40mg compared with Ezetimibe 10mg + Atorvastatin 40mg
Company's base case[a]	30,129[a]	58,474[a]	17,553	30,940
Step 1 (as calculated by ERG)	26,253	48,886	16,563	29,351
Steps 1+2 (as calculated by ERG)	25,274	46,479	17,871	32,970
Steps 1+2+3 (as calculated by ERG)	25,479	47,045	14,988	27,937
Steps 1+2+3+4 (as calculated by ERG)	31,939	75,950	17,279	36,042
Scenario A	See Table 13			
Scenario B	-	-	-	115,354
[a] Includes age -adjusted risk fix provided in response to clarification for the primary prevention population				

Source: adapted from tables from tables 22 and 28 to 46 from the ERG report

Table 13 ERG exploratory analyses: deterministic base-case ICERs for scenario A (multiplicative effect of ezetimibe on LDL-c) (cost per QALY)

Scenario	Primary prevention: As an add-on to a statin Atorvastatin 20mg compared to Ezetimibe 10mg + Atorvastatin 20mg	Secondary prevention: As an add-on to a statin Atorvastatin 40mg compared to Ezetimibe 10mg + Atorvastatin 40mg
Company's base case (additive approach)[a]	58,474 [a]	30,940
Post statin LDL-c attainment of 2 mmol/L	116,246	51,975
Post statin LDL-c attainment of 2.5 mmol/L	81,021	37,755
Post statin LDL-c attainment of 3 mmol/L	58,522	28,496
Post statin LDL-c attainment of 3.5 mmol/L	43,230	22,056
[a] Includes age -adjusted risk fix provided in response to clarification for the primary prevention population		

Source: adapted from tables from tables 44, 45 from the ERG report

Innovation

5.36 Justifications for considering ezetimibe to be innovative:

- The company considered that ezetimibe was an innovation for the management of high cholesterol levels when launched in 2003 and should continue to be considered an innovation because it is the only non-statin to demonstrate an associated reduction in CV events.

5.37 Justification for not considering ezetimibe to be innovative:

- A professional organisation commented that ezetimibe is a unique drug because it is the only available drug in the cholesterol absorption inhibitor class; however, it is no longer considered innovative, or a step change in management.

6 Equality issues

6.1 No equality issues were raised during the scoping process or in the submissions, and none were described in the original guidance technology appraisal guidance on ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia (TA132)

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia [ID627]

Merck Sharp & Dohme: Evidence submission

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Contents

Tables and figures

Abbreviations

ACC	American College of Cardiology
ACS	Acute Coronary Syndrome
AE	Adverse Event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
AUC	Area under the curve
BHF	British Heart Foundation
BMA	British Medical Association
BMI	Body Mass Index
BNF	British National Formulary
CBAG	Coronary Artery Bypass Grafting
CEA	Cost-Effectiveness Analysis
CFB	Change from baseline
CHD	Coronary Heart Disease
CHF	Congestive Heart Failure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CK	Creatine Kinase
CKD	Chronic Kidney Disease
CPK	Creatine Phosphokinase
CPRD	Clinical Practice Research Datalink
CSR	Clinical Study Report
CTTC	Cholesterol Treatment Trialists Collaboration
CUA	Cost Utility Analysis
CV	Cardiovascular
CVD	Cardiovascular disease
DM	Diabetes mellitus
DSU	Decision Support Unit
EAS	European Atherosclerosis Society
EMA	European Medicines Agency
ERG	Evidence Review Group
ESC	European Society of Cardiology
EQ-5D	EuroQoL 5 Dimensions
FAS	Full-analysis set
FDA	Food and Drug Administration
FH	Familial hypercholesterolaemia
GDG	Guideline Development Group
GFR	Glomerular Filtration Rate
HDL	High-density lipoprotein
HeFH	Heterozygous Familial Hypercholesterolaemia
HF	Heart Failure
HR	Hazard ratio
HRQoL	Health-related quality of life
HoFH	Homozygous Familial Hypercholesterolaemia
HSCIC	Health & Social Care Information Centre
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
IHD	Ischaemic Heart Disease

ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	Intention-to-treat
JBS	Joint British Societies'
KM	Kaplan-Meier
LDL-c	Low-density lipoprotein cholesterol
LLT	Lipid lowering therapy
LMT	Lipid modifying therapy
LYG	Life years gained
MD	Mean difference
MHRA	Medicines and Healthcare Products Regulatory Agency
MI	Myocardial Infarction
MIMS	Monthly Index of Medical Specialities
MSD	Merck Sharp and Dohme Ltd
MTA	Multiple Technology Appraisal
MVE	Major Vascular Events
NCCPC	National Collaborating Centre for Primary Care
NDA	National Diabetes Audit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NSTEACS	Non-ST-Segment Elevation Acute Coronary Syndrome
NSTEMI	Non-ST-Segment Elevation Myocardial Infarction
NT	No treatment
ONS	Office for National Statistics
OR	Odds ratio
PAD	Peripheral Artery Disease
PCI	Percutaneous Coronary Intervention
PSA	Probabilistic Sensitivity Analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PVD	Peripheral Vascular Disease
QALY(s)	Quality-Adjusted Life Year(s)
QOF	Quality and Outcomes Framework
RCT	Randomised Controlled Trial
SCORE	Systematic Coronary Risk Evaluation
SD	Standard Deviation
SE	Standard Error
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
STA	Single Technology Appraisal
STEMI	ST-Segment Elevation Myocardial Infarction
TA	Technology Appraisal
TC	Total Cholesterol
TG	Triglycerides
TIA	Transient Ischaemic Attack
TTO	Time Trade Off
UA	Unstable Angina
VAT	Value-Added Tax
RR	Target Response Rate
VLDL	Very-low-density lipoprotein
WHO	World Health Organisation

1 Executive summary

Brief background to the condition

Hypercholesterolaemia is defined as a form of dyslipidaemia characterised by abnormalities of lipoprotein transport associated with high levels of cholesterol, especially LDL-c and TC in plasma.[1] Primary hypercholesterolaemia is related to the interaction between genetic predisposition and environmental factors that lead to raised cholesterol. There is compelling evidence that the reduction of LDL-c and TC can prevent cardiovascular disease (CVD). CVD is a leading cause of mortality in the Western world, and in 2013 in England and Wales, approximately 28% of deaths were caused by CVD, with the cost of treating CVD in the NHS more than £7.2 billion.[2;3] Death rates from CVD have fallen by more than 50% in England since 1993, however CVD remains the major cause of morbidity and mortality in the population and continues to be a major focus by the Department of Health.[4] Cholesterol is a major modifiable risk factor that contributes to an individual's risk of developing CVD, therefore the control of cholesterol levels in the population is critical in reducing CVD.

A number of initiatives including national QOF targets and clinical guidelines have focused on target levels for cholesterol; however, a large number of patients are still not reaching recommended cholesterol levels. In 2011, the Health Survey for England reported that 60% of men and 38% of women with CVD (the expectation is that the majority had received advice on lifestyle modification and drug treatment where deemed advisable) had TC levels below 5 mmol/L (the NICE CG67[5] 'audit level' for those with CVD, diabetes or hypertension who are on drug treatment), while only 27% and 10% respectively had levels below 4 mmol/L (the then-NICE 'target level' for this high risk group) in 2011. [6]

Generic statins are considered the standard of care in the UK for managing a person's TC and LDL-c, and their use has contributed significantly to the reduction in CVD mortality rates. The evidence base for statins is considerable and randomised controlled trials (RCTs) have demonstrated their effectiveness in lowering TC, LDL-c and reducing clinical endpoints.

Ezetimibe has been available since 2003 for the treatment of primary (familial and non-familial) hypercholesterolaemia, is well tolerated and has an established role in lipid management when co-administered with a statin and in monotherapy where statin therapy is inappropriate or is contraindicated or not tolerated. The evidence base for ezetimibe is substantial, and includes RCTs that demonstrate the effectiveness in lowering TC and LDL-c in a broad population, reduction of CV events, as well as the first non-statin to show an incremental clinical benefit when used in combination with a statin. In 2007, ezetimibe was appraised by NICE and was found to be a clinical and cost effective use of NHS resources.[7]

1.1 Statement of decision problem

To evaluate the clinical and cost effectiveness of ezetimibe within its licensed indication for treating primary hypercholesterolaemia in adults. The decision problem addressed in the submission is presented in Table 1 .

Table 1 The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with primary heterozygous familial or non-familial hypercholesterolaemia: • whose condition is not appropriately controlled with a statin alone **or** • in whom a statin is considered inappropriate or is not tolerated	People with primary heterozygous familial or non-familial hypercholesterolaemia: • Co-administered with a statin in people whose condition is not appropriately controlled with a statin alone, either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance. • As monotherapy in patients where a statin is considered inappropriate or is contraindicated or not tolerated. The following populations are considered: • Primary prevention (10-30% 10-year risk of developing CVD) • Secondary prevention	The monotherapy population is the same as the final scope. The population co-administration with a statin has been focused to consider patients not appropriately controlled with a statin alone where up-titration is inappropriate or not tolerated. This is in-line with clinical practice and updated NICE guidance, Clinical Guideline CG181.[8] The base case populations for primary and secondary prevention are in-line with NICE guidance.

		(established CVD)	
Intervention	Ezetimibe alone or in combination with a statin.	• Ezetimibe monotherapy • Ezetimibe in combination with a statin	In line with NICE final scope
Comparator (s)	For people with primary heterozygous familial or non-familial hypercholesterolaemia whose condition is not appropriately controlled with a statin alone: • Optimal statin therapy For people with primary heterozygous familial or non-familial hypercholesterolaemia in whom a statin is considered inappropriate or is not tolerated: • Other lipid-regulating drugs	For people with primary heterozygous familial or non-familial hypercholesterolaemia whose condition is not appropriately controlled with a statin alone: • Optimal statin therapy (maximum tolerated dose) For people with primary heterozygous familial or non-familial hypercholesterolaemia in whom a statin is considered inappropriate or is not tolerated: • No treatment	Ezetimibe monotherapy: Once a statin is considered inappropriate or not tolerated, then available pharmacological options (apart from ezetimibe) include fibrates, nicotinic acid, bile acid sequestrants and Omega-3 fatty acid derivatives. The limited evidence base for the use of the above provides no evidence that they reduce CV outcomes. The updated NICE guidance, Clinical Guideline CG181 does not recommend the use of nicotinic acid, bile acid sequestrants or omega-3 fatty acid compounds.[8] Additionally, CG181 does not routinely recommend the use of fibrates, which are more applicable in treating hypertriglyceridaemia, so if patients are intolerant or contraindicated to statins, then CG181 recommends ezetimibe as the only treatment option. When considering the above comparators for the review of ezetimibe TA132[7] it was

			concluded that the above comparators would add costs with no benefit and for this reason no treatment was chosen as the comparator.
Outcomes	The outcome measures to be considered include: • Plasma lipid and lipoprotein levels, including LDL cholesterol, non-HDL cholesterol, apolipoprotein B and lipoprotein a • Requirement of procedures including LDL apheresis and revascularisation • Fatal and non-fatal cardiovascular events • Coronary events • Stroke • Mortality • Adverse effects of treatment • Health-related quality of life	Outcome measures: • Mean % change in LDL-c and TC, apolipoprotein B and lipoprotein A • Survival/mortality • Fatal and non-fatal cardiovascular events • Stroke • Adverse effects of treatment • Health-related quality of life	• non-HDL-c was not considered as an outcome as this was not routinely reported in the ezetimibe clinical trials, whose primary endpoints are generally based on change in LDL-c levels from baseline and attainment of goals based on a patient's LDL-c level. Additionally, there is a challenge that non-HDL-c is not routinely requested or reported. • Coronary events is considered under non-fatal CV events. • LDL-c apheresis is primarily used in patients with HoFH. HoFH is not relevant to this appraisal. • Revascularisation has been considered as part of the health state costs applied in the cost-effectiveness analysis.
Economic	The reference case stipulates that the cost effectiveness of treatments	• The cost-effectiveness analyses is expressed as incremental	Consistent with NICE final scope

analysis	should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	cost per quality-adjusted life year (QALY) • Lifetime time horizon • NHS and Personal Social Services perspective	
Subgroups to be considered	If the evidence allows, consideration will be given to the following subgroups: • Presence or risk of cardiovascular disease • People with heterozygous familial hypercholesterolaemia • People with statin intolerance • Severity of	Where evidence allows, analysis of subgroups will be considered in: • Primary prevention in people with diabetes • People with CKD • People with heterozygous-familial hypercholesterolaemia	The presence or risk of CVD is considered by using the primary prevention population 10-30% 10-year CV risk. People with statin intolerance are considered in the base-case as ezetimibe monotherapy population. Severity of hypercholesterolaemia is considered as part of the CV risk score and baseline LDL-c values will be modelled. Subgroups for diabetes and CKD are considered if evidence allows. This is after consultee feedback on the draft scope, as

	hypercholesterolaemia		well as an acknowledgement that people with CKD and/or diabetes are at greater risk of adverse events as a result of taking high dose statins than people without renal deficiency (also restrictions in the SPC of statins for the CKD population).
Special considerations including issues related to equity or equality	None	None	In line with NICE final scope

1.2 Description of the technology being appraised

The technology being appraised is described in Table 2 below:

Table 2 Technology being appraised

UK approved name and brand name	Ezetimibe (Ezetrol®)
Marketing authorisation/CE mark status	Marketing authorisation number: PL 00025/0609
Indications and any restriction(s) as described in the summary of product characteristics	***Primary Hypercholesterolaemia*** Ezetrol, co-administered with an HMG-CoA reductase inhibitor (statin) is indicated as adjunctive therapy to diet for use in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia who are not appropriately controlled with a statin alone. Ezetrol monotherapy is indicated as adjunctive therapy to diet for use in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia in whom a statin is considered inappropriate or is not tolerated. *The full marketing authorisation wording can be found in section 2.2.1. The above wording relates to the current appraisal.*
Method of administration and dosage	Ezetimibe is administered orally at a dose of 10 mg once daily.

1.3 Summary of the clinical effectiveness analysis

The evidence presented here demonstrates that ezetimibe provides a valuable treatment option for patients that require cholesterol lowering in order to reduce their risk of developing CVD or a CV related event.

The IMPROVE-IT and SHARP trials provide evidence demonstrating the clinical benefit of ezetimibe. Additionally, both trials provide support for the LDL hypothesis from the CTTC meta-analysis which shows that a reduction in LDL-c of 1 mmol/L reduces the incidence of

major vascular events by 22%.[9] This analysis utilises the use of a large body of RCT evidence for ezetimibe that demonstrates the consistent LDL-c lowering in a wide population, with associated event reduction.

The SHARP trial was a multicentre, randomised, double-blind, placebo-control study in 9,270 patients with CKD and unknown history of myocardial infarction or coronary revascularisation. All subjects entering the study were assigned to randomised, double-blind treatment in a 4:4:1 ratio to either ezetimibe/simvastatin combination 10/20 mg once daily, placebo once daily, or simvastatin 20 mg to assess the safety of ezetimibe during the first year. The simvastatin 20 mg arm was re-randomised after one year (no safety concerns identified) to either ezetimibe/simvastatin 10/20 mg once daily or placebo once daily. The median duration of follow-up was 4.9 years, after which ezetimibe/simvastatin resulted in a 17% proportional reduction in the primary efficacy endpoint composite of CHD death, non-fatal MI, revascularization, or non-fatal non-haemorrhagic stroke compared to treatment with placebo (RR 0.83, 95% CI 0.74; 0.94 *p*=0.0021). In addition to the clinical endpoints the SHARP trial showed a mean reduction in LDL-c of 61% when ezetimibe was combined with simvastatin versus placebo. The trial revealed no new safety findings related to study therapy.[10]

The IMPROVE-IT trial was a multicentre, randomised, double-blind, active-control study in 18,144 individuals presenting with stabilised acute coronary syndrome (ACS). All individuals entering the study were assigned to randomised, double-blind treatment in a 1:1 ratio to either ezetimibe/simvastatin combination 10/40 mg once daily or simvastatin 40 mg once daily. The median follow-up was 6 years, after which treatment with ezetimibe/simvastatin resulted in a 6.4% relative risk reduction in the primary efficacy endpoint composite of CV death, major coronary event, or non-fatal stroke compared to treatment with simvastatin alone (HR 0.936, 95% CI 0.89; 0.99 *p*=0.016). In addition to the clinical endpoints the IMPROVE-IT trial showed a further reduction in LDL-c of 24% when ezetimibe was combined with simvastatin versus simvastatin alone. The trial revealed no new safety findings related to study therapy.[11]

The majority of the remaining ezetimibe RCTs assess the cholesterol lowering ability of ezetimibe in various populations. These have been systematically reviewed and analysed; relevant for this appraisal:

- Where ezetimibe is used as monotherapy, a meta-analysis of 15 RCTs revealed that ezetimibe provides a significant 20.4% reduction in LDL-c.
- Where ezetimibe is used in combination with a statin, a meta-analysis of 18 RCTs revealed that ezetimibe provides a further 23.5% lowering in LDL-c when combined with a statin versus statin alone.

The clinical evidence presented in this submission demonstrates that ezetimibe continues to provide the only valuable treatment option other than a statin that can lower LDL-c and provide clinical benefit to patients where significant unmet need remains.

1.4 Summary of the cost-effectiveness analysis

The cost-effectiveness of ezetimibe as a monotherapy or co-administered with a statin has been demonstrated previously in the original NICE MTA in 2007.[7] The updated cost-effectiveness analyses confirm the original findings that ezetimibe is cost-effective in high-risk groups where dose titration of the statin is inappropriate and/or limited by intolerance (such as people with CKD), or in monotherapy for those that are intolerant or contraindicated to statins.

A Markov model over a lifetime time horizon has been developed based on the modelling approaches developed by Ward *et al.* for TA94[12] (statins) and Ara *et al.* for the original TA132 review. The model considers the benefits of ezetimibe treatment on the reduction of major CV events (unstable angina, myocardial infarction and stroke). Patients enter the model as primary prevention (no established CVD) in the 'Well' health state or as secondary prevention (with established CVD), and can transition to non-fatal CV or fatal (CV or non-CV death) health states.

Whilst the IMPROVE-IT and SHARP trials provide evidence demonstrating the clinical benefit of ezetimibe, these studies were conducted in sub-populations of the wider ezetimibe license. Extrapolation of the CV event reduction from these trials to the wider ezetimibe co-administered with a statin population is challenging as baseline characteristics, CV risk and the patient pathway would be significantly different to the other populations, e.g. primary prevention and treatment of high risk primary hypercholesterolaemia patients with diabetes, as well as monotherapy. As the clinical evidence has demonstrated that the benefit

associated with ezetimibe is consistent with the CTTC meta-analysis, the association between absolute LDL-c reduction and CV risk reductions established by CTTC has been used in the model, employing the percentage LDL-c reductions from the meta-analyses performed. The recent CTTC analysis from 2010 that included 26 RCTs showed that a reduction in LDL-c of 1.0 mmol/L reduced the risk of major vascular events by up to 22%.

Section 5 details the development of the cost-effectiveness model for ezeimibe, with Table 3 below presenting the results for the four populations in the base case. In the base case analysis for the primary prevention population at a 10-year CV risk of 20%, the ICER is £29,286 for monotherapy and £56,394 for add-on to statin. In the secondary prevention population, the ICER is £17,553 for monotherapy and £30,940 for ezetimibe co-administered with statin treatment. For the add-on to statin analysis where a lower dose of atorvastatin is applied (i.e atorvastatin 20 mg) the results are expected to be an underestimate. This is because the statin relative risk estimates applied reflect a pooled analysis of all high intensity doses of atorvastatin (20 – 80 mg).

Table 3 Incremental cost-effectiveness results

Technologies (and comparators	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
Primary Prevention population, ezetimibe monotherapy							
No Treatment	£7,827	23.89	11.88	-	-	-	-
Ezetimibe 10mg	£12,997	24.36	12.05	£5,169	0.474	0.177	£29,286
Primary Prevention population, add-on to statin							
Atorvastatin 20mg	£7,891	24.73	12.18	-	-	-	-
Ezetimibe 10mg + Atorvastatin 20mg	£13,320	24.99	12.27	£5,429	0.268	0.096	£56,394
Secondary Prevention, ezetimibe monotherapy							
No Treatment	£31,072	13.80	5.76	-	-	-	-
Ezetimibe 10mg	£34,957	14.49	5.98	£3,885	0.683	0.221	£17,553
Secondary Prevention, add-on to statin							
Atorvastatin 40mg	£31,699	6.24	15.30	-	-	-	-
Ezetimibe 10mg + Atorvastatin 40mg	£35,811	6.37	15.73	£4,113	0.422	0.133	£30,940

There are three relevant sub-groups due to the differences in the baseline CV risk and the lipid-modification management strategies appropriate for these sub-groups: primary prevention for people with diabetes, people with CKD and patients with HeFH. In the base

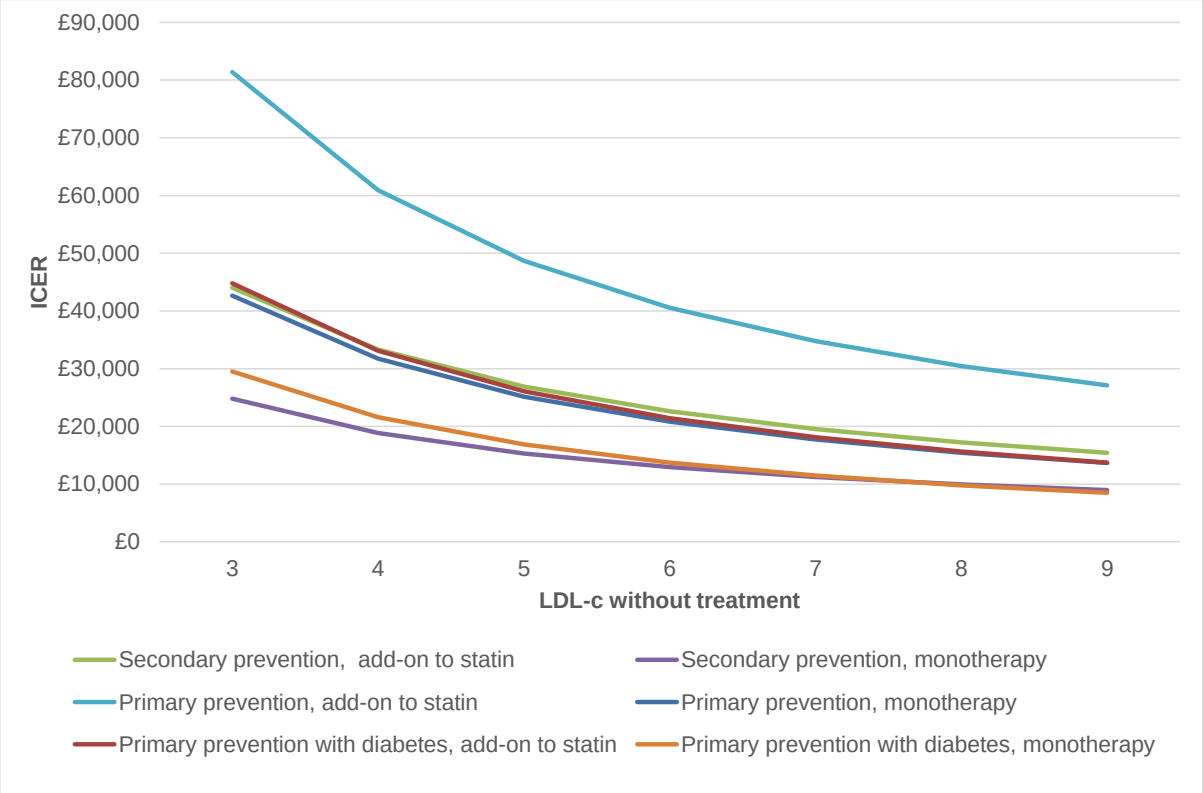
case analysis for the primary prevention population with diabetes, at a 10-year CV risk of 20%, the ICER is £19,852 for monotherapy and £30,503 for add-on to statin (Table 4). No specific analyses were possible for people with type 1 diabetes, however, the elevated risk associated with these patients is reflected by the type 2 diabetes analyses. An analysis reflecting a maximum atorvastatin dose of atorvastatin 20mg has been evaluated for the secondary prevention population with CKD, with an estimated ICER of £30,953. This is a conservatative estimate as the baseline risk is expected to be an underestimate for this population because no specific data for this group was identified. Patients with HeFH have extremely high LDL-c levels, and while no specific analyses for this subgroup was possible due to lack of baseline risk data, increased LDL-c levels to such high levels, has shown that ezetimibe is a cost-effective option in the analyses.

Table 4 Incremental cost-effectiveness results (sub-groups)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
Primary prevention for people with type 2 diabetes, monotherapy							
No Treatment	£8,494	18.07	9.39	-	-	-	-
Ezetimibe 10mg	£12,582	18.55	9.60	£4,089	0.478	0.206	£19,852
Primary prevention for people with type 2 diabetes, add-on to statin							
Atorvastatin 20mg	£8,512	18.96	9.77	-	-	-	-
Ezetimibe 10mg + Atorvastatin 20mg	£12,496	19.30	9.91	£4,345	0.334	0.142	£30,503
Secondary prevention for people with CKD, add-on to statin							
Atorvastatin 20mg	£31,694	15.30	6.24	-	-	-	-
Ezetimibe 10mg + Atorvastatin 20mg	£35,807	15.73	6.37	£4,112	0.422	0.133	£30,939

At higher baseline LDL-levels for all poulations examined and higher 10-year risk levels for the primary prevention population, the cost-effectiveness of ezetimibe increases (as shown in Figure 1).

Figure 1 Incremental cost-effectiveness ratios (ICERs), by varying baseline LDL-c levels



Finally, the patent expiry for ezetimibe is anticipated in April 2018 and significant price falls are expected in-line with other lipid-lowering therapies. The ICERs for ezetimibe fall substantially under the £20,000 per QALY threshold when this is applied in year 3 onwards of the analysis.

Overall, the evidence presented in this submission demonstrates that ezetimibe is a clinically and cost-effective option in high-risk groups where dose titration of the statin is inappropriate and/or limited by intolerance (such as people with CKD), or in monotherapy for those that are intolerant or contraindicated to statins.

2 The technology

2.1 Description of the technology

Ezetimibe (Ezetrol®) is a 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, ezetimibe can also be combined with a statin (which inhibits the synthesis of cholesterol) to provide complementary cholesterol reduction. Ezetimibe is administered orally at a dose of 10 mg once daily. A fixed-dose combination tablet containing ezetimibe and simvastatin is available (Inegy, MSD Limited). The pertinent details for Inegy can be found in Appendix 1

2.2 Marketing authorisation/CE marking and health technology assessment

2.2.1 Current marketing authorisation of ezetimibe

Primary Hypercholesterolaemia

Ezetrol, co-administered with an HMG-CoA reductase inhibitor (statin) is indicated as adjunctive therapy to diet for use in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia who are not appropriately controlled with a statin alone.

Ezetrol monotherapy is indicated as adjunctive therapy to diet for use in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia in whom a statin is considered inappropriate or is not tolerated.

Homozygous Familial Hypercholesterolaemia (HoFH)

Ezetrol co-administered with a statin, is indicated as adjunctive therapy to diet for use in patients with HoFH. Patients may also receive adjunctive treatments (e.g. LDL apheresis).

Homozygous Sitosterolaemia (phytosterolaemia)

Ezetrol is indicated as adjunctive therapy to diet for use in patients with homozygous familial sitosterolaemia.

2.2.2 Proposed change in therapeutic indication

A change to the licensed indication for ezetimibe was submitted to the EMA on 29 April 2015, with an anticipated approval of [redacted]. The following changes are highlighted below (commercial in confidence):

Ezetimibe

Primary Hypercholesterolaemia

Ezetrol, co-administered with an HMG-CoA reductase inhibitor (statin) is indicated as adjunctive therapy to diet for use in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia who are not appropriately controlled with a statin alone.

Ezetrol monotherapy is indicated as adjunctive therapy to diet for use in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia in whom a statin is considered inappropriate or is not tolerated.

[redacted]

Homozygous Familial Hypercholesterolaemia (HoFH)

Ezetrol co-administered with a statin, is indicated as adjunctive therapy to diet for use in patients with HoFH. Patients may also receive adjunctive treatments (e.g. LDL apheresis).

Homozygous Sitosterolaemia (phytosterolaemia)

Ezetrol is indicated as adjunctive therapy to diet for use in patients with homozygous familial sitosterolaemia.

Dosage and administration

Ezetimibe

The recommended dose is one Ezetrol 10 mg tablet daily. Ezetrol can be administered orally at any time of the day, with or without food. When Ezetrol is added to a statin, either the indicated usual initial dose of that particular statin or the already established higher statin dose should be continued. In this setting, the dosage instructions for that particular statin should be consulted.

2.2.3 Contraindications included in the summary of product characteristics (SmPC)

Ezetimibe

- Hypersensitivity to the active substance or to any of the excipients.
- When Ezetrol is co-administered with a statin, please refer to the SPC for that particular medicinal product.
- Therapy with Ezetrol co-administered with a statin is contraindicated during pregnancy and lactation.
- Ezetrol co-administered with a statin is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases.

2.2.4 Inclusion of SmPC

The current SmPC has been included as an appendix – see Appendix 2.

2.2.5 EMA assessment report

Not applicable for the original label and MSD anticipate to receive the EMA assessment report for the change in indication around CHMP opinion in [redacted].

2.2.6 Summary of the main issues discussed by the regulatory authorities

Not applicable

2.2.8 Regulatory approval outside the UK

Ezetimibe completed the EU Mutual Recognition Procedure (MRP) in 2003 and has also been approved by the FDA.

2.2.9 Other health technology assessments in the UK

Ezetimibe was appraised by the SMC in September 2003 and the SMC advice[13] was superseded by NICE MTA TA132[7].

2.3 Administration and costs of the technology

Ezetimibe is administered orally at a dose of 10 mg once daily. It is routinely prescribed in primary care and may also be prescribed in secondary care by specialists such as cardiologists and lipidologists. There are no specific administration requirements for ezetimibe. Table 5 below summarises the administration and technology costs.

Table 5 Costs of the technology being appraised

	Cost	Source
Pharmaceutical formulation	Tablet	SmPC[14]
Annual acquisition cost (excluding VAT)	£343.20	MIMS, March 2015[15]
Method of administration	Oral	SmPC[14]
Doses	10 mg	SmPC[14]
Dosing frequency	Once daily	SmPC[14]
Dose adjustments	None	SmPC[14]
Anticipated care setting	Primary Care	Current clinical practice

2.4 Changes in service provision and management

2.4.1 Additional tests or investigations needed

Additional tests, investigations or infrastructure in the NHS are not needed for implementation of the technology. Ezetimibe has been available since April 2003 and is considered part of standard of care within the lipid modification therapy pathway for the primary and secondary prevention of CVD.

2.4.2 Main resource use to the NHS associated with the technology being appraised

Since the original marketing authorisation in 2003 and NICE technology appraisal of ezetimibe in 2007 (TA132[7]) there have been significant changes in the management, pathway, environment and available treatment options for patients that require lipid-modifying therapy. Table 6 details the significant changes from TA132[7] to this review.

Table 6 Differences between the approach for TA132 and the current environment

TA132[7] approach (Nov 2007)	Approach for the review of TA132 (June 2015)	Comments
Populations. TA132 considered five distinct populations for the cost-effectiveness analysis. 1. Ezetimibe co-administered with current statin therapy versus current statin therapy titrated to the next dose (generic simvastatin) 2. Ezetimibe monotherapy versus no treatment 3. Ezetimibe co-administered with non-proprietary simvastatin versus atorvastatin 4. Ezetimibe co-administered with current statin therapy versus current statin therapy alone 5. Ezetimibe co-administered with rosuvastatin versus rosuvastatin monotherapy	For the review of TA132: 1. Not considered 2. Ezetimibe monotherapy versus no treatment 3. Not considered 4. Ezetimibe co-administered with current statin therapy versus current statin therapy alone 5. Not considered	1. This population was not considered, as according to clinical practice and NICE guidance (CG181) if a patient can tolerate up-titration of their statin to the next dose, this should be investigated prior to the addition of ezetimibe.[8] 2. Considered in this appraisal 3. Atorvastatin is now generic and first-line option for treatment 4. Considered in this appraisal 5. NICE concluded in CG181 that due to the availability of low cost statins, atorvastatin should be considered over rosuvastatin.[8] There is however historical usage of ezetimibe in combination with rosuvastatin. The focus of this appraisal is on the first choice statin option (Atorvastatin).
For the co-administration with a statin population in the 2007 appraisal of ezetimibe,	For the co-administration with a statin population, this review will only consider patients that cannot	In the 2007 appraisal of ezetimibe there were limited generic statin options, therefore it was

up-titration of the statin dose was considered a comparator.	increase their statin dose due to intolerance or contraindication.	appropriate to consider up-titration of the statin dose as a comparator to adding ezetimibe in the co-administer with a statin population. In today's environment there are many low-cost statin options, therefore increasing the dose of statin should always be considered before adding ezetimibe. For this reason MSD consider up-titration of a statin to not be a comparator to co-administration of ezetimibe with a statin.
Simvastatin was considered standard of care.	Atorvastatin 10 – 80 mg is considered standard of care depending on the population.	Since atorvastatin became generic in May 2012 it has replaced simvastatin as the first-line statin of choice, and is also the first statin of choice in CG181.[8]
CV risk. Clinical practice and guidelines focused on a person's 10-year risk of CVD being over/equal to 20% before starting treatment with lipid-lowering therapy.	The appraisal will consider the use of ezetimibe with 10-30% 10-year risk of CVD to align with current guidance.	Since the original appraisal of ezetimibe (TA132)[7], NICE Clinical Guideline CG181 has changed so that lipid modifying treatment can be considered for people whose 10-year risk of developing CVD is 10% or greater.[8] Whilst the Marketing Authorisation for ezetimibe does not consider a person's risk of CVD for treatment with ezetimibe, this appraisal will consider people whose 10-year risk of developing CVD is 10-30% to reflect the evolution of clinical practice.

Historically, in clinical practice Framingham risk scoring has been used to estimate a person's risk of CVD [5]	QRISK2 will be used.	In line with CG181 QRISK2 is the risk scoring tool of choice to assess CVD risk for the primary prevention.[8]

In the NICE review of ezetimibe TA132[7] in 2007 it was noted that there was no evidence of the effectiveness of ezetimibe in reducing clinical events, therefore the Cholesterol Treatment Trialists Collaboration (CTTC) meta-analysis was used to link changes in lipid measurements to CV events and an assumption was made that the relationship between statin induced changes in LDL-c and CV events is equivalent for ezetimibe in monotherapy and as an add-on to statin.[16] Since this appraisal in 2007, three clinical outcome trials have explored the question of the effectiveness of ezetimibe in reducing CV events in three distinct populations; see Table 7. Whilst these outcomes trials have shown that ezetimibe further reduces CV events on top of a statin (IMPROVE-IT)[11] and reduces CV events when used in combination with a statin (SHARP)[10], these studies have assessed ezetimibe in a small part of the eligible population. To assess the full ezetimibe license in this appraisal we show that IMPROVE-IT[11] and SHARP[10] are consistent with CTTC and use the reduction in LDL-c and link to CV outcomes to model the appropriate populations: see section 4 Clinical effectiveness for a more detailed discussion.

Table 7 Ezetimibe CV Outcomes Trials

Study	Design	Median Duration (yrs)	Population	Intervention	Comparator	Primary Outcome
SHARP (Study of Heart and Renal Protection)[10]	Multi-centre, double-blind, placebo-controlled RCT	4.9	Patients (n=9,270 [3023 on dialysis and 6247 pre-dialysis] aged ≥40 with chronic kidney disease	Ezetimibe (10 mg/day) co-administered with simvastatin (20 mg/day)	Placebo	Reduction in major atherosclerotic events: CHD death, non-fatal MI, revascularization, or non-fatal non-haemorrhagic stroke (RR 0.83, 95% CI 0.74; 0.94 *p*=0.0021)
IMPROVE-IT (IMProved reduction of Outcomes: Vytorin Efficacy International Trial) [11]	Multi-centre, double-blind, active-control RCT	6.0	Patients (n=18,144 aged 24 to 95) presenting with stabilised ACS, and randomised within 10 days of qualifying event	Ezetimibe (10 mg/day) co-administered with simvastatin (40 mg/day)	Simvastatin (40 mg/day)	Reduction in the composite of CV death, major coronary event, or non-fatal stroke (HR 0.936, 95% CI 0.887; 0.988 *p*=0.016)
SEAS (Simvastatin and Ezetimibe in Aortic Stenosis)[17]	Multi-centre, double-blind, placebo-controlled RCT	4.4	Patients (n=1,873 aged 45 to 85) with asymptomatic, mild-to-moderate aortic-valve stenosis	Ezetimibe (10 mg/day) co-administered with simvastatin (40 mg/day)	Placebo	Composite of major cardiovascular events: death from CV causes, aortic-valve replacement, nonfatal MI, hospitalisation for unstable angina pectoris, heart failure, coronary-artery bypass grafting, PCI, or non-haemorrhagic stroke (HR 0.96, 95% CI 0.83; 1.12 *p*=0.59)

2.5 Innovation

Ezetimibe was an innovation for the management of high cholesterol levels when launched in 2003. It should be continue to be considered an innovation as it has now become the only non-statin to demonstrate an associated reduction in CV events.

3 Health condition and position of the technology in the treatment pathway

3.1 Brief overview of the disease/condition for which the technology is being used

3.1.1 Hypercholesterolaemia

Hypercholesterolaemia is defined as a form of dyslipidaemia characterised by abnormalities of lipoprotein transport associated with high levels of cholesterol, especially LDL-c in plasma.[1] LDL-c and total cholesterol (TC) have received most attention because they can be modified by lifestyle changes and there is good evidence that their reduction can prevent CVD. Other types of dyslipidaemia also increase the risk of CVD, including raised triglycerides (TG) and very low-density lipoprotein cholesterol (VLDL-c), and reduced high-density lipoprotein cholesterol (HDL-c).[18]

The definition and prevalence of hypercholesterolaemia has changed over time and the criteria used to define cut-off values for TC and LDL-c have evolved with emerging evidence from randomised controlled clinical trials which have demonstrated the benefits of lower levels of LDL-c and reducing CV risk. Using the Quality and Outcomes Framework's (QOF) target of TC ≤ 5.0 mmol/L, hypercholesterolaemia is present in the majority of adults (58% of men and 61% of women in England).[2;19]

3.1.2 Primary and secondary hypercholesterolaemia

The development of hypercholesterolaemia may be related to the interaction between genetic predisposition and environmental factors (primary hypercholesterolaemia). Alternatively, a patient may present with hypercholesterolaemia secondary to other diseases and conditions caused by a disorder or a drug that increases cholesterol and/or TG (secondary hypercholesterolaemia). Secondary hypercholesterolaemia is not relevant to the remit of this appraisal.

The most frequent presentations of primary hypercholesterolaemia, prevalence and associated lipid profiles are shown in Table 8. The most common form is polygenic or non-familial hypercholesterolaemia. The raised levels of LDL-c that characterise this condition are caused by hepatic overproduction of very low-density VDL-c due to the individual's genetic response to high-fat dietary intake. There is no clear pattern of inheritance since a combination of more than one genetic variants is required – hence 'polygenic' hypercholesterolaemia.

Table 8 Causes of primary hypercholesterolaemia[20]

Diagnosis	Lipid profile	Prevalence*	Relevant for this appraisal
Non-familial/common hypercholesterolaemia**	Raised cholesterol owing to LDL-c	70%	Yes
Combined hyperlipidaemia†	Raised TG and cholesterol owing to VDL-c	10%	No
Heterozygous familial hypercholesterolaemia	Raised cholesterol owing to LDL-c	0.2%	Yes
Familial defective apoliprotein B	Raised cholesterol owing to LDL-c	0.2%	No
Severe hypertriglycidaemia (> 10.00 mmol/L)	Raised TG owing to fasting chlyomicronaemia and raised VLDL-c	0.1%	No
*Approximate prevalence in the adult population of the UK **Defined as TC ≥ 5.0 mmol/L in middle age †Defined as TC ≥ 5.0 mmol/L and TG ≥ 1.7 mmol/L in the absence of diagnostic features of familial hypercholesterolaemia			
LDL-c = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglycerides; VLDL-c = very low-density lipoprotein cholesterol			

In contrast, familial hypercholesterolaemia (FH) is an autosomal dominant disorder caused by specific mutations in known genes; e.g. the LDL-receptor, apolipoprotein B and PCSK9. The prevalence of heterozygous and homozygous FH in Europe is usually reported as respectively 1 in 500 and 1 in 1,000,000, but recent estimates suggest that these primary hypercholesterolaemia may occur more frequently at 1 in 200 in heterozygotes and 1 in 640,000 in homozygotes.[21]

People with hypercholesterolaemia are at increased risk of CVD due to the fact that long-term elevations of cholesterol that are known to accelerate the build-up of fatty deposits in the arteries.

This appraisal is concerned with the effectiveness of ezetimibe in primary non-familial hypercholesterolaemia and heterozygous familial hypercholesterolaemia.

3.1.3 CVD in the UK

Cardiovascular disease (CVD) is a leading cause of mortality in the Western world. Of the deaths registered in England and Wales in 2013, approximately 141,000 (28%) were related to CVD. Around 64,000 deaths were caused by ischaemic heart disease, and 35,000 caused by strokes. Of the 141,000 deaths, 36,000 occurred in people under 75 years, and the

number of deaths in males and females were equal.[3] The cost of treating CVD within the NHS in England in 2012/13 was more than £6.8 billion, with 63% within secondary care and 21% primary care. In the same period, the NHS in Wales spent more than £440 million on treating CVD .[2] Data on the indirect costs of CVD for the UK are not regularly published. In 2009 the BHF published statistics that suggested that production losses due to mortality and morbidity associated with CVD cost in the UK was over £6 billion (around 21% due to death and 13% due to illness in those of working age). The cost of informal care for people with CVD in the UK was around £3.8 billion.[2]

Since 1993, death rates from CVD have fallen by more than 50% in England. Despite this, CVD remains the major cause of morbidity and mortality in England. More patients are surviving their initial CVD event but remain at high risk of subsequent events. Additionally, and of concern, the prevalence of several risk factors, such as obesity and diabetes, are increasing in the population, thus contributing to increases in CVD and CVD risk.

In 2013 the Department of Health published its Cardiovascular Disease Outcomes Strategy. In acknowledgement that the UK does not perform well compared with a range of similar countries in CVD mortality and disability rates, ten key actions to improve outcomes for CVD patients were implemented. These include the better identification of FH patients, better early management and secondary prevention in the community and improving care for patients living with CVD.[4]

There are many risk factors that contribute to an individual's risk of developing CVD. Non-modifiable factors include age, sex, family history of CVD, ethnicity, with modifiable factors including smoking, raised blood pressure and cholesterol. Increased total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-c) are major modifiable risk factors for CVD, and, as such, therapies that lower TC and LDL-c levels are a vital part of preventing CVD. Of particular concern are patients at high risk of CVD (e.g. CHD, diabetes mellitus [DM] or familial hypercholesterolaemia [FH]) as these patients will require more effective control of their cholesterol levels in order to reduce their risk of CV events.

3.1.4 People with diabetes and/or CKD

Type 2 diabetes is a chronic and progressive disease, where patients are at increased risk of developing macrovascular and microvascular complications. Patients with diabetes are at two to three times higher risk of cardiovascular events compared to those without diabetes.[22] Further data has also demonstrated that patients with diabetes have an equivalent CHD risk to those patients without diabetes and with established CHD.[160,161] In 2013, there were over 2.9 million people with diabetes in England and Wales.[23] Patients with diabetes face particular issues with choice of effective LMT. These patients are particularly at risk of

myopathy and a prior study identified that statin initiation was associated with an approximate doubling of the risk for any myopathic event compared to non-diabetics.[24] An additional complication is that at least one third of people with type 2 diabetes are expected to develop CKD, which equates to over 900,000 people with type 2 diabetes.

CKD is also a progressive disease and it is thought that the risk of CVD death far outweighs the risk of progression to 'end-stage' kidney disease.[25] For this reason, CVD risk management in CKD patients is critical, particularly in the CKD stage 3-5 population. A meta-analysis has demonstrated that a lower eGFR is associated with an increased risk of death from CVD. Also, a higher level of albuminuria is associated with an increased risk of CVD.[26]

3.1.5 Familial hypercholesterolaemia

Familial hypercholesterolaemia (FH) is caused by a specific genetic defect, inherited from either parent.[21] One of the pair of LDL-c receptor genes is defective or mutated and impairs the LDL-c receptor activity. Occasionally, HeFH syndrome can be caused by mutations of genes other than the LDL-c receptor, proprotein convertase subtilisin/Kexin 9 (PCSK9) or apo B. LDL-c levels in FH patients can be two to four times higher than the general population, which may lead to the early development of atherosclerosis and CHD. Generally TG levels are normal, but can occasionally be raised in adults, particularly if they are obese. The risk related to HeFH can be substantially improved by early treatment. Untreated, the majority of affected men and women will have symptomatic coronary disease by 60 years of age and half of the men and 15% of the women will have died. Patients that start attending a lipid clinic before they develop clinical coronary arterial disease may enjoy a normal life expectancy if well managed. Clinical diagnosis is based on family history, clinical findings and cholesterol concentration, which can be used in a diagnosis tool such as the Simon Broome criteria that can then lead to genetic testing for a definitive diagnosis. Once an individual has a confirmed diagnosis, then cascade screening of families should be performed. The prevalence of FH is at least 1 in 500 (106,000 in England).

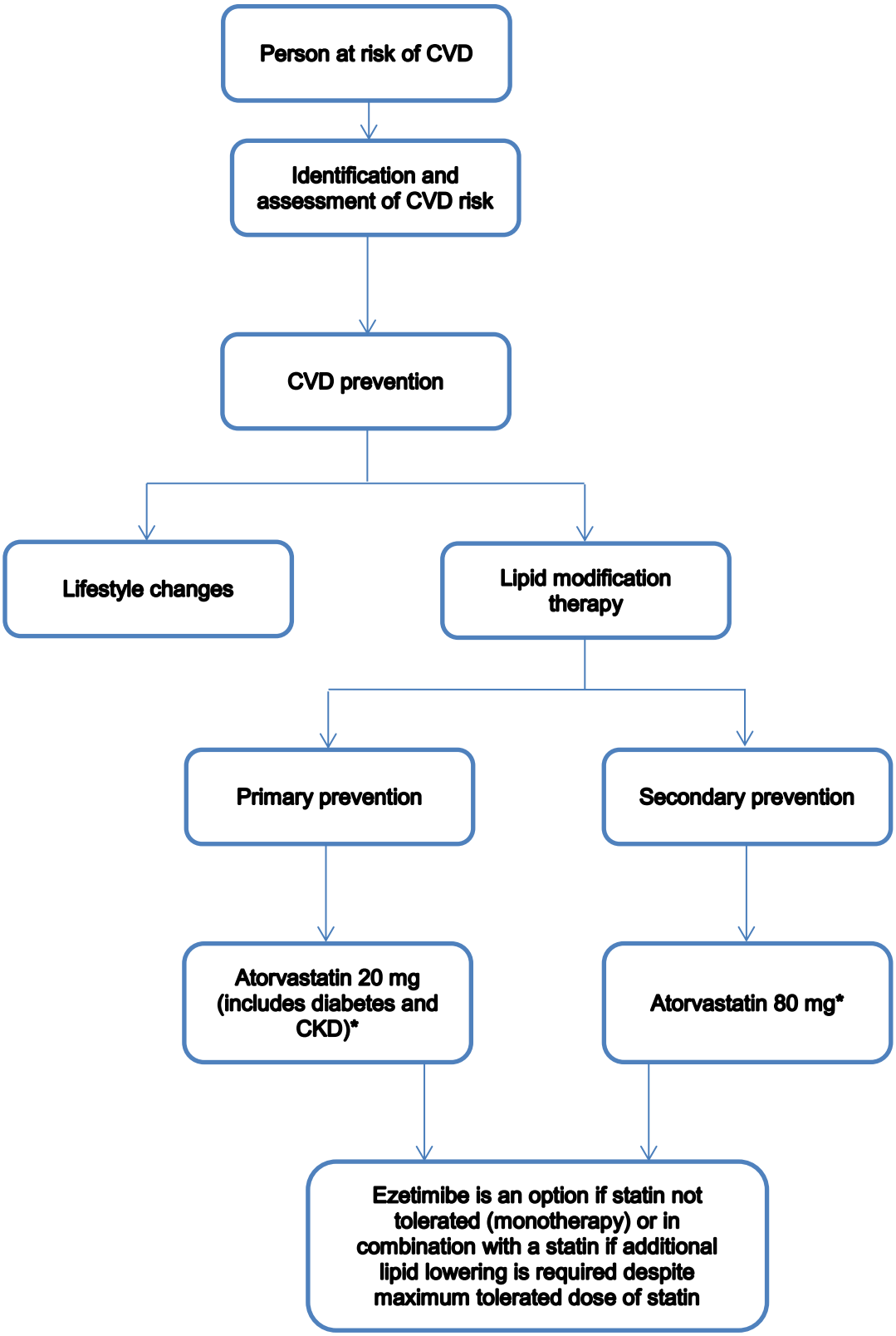
3.2 Clinical pathway of care showing the context of the proposed use of the technology

The pathway of care for the management of cholesterol has evolved over the years, with the greatest changes coming upon introduction of statins and their subsequent significant decrease in price upon patent expiry. The prevention of CVD, and in particular cholesterol management is primarily undertaken in primary care, Figure 2. A specialist in secondary care can be involved, particularly for high risk patients, i.e. those with CKD, type 1 and type 2 diabetes, those with CVD, genetic dyslipidaemias and those that are intolerant to statins.

The most significant factor affecting the care of patients with hypercholesterolaemia was the introduction of the Quality Outcomes Framework (QOF) in 2006 that incentivised primary-care practices to reduce TC < 5.0 mmol/L for specific subgroups of the population, see section 3.2.2.

Statins (3-hydroxy-3-methylglutaryl coenzyme A [HMG-CoA] reductase inhibitors) are unarguably considered the standard of care in the UK for managing a person's TC and LDL-c, where diet and lifestyle advice is inadequate and their use has contributed significantly to the reduction in CVD mortality rates in the UK. All statins apart from rosuvastatin (Crestor®) are now generic. The evidence base for statins is considerable and randomised controlled trials (RCTs) have demonstrated their effectiveness in lowering TC, LDL-c and thereby reducing clinical endpoints. In addition, a prospective meta-analysis of RCTs of statins from the Cholesterol Treatment Trialists' Collaborators (CTTC) showed that for every mmol/L reduction in LDL-c there is a 22% reduction in CV events.[9]

Figure 2 Primary care clinical pathway of care



* If the patient is intolerant to atorvastatin a number of alternatives are available, such as trying an alternative statin.

3.2.1 Lipid levels in the UK

In 2011, the Health Survey for England focused on CVD and examined trends in TC.[6] For the population sampled (14% had diagnosed CVD, with varying numbers on lipid-modifying therapy depending on morbidity, age and sex), average levels of TC were lower in men than women (5.1 mmol/L and 5.2 mmol/L respectively. By age, the highest TC levels were in men age 45-54 (5.6 mmol/L) and women age 55-64 (6.0 mmol/L). In men, total cholesterol rose with age up to 45-54, and then declined. In women, the total cholesterol increased up to the 55-64 year old age group with a smaller decrease to age 75 and over. Socioeconomic variation in TC was small for both sexes.

A recent CPRD study in the UK examined two populations between 1993 and 2011, the general population (n=3,807,977) and patients initiated on statins (n=300,914).[27] Patients with established CVD or diabetes mellitus were excluded. Cholesterol levels (TC) in the general population were lower than those initiated on a statin, and cholesterol levels of women were higher than men, Table 9, which supports the Health Survey of England. The percentage of statin users with TC ≥6 mmol/L did not differ by age. The mean LDL-c of those patients starting statin treatment was 4.32 mmol/L.

Table 9 Baseline characteristics of patients

	General population without CVD or diabetes		Statin users	
	Men (n=1,890,530)	Women (n=1,917,447)	Men (n=161,377)	Women (n=139,537)
TC recorded	462,057 (24.4%)	484,668 (25.3%)	146,672 (90.9%)	126,441 (90.6%)
≥6 mmol/L	125,193 (27.1%)	150,901 (31.1%)	94,067 (64.1%)	101,886 (80.6%)

3.2.2 Lipid targets in the UK

In the UK a patient centred approach should be considered, with the patient and clinician discussing and agreeing individualised targets for cholesterol. There is variation in the approach that is taken, with a mixture of TC, LDL-c and non-HDL-c, as well as percent reduction and numerical targets being used. Traditionally TC and LDL-c were the primary measures along with numerical targets. More recently non-HDL-c has been recommended, however, the implementation of this is challenging as non-HDL-c is not routinely requested or reported by labs.

The recent NICE Clinical Guideline CG181[8] recommends that people who have been started on high-intensity statin treatment should aim for a greater than 40% reduction in non-HDL-c.[8]

Prior to this guideline, the need for targets and follow-up in secondary prevention was recognised by NICE and an 'audit' level of TC of 5 mmol/L was recommended to assess progress in populations or groups of people with CVD[5] and TC of 4 mmol/L for patients with diabetes.[28] Based on this proposed cholesterol level the Quality Outcomes Framework (QOF) introduced specific indicators that incentivised primary-care practices to reduce TC < 5.0 mmol/L for specific subgroups of the population, including secondary prevention of CHD, peripheral arterial disease, stroke, and diabetes.[23] The diabetes indicator remains in place for 2015/2016 and incentivises GP practices to measure "the percentage of patients with diabetes, on the register, whose last measured total cholesterol is 5 mmol/L or less".[19] Since the use of recommended cholesterol levels adopted from the NICE guideline (CG67[5]) by the QOF, the improvement in the outcomes for patients with CVD has been considerable (e.g. mortality rates for patients under 75 years of age with CVD have reduced by 40% between 2001 and 2010.[4]

The recently released consensus from Joint British Societies' (JBSIII) guidelines continued to recommend a treatment aim on a non-HDL-c lowering to achieve <2.5 mmol/L (equivalent to an LDL-c level of <1.8mmol/L) in patients with acute coronary syndrome and to a level corresponding to LDL-c <2 mmol/L in patients at high risk of CVD (established CVD, Type 2 diabetes, CKD 3-5).[29]

The most recent ESC/EAS guidelines, based on Class 1, Level A evidence, recommend an LDL-c goal of 2 mmol/L (or ≥50% reduction) in those with known CVD, Type 2 or 1 diabetes with target organ damage, moderate to severe CKD or a SCORE risk estimation level of >10%.[18]

3.2.3 Attainment to targets in the UK

Whilst a number of initiatives including national QOF targets have enabled a large drop in clinical events for people at risk of CVD, a considerable number of patients are still not reaching recommended cholesterol levels and therefore remain at risk.[4] In 2011 the Health Survey for England reported that 44% of men and 43% of women had TC levels below 5 mmol/L (the NICE CG67[5] 'audit level' for those with CVD, diabetes or hypertension who are on drug treatment), while only 14% and 12% respectively had levels below 4 mmol/L (the then-NICE 'target level' for this high risk group) in 2011.[6] The numbers achieving recommended TC levels also varied with age, with lowest attainment to TC levels below 5 mmol/L in the 45-54 age group in both sexes (24% men and 30% women).

In a recent retrospective observational study in IMS Disease Analyzer, patients at high risk of CVD (CHD, atherosclerotic vascular disease, diabetes mellitus or FH) taking atorvastatin monotherapy were examined to see whether they had attained the previously recommended

levels of TC <4.0 mmol/L or LDL-c <2.0 mmol/L. This study showed that across all doses of atorvastatin, 89% of patients achieved a target of TC <5.0 mmol/L, but only 46% achieved the recommended target of TC <4.0 mmol/L. Further, only 64% of the very high risk patients (co-morbid CHD and DM) reached the TC <4.0 mmol/L or LDL-c <2.0 mmol/L level.[30]

The DYSlipidaemia International Study (DYSIS) was a multi-centre, cross-sectional, observational study of the lipid profile of statin-treated outpatients. In the UK analysis, patients (n=1277) had a clinical diagnosis of coronary or other atherosclerotic disease, or were at high risk of developing CVD. Despite being actively treated with a statin, 56.1% of patients had an LDL-c ≥2.0 mmol/L.[31]

With regards to specific patient groups, the H&SCIC produce the National Diabetes Audit (NDA) that reports on the quality of care for people with diabetes in England and Wales[32] and tracks attainment of treatment targets, one of which is cholesterol. Between 1st January 2012 and 31 March 2013 the following data was obtained for cholesterol levels (there was a trend that a higher proportion of older people achieved treatment targets):

- TC <4 mmol/L
    - 28.7% of people with Type 1 diabetes
    - 40.5% of people with Type 2 diabetes
- TC <5 mmol/L
    - 70.2% of people with Type 1 diabetes
    - 76.8% of people with Type 2 diabetes

3.2.4 Details of relevant NICE guidance, pathways or commissioning guides

There are a number of guidelines in the UK that provide recommendations for the management of primary hypercholesterolaemia, and the utilisation of lipid-modifying therapy for the management of cholesterol. NICE CG181[8], the Joint British Societies' (JBS3)[29] and ESC/EAS guidelines can all be used for the care of people with hypercholesterolemia.[18] Table 10 provides a summary of the guidelines.

Table 10 Summary of guidelines available in the UK

Guideline	Published	Risk tool	Recommendation	Lipid targets (mmol/L)
NICE CG181 Lipid Modification[8]	July 2014	QRISK2	Atorvastatin 20 mg: • Primary prevention of CVD to people who have a 10% or greater 10-year risk of developing CVD • Primary prevention for people with type 1 diabetes • Primary prevention for people with type 2 diabetes who have a 10% or greater 10-year risk of developing CVD • People with CKD for the primary or secondary prevention of CVD Atorvastatin 80 mg: • Secondary prevention, people with CVD	40% reduction in non-HDL-c
JBS3[29]	July 2014	JBS3 lifetime risk calculator based on QRISK 2	Cholesterol-lowering drug therapy is recommended in: • Patients with established CVD • High risk of CVD: diabetes age > 40 years, patients with CKD stages 3-5, or FH • Individuals with high 10-year or lifetime CVD risk	Evidence of benefit for LDL-c levels <2 mmol/L. LDL-c <1.8 mmol/L in patients with established CVD
ESC/EAS[18]	June 2011	SCORE, some groups automatically high risk	• Choose a statin that, on average, can provide this reduction • Since the response to statin treatment is variable, up-titration to reach target is mandatory • If the statin cannot reach the goal, consider drug combinations.	LDL-c of 1.8 mmol/L or a ≥50% reduction (very high risk) LDL-c of 2.5 mmol/L (high risk) LDL-c of 3 mmol/L (moderate risk)

NICE lipid modification Clinical Guideline CG181 [8]

NICE updated the lipid modification clinical guideline in July 2014, and made a number of important changes including measuring non-HDL-c, lowering of the primary prevention threshold from 20% to 10% 10-year CVD risk as calculated by QRISK2, and the use of atorvastatin as the first choice statin. [8]

An emphasis has been made on the use of non-HDL-c as a marker for CV risk rather than LDL-c in recognition that non-HDL-c has been shown to perform better on risk prediction compared to LDL-c. A challenge in the short-term, however is that non-HDL-c is not routinely requested or reported. Additionally, Primary Care is accustomed to TC targets).

For lipid modification therapy, statins are considered first-line therapy for the primary and secondary prevention of CVD. Table 10 summarises the recommendations:

Recommendations for other lipid-modifying therapy in CG181[8]:

- Do not routinely offer fibrates in monotherapy or in combination with a statin for the prevention of CVD in all populations.
- Do not offer nicotinic acid, bile acid sequestrants or omega-3 fatty acid compounds in monotherapy or in combination with a statin for the prevention of CVD in all populations.
- Rosuvastatin is not recommended within CG181[8]. The full guideline states 'Given the considerably higher cost of using rosuvastatin, it would need to be considerably more effective than atorvastatin for there to be a possibility that its use could be cost effective. In the absence of trial evidence of greater effectiveness the guideline development group are therefore unable to recommend the use of rosuvastatin'.
- Ezetimibe is recommended in-line with TA132[7]: People with primary hypercholesterolemia should be considered for ezetimibe treatment in line with NICE technology appraisal guidance TA132[7], "Ezetimibe for the treatment of primary (heterozygous familial and non-familial) hypercholesterolemia". This means that ezetimibe is an option for people with primary (heterozygous-familial or non-familial) hypercholesterolemia in the following situations:
    - Monotherapy as an alternative to a statin in adults in whom statins are contraindicated or not tolerated.
    - In combination with a statin in adults who have initiated statin treatment but whose serum total or LDL cholesterol concentration is not appropriately controlled (either after appropriate dose titration or because dose titration is

limited by intolerance to the initial statin therapy) **and** consideration is being given to changing from initial statin therapy to an alternative statin.

NICE familial hypercholesterolemia Clinical Guideline (CG71)[33]

LDL-c levels in FH patients can be two to four times higher than the general population, which may lead to the early development of atherosclerosis and CHD. The prevalence of FH is at least 1 in 500 (106,000 in England). In 2008, NICE produced a clinical guideline on the identification and management of FH:

- People suspected of having FH should be referred to a specialist for diagnosis
- Diagnosis should be based on raised TC and LDL-c, as well as using the Simon Broome criteria
- High-intensity statin should be considered to achieve a >50% reduction in LDL-c
- Ezetimibe can be used in-line with TA132[7]

3.2.5 Details of other clinical guidelines and national policies

JBSIII[29]

In July 2014 the Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3) was published. In this they recommend:

- The JBS3 risk calculator that evaluates a person's CVD risk over the lifetime, so as to identify those people that are at low short term risk, but at high lifetime risk in order to treat earlier.
- All high risk people should receive professional lifestyle support to reduce TC and LDL-c, raise HDL-c, and lower triglycerides to reduce their CVD risk.
- Cholesterol-lowering drug therapy is recommended in:
  - Patients with established CVD
  - Individuals at particularly high risk of CVD: diabetes age > 40 years, patients with CKD stages 3-5, or FH
  - Individuals with high 10-year CVD risk (threshold to be defined by NICE guidance)
  - Individuals with high lifetime CVD risk estimated from heart age and other JBS3 calculator metrics, in whom lifestyle changes alone are considered insufficient by the physician and person concerned

- Statins are recommended as they are highly effective at reducing CVD events with evidence of benefit to LDL-c levels <2 mmol/L which justifies intensive non-HDL-c lowering.
- In patients with established CVD, statins should be prescribed with a 'lower is better' approach to achieve values of <2.5 mmol/L non-HDL-c (equivalent to <1.8 mmol/L LDL-c).
- Statins are safe with trial evidence showing no effect on non-cardiovascular mortality or cancer. There is a small increase in risk of developing diabetes but the benefits of cholesterol lowering greatly exceed any risk associated with diabetes. If statin intolerance develops a stepwise strategy involving switching agents and re-dosing is recommended.
- Ezetimibe is an option to be used as per the recommendations in NICE TA132.[7]
- A bile acid sequestrant is an option in statin intolerant patients.

JCBIII guidance on familial hypercholesterolemia

- Diagnosis and management of FH patients should involve referral to specialist lipid clinics
- At least a 50% reduction in LDL-c should be targeted with the aim of reaching LDL values found in the general population.
- Statins are first line therapy, followed by combination which includes ezetimibe.
- Almost half of patients do not achieve >50% reduction in LDL-c, and only 21% reach LDL-c <2.5 mmol/L.

ESC/EAS Guideline[18]

A task force for the ESC/EAS developed guidance for the management of dyslipidaemias. The main recommendations are as follows:

- For CV risk estimation:

  Those with

  - known CVD
  - type 2 diabetes or type 1 diabetes with microalbuminuria
  - very high levels of individual risk factors
  - chronic kidney disease (CKD)

  are automatically at very high or high total cardiovascular risk and need active management of all risk factors.

- For all other people, the use of a risk estimation system such as SCORE is recommended to estimate total CV risk because many people have several risk factors which, in combination, may result in unexpectedly high levels of total CV risk.
- An absolute reduction to an LDL-c level of 1.8 mmol/L or at least a 50% relative reduction in LDL-c provides the best benefit in terms of CVD reduction.
    - For patients with very high CV risk an LDL-c level of 1.8 mmol/L or a ≥50% reduction from baseline LDL-c.
    - For patients at high risk an LDL-c level of 2.5 mmol/L should be considered.
    - For patients at moderate risk an LDL-c level of 3 mmol/L should be considered.
- Once the CV risk has been determined:
    - Involve the patient with decisions on CV risk management
    - Identify the LDL-c target for that risk level
    - Calculate the percentage reduction of LDL-c required to achieve that goal
    - Choose a statin that, on average, can provide this reduction
    - Since the response to statin treatment is variable, up-titration to reach target is mandatory
    - If the statin cannot reach the goal, consider drug combinations.

ESC/EAS Guideline on familial hypercholesterolemia[18]

- People can be diagnosed using a number of tools such as the MedPed and WHO criteria, or the Simon Broome criteria.
- Treatment should involve access to a lipid clinic for investigations to detect the presence of significant atherothrombotic disease.
- Maximum tolerated statin dose should be used to target LDL-c <1.8 mmol/L, however with high pre-treatment LDL-c this might not be possible.
- When LDL-c remains too high combination therapy should be considered

3.2.6 Ezetimibe in the care pathway

In 2007 NICE appraised ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolemia.[7] It is recommended in the following populations:

- Ezetimibe monotherapy is recommended as an option for the treatment of adults with primary (heterozygous-familial or non-familial) hypercholesterolaemia who would otherwise be initiated on statin therapy (as per NICE guidance TA 94 in adults with non-familial hypercholesterolaemia) but who are unable to do so because of contraindications to initial statin therapy.
- Ezetimibe monotherapy is recommended as an option for the treatment of adults with primary (heterozygous-familial or non-familial) hypercholesterolaemia who are intolerant to statin therapy.
- Ezetimibe, co-administered with initial statin therapy, is recommended as an option for the treatment of adults with primary (heterozygous-familial or non-familial) hypercholesterolaemia who have been initiated on statin therapy (as per NICE guidance TA 94 in adults with non-familial hypercholesterolaemia) when:
    - serum total or low-density lipoprotein (LDL) cholesterol concentration is not appropriately controlled either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance to the initial statin therapy

      and
    - consideration is being given to changing from initial statin therapy to an alternative statin.

3.2.7 Statin side effects and intolerance

For the purposes of TA132[7], intolerance to initial statin therapy was defined as:

'defined as the presence of clinically significant adverse effects from statin therapy that are considered to represent an unacceptable risk to the patient or that may result in compliance with therapy being compromised. Adverse effects include evidence of new-onset muscle pain (often associated with levels of muscle enzymes in the blood indicative of muscle damage), significant gastrointestinal disturbance or alterations of liver function tests.' (TA132[7])

In the costing report it was stated that approximately 2% of eligible patients are unable to take statins because of contraindication or intolerance.[34] This number was based on feedback from a single clinical expert during the appraisal. Skeletal muscle-related events are the most common adverse events arising from statin exposure, specifically statin induced myalgia and myopathy.[35-37] Muscle pain without elevation of serum creatine phosphokinase (CPK) (myalgia) is the most common medication-related adverse effect of

statin therapy, however, statin-induced myopathy can (rarely) manifest with severe and potentially fatal cases of rhabdomyolysis.[38;39] The small amount of CPK that is normally present in the blood comes primarily from skeletal muscles. Any condition that causes muscle damage and/or interferes with muscle energy production or use can cause an increase in CPK. Rhabdomyolysis, a severe breakdown of skeletal muscle tissue that causes muscle pain, tenderness, weakness and swelling, is associated with significantly elevated levels of CK, often 100 times normal. Measurement of CK is used to assess the extent of muscle damage and to monitor its progress. Diabetic patients are particularly at risk of myopathy and a prior study identified that statin initiation was associated with an approximate doubling of the risk for any myopathic event compared to non-diabetics.[24]

The levels of statin intolerance have been reported to be much higher in clinical practice than those seen in RCTs, most likely due to the exclusions of elderly and sick patients in trials.[40] A number of factors are associated with statin intolerance including age, female gender, low BMI, renal insufficiency, hypertension and use of some drugs such as warfarin, azole antifungals, macrolide antibiotics which increase statin exposure.[39;41;42] Clearly the older and more fragile the population the higher risk of statin intolerance. However, these older patients are also at higher risk from CVD events, so this population is a challenge to treat.[40] In the PRIMO (Prediction of Muscular Risk in Observational conditions) study it was found that 10.5% of patients on high-dose statins reported muscle-related symptoms[43], while it has been reported as high as 20% in other cases.[44] This is associated with the manner in which RCTs are conducted. For example, RCTs exclude those patients that cannot tolerate the treatment during the run-in period and these people are subsequently not included in the intention-to-treat analysis. In TNT (Treating to New Targets), for example, of the 15,464 patients that were eligible to enter the run-in period, 5,461 patients (35.3%) were excluded.[45] Additionally, the controlled environment of RCTs and the extensive follow-up of patients is not the same as the routine clinical environment.

General practitioners (GPs) usually base their diagnosis of statin intolerance on presenting symptoms as there is no definitive test except the CK test, which is not affected in myalgia cases. Statin intolerance attributable to myalgia is a significant barrier to effective treatment of hyperlipidaemia, as it frequently results in patient non-compliance, cessation of treatment or down-titration from a clinically effective dose. Historical and current management options are similar in UK, Europe and USA [8,5,42;46], and involve:

- cessation of treatment with re-challenge,
- lower dose of the same statin (with possible re-challenge at higher dose at a later date),
- switch to another statin,

- off-label switch to another high intensity statin with less frequent dosing such as rosuvastatin, every other day or once weekly. JBSIII[29] recommends trying pravastatin at 10 mg or rosuvastatin at 5 mg with or without infrequent dosing,
- introduction of a non-statin treatment such as ezetimibe, either as concomitant therapy with infrequent statin use or low dose; or as monotherapy (JBS III recommends this switch if three previous statin therapies fail to reduce or control cholesterol at target)

None of the above guideline statin reduction strategies have been tested in real world populations over the long-term, but clinical trials have shown that TC and LDL-c cholesterol level reductions are minimised when statin is reduced in this way.[40;42]

Patients who have symptoms of statin intolerance and are stopped and re-challenged often have renewed symptoms, which do not abate on switch to another statin.[47;48] showed that in 104 patients evaluated for statin intolerance, the majority were intolerant to two or more statins (regardless of type) and cholesterol control in these patients remained poor in the long term. The PRIMO study reported that rates of statin intolerance myalgia varied by type of statin with atorvastatin adversely affecting 14.9% of patients and simvastatin 18.2% respectively, suggesting that some types of statin, including pravastatin, may have lower statin intolerance profiles. However, in the PRIMO study 20% of patients were discontinued on statin therapy and a further 17% experienced dose reduction.[43] Whilst it is not clear if patients with symptoms of statin intolerance, such as muscle pain, truly have statin intolerance, they may be treated as such by the GP. These patients frequently experience down titration or treatment cessation, and thus will have sub-optimal lipid therapy, poor lipid control and subsequently an increased risk of CV events.

3.2.8 Current ezetimibe usage in the NHS

In 2014, there were 1,716,950 and 112,920 prescriptions of ezetimibe in England and Wales respectively, costing about £53.5 million in England and £3.1 million in Wales. This was a decrease compared to 2013 with 1,797,620 and 121,003 prescriptions of ezetimibe in England and Wales respectively, costing about £56.7 million in England (0.8% of the NHS yearly spend on CVD) and £3.3 million in Wales.[49;50].

From the latest prescription data available for ezetimibe, year to January 2015, in the UK 38% of the patients receiving ezetimibe were on monotherapy and 62% co-prescribed with a statin[1].

[1] IMS Health, UK Disease Analyzer, MAT Jan 2015.

3.3 Equality issues

MSD believe that the technology is unlikely to raise any equality issues, with no potential issues that:

- could exclude from full consideration any people protected by the equality legislation that fall within the patient population for whom the technology is or will be licensed.
- could lead to recommendations that have a different impact on people protected by the equality legislation compared with the wider population, for example by making it more difficult in practice for a specific group to access the technology.
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

3.4 Overall aims and objectives of the assessment

The aim of this assessment is to appraise the clinical and cost effectiveness of ezetimibe in people with primary heterozygous familial or non-familial hypercholesterolaemia:

- Co-administered with a statin in people whose condition is not appropriately controlled with a statin alone, either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance.
- As monotherapy in patients where a statin is considered inappropriate or is contraindicated or not tolerated.

4 Clinical effectiveness

Summary of clinical effectiveness section

- The IMPROVE-IT and SHARP trials provide evidence demonstrating the clinical benefit of ezetimibe. Additionally, both trials provide support for the LDL hypothesis from the CTTC meta-analysis which shows that a reduction in LDL-c of 1 mmol/L reduces the incidence of major vascular events by 22%. This analysis utilises the use of a large body of RCT evidence for ezetimibe that demonstrates the consistent LDL-c lowering in a wide population, with associated event reduction.

The majority of the remaining ezetimibe RCTs assess the cholesterol lowering ability of ezetimibe in various populations. These have been systematically reviewed and analysed; relevant for this appraisal:

- Where ezetimibe is used as monotherapy, a meta-analysis of 15 RCTs revealed that ezetimibe provides a significant 20.4% reduction in LDL-c.
- Where ezetimibe is used in combination with a statin, a meta-analysis of 18 RCTs revealed that ezetimibe provides a further 23.5% lowering in LDL-c when combined with a statin versus statin alone.

Ezetimibe CV outcome evidence and linking changes in lipids to clinical outcomes

There have been numerous clinical outcomes trials that have established that lowering LDL-c is associated with a reduction in the risk of CV events. Several systematic reviews and meta-analyses have demonstrated a link between reducing LDL-c and reducing the risk of CV events. Law *et al.* studied 58 RCTs (n=148,321) and showed that a reduction in LDL-c of 1.0 mmol/L reduced the risk of CHD events by up to 36% over six or more years of treatment.[51] More recently, the Cholesterol Treatment Trialists' Collaboration (CTTC) have performed meta-analyses of statin RCTs to demonstrate the link between lowering LDL-c and reducing coronary events.[9;16] The most recent meta-analysis from 2010 included 26 RCTs (five trials more versus less intensive statin regimens, n=39,612; 21 trials statin versus control, n=129,526) showed that a reduction in LDL-c of 1.0 mmol/L reduced the risk of major vascular events by up to 22%. The reduction in risk across individual endpoints is presented in

Table 11.

Table 11 Individual endpoints from the CTTC meta-analysis[9]

Endpoint	Reduction per 1.0 mmol/L LDL-c reduction (%)	Relative Risk
All-cause mortality	10	0.90, 95% CI 0.87;0.93 *p*<0.0001
CHD death	20	0.80, 95% CI 0.75;0.85 *p*<0.0001
Non-fatal MI	27	0.73, 95% CI 0.70; 0.77 *p*<0.0001
Stroke	16	0.84, 95% CI 0.79;0.89 *p*<0.0001
Coronary revascularisation	25	0.75, 95% CI 0.72;0.78 *p*<0.0001

Overall the CTTC analysis included 26 RCTs with male and female patients, mean trial baseline LDL-c levels ranged from 2.09 to 4.96 mmol/L, and contained populations with a variety of comorbidities including diabetes, CKD, prior CHD and hypertension, but not HeFH.[9]

As stated in section 2.4.2, in the NICE review of ezetimibe TA132 in 2007 it was noted that there was no evidence of the effectiveness of ezetimibe in reducing clinical endpoints, therefore the CTTC data was used to link changes in lipid measurements to CV events.[7] Since this appraisal there have been three clinical outcome trials that have examined the effectiveness of ezetimibe in reducing CV events in three distinct populations and these are described in the following section.

SHARP trial[10]

SHARP was a multicentre, randomised, double-blind, placebo-control study in patients with CKD (plasma creatine of at least 150 µmol/L [1.7 mg/dL) in men or 130 µmol/L [1.5 mg/dL] in women) and no known history of myocardial infarction or coronary revascularisation. All subjects entering the study were assigned to randomised, double-blind treatment in a 4:4:1 ratio to either ezetimibe/simvastatin combination 10/20 mg once daily, placebo once daily, or simvastatin 20 mg to assess the safety of ezetimibe during the first year. The simvastatin 20 mg arm was re-randomised after one year (no safety concerns identified) to either ezetimibe/simvastatin 10/20 mg once daily or placebo once daily. The trial was specified to

end after all subjects had been followed for a minimum of 4 years. All subjects, including subjects who discontinued treatment, were to be monitored for clinical endpoint events until the termination of the study.

Demographic and baseline disease characteristics were similar between the two treatment groups. Mean age at baseline was 62 years, and one-third of subjects randomised into the trial were female. Approximately one-third of subjects qualified for the study were on dialysis, with the remaining not on dialysis. The median duration of follow-up was 4.9 years.

The primary composite efficacy endpoint outcome measure, major atherosclerotic events, was the time from randomisation to the first occurrence of one of the following: CHD death, non-fatal MI, or revascularization, or non-fatal non-haemorrhagic stroke. Treatment with ezetimibe/simvastatin resulted in a 17% proportional reduction in the primary efficacy endpoint compared to treatment with placebo (RR 0.83, 95% CI 0.74; 0.94 *p*=0.0021). The consistency of the treatment effect across over 20 pre-specified subgroups was assessed for the primary endpoint. It should be noted that the study was not powered to adequately assess subgroup differences, and no adjustment for multiplicity for the subgroup analyses was applied. The effect of ezetimibe/simvastatin relative to placebo on the primary composite endpoint was generally consistent across the subgroups including gender, age, ethnicity, on dialysis or not, and comorbidities (e.g. diabetes).

Safety and tolerability

The overall safety and tolerability of ezetimibe/simvastatin in SHARP, as assessed by evaluation of adverse experiences, revealed no new safety findings related to study therapy, and was consistent with current ezetimibe/simvastatin product labeling. There were no meaningful differences between the treatment groups in clinical adverse events, including those leading to discontinuation of study drug, those reported as serious, and those deemed by the blinded investigators to be related causally to study drug. There were no clinically meaningful differences in the protocol specified adverse events of special interest such as myopathy/rhabdomyolysis, hepatic safety, and malignancy.

LDL-c changes

The mean LDL-c at the time of the qualifying event was 2.77 to 2.78 mmol/L in each treatment group. Average change in LDL-c at 26-31 months, the ezetimibe/simvastatin treatment group achieved an additional mean reduction in LDL-c of 0.85 mmol/L or 61% relative to placebo.

Linking LDL-c to CV events

In the 2010 CTTC meta-analysis three trials were included in patients with CKD.[9] None of these trials reported a significant reduction in its primary vascular disease outcome, leading to uncertainty about whether lowering LDL-c is effective in renal patients. SHARP has demonstrated that lowering LDL-c with combination of ezetimibe/simvastatin 10/20 mg once daily reduces the risk of major atherosclerotic events in a wide range of patients with CKD, particularly CKD stage 3 and stage 4.

The effects of lowering LDL-c with a statin in populations without chronic kidney disease have been described by the CTTC meta-analysis, and show that statin therapy reduces the risk of myocardial infarction or coronary death, stroke, or coronary revascularisation by about a fifth per 1 mmol/L LDL cholesterol reduction. In the SHARP trial, an average reduction of 0·85 mmol/L yielded a significant 17% reduction in major atherosclerotic events, which is similar to the effects seen in the CTTC with statin regimens of equivalent LDL-c lowering efficacy.[9] The reduction in non-fatal myocardial infarction or coronary death (RR 0·92, 95% CI 0·76–1·11) in SHARP was not statistically significant, but the trial lacked power for separate assessment of components of major atherosclerotic events, and the confidence interval is consistent with the results of the CTTC meta-analysis.[9]

IMPROVE-IT trial[11]

IMPROVE-IT was a multicentre, randomised, double-blind, active-control study in high-risk subjects presenting with stabilised acute coronary syndrome (ACS) and had an LDL-c ≥ 1.3 mmol/L (and ≤3.2 mmol/L) at the time of presentation with ACS if they had not been taking lipid-lowering therapy, or ≤2.6 mmol/L if they had been receiving lipid-lowering therapy. All subjects entering the study were assigned to randomised, double-blind treatment in a 1:1 ratio to either ezetimibe/simvastatin combination 10/40 mg once daily or simvastatin 40 mg once daily. Subsequently, if LDL-c was found to be >2.05 mmol/L on two consecutive measurements in compliant patients in either treatment group, the dose of simvastatin was increased to 80 mg in a double-blind manner.

The trial was specified to end after all subjects had been followed for a minimum of 2.5 years and a primary endpoint event had been documented in at least 5250 subjects. All subjects, including subjects who discontinued treatment, were to be monitored for clinical endpoint events until the termination of the study.

Table 12 Endpoints in the IMPROVE-IT trial[11]

	Endpoint
Primary endpoint	Composite of CV death, major coronary events, and non-fatal stroke
Secondary endpoints	Composites of: • death from any cause, major coronary events, or non-fatal stroke • CHD death, non-fatal MI, or urgent coronary revascularisation ≥30 days after randomisation • CV death, non-fatal MI, documented UA requiring hospitalisation, all revascularisation, or non-fatal stroke
Tertiary endpoints	Individual CV endpoints
Other	Adverse events

Subject characteristics at the time of randomisation are presented in Appendix 3. Demographic and baseline disease characteristics were similar between the two treatment groups and generally consistent with an adult population with high-risk ACS meeting the protocol-specified entry criteria.

Patients (n=18,144) underwent randomisation with a mean age at baseline of 63.6 years, and one-quarter of subjects randomised into the trial were female. Approximately two-thirds of subjects qualified for the study with NSTEACS, and approximately one-third qualified with a STEMI. Mean time from qualifying event to randomization was 5.4 days[2]. One-third of subjects reported prior lipid lowering therapy experience[b].

The primary composite efficacy endpoint outcome measure was the time from randomisation to the first occurrence of one of the following: CV death, non-fatal MI, documented unstable angina that requires admission into a hospital, or coronary revascularisation with either PCI or CABG occurring at least 30 days after randomization, or non-fatal stroke. Appendix 3 also displays the observed incidences of the composite and its component event categories in the two treatment groups, with estimates of hazard ratios, 95% confidence intervals and p-

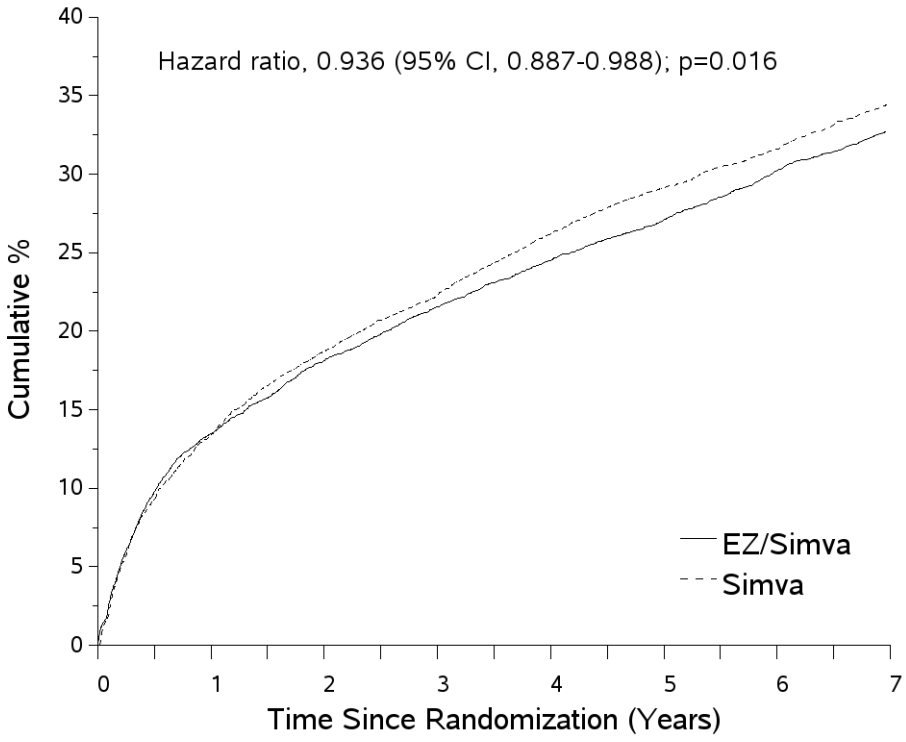
[2] The maximum value for time from qualifying event to randomization is 368 days which is reflective of a data entry error for subject 003376. Date of randomization is 09-November 2006, however the date of qualifying ischemia is incorrectly recorded as 06-November-2005.

[b] A subject was considered to be receiving chronic prescription lipid-lowering therapy if he/she had been receiving any prescription lipid-lowering therapy continuously for >4 weeks prior to and continuing until the qualifying ACS hospital admission. All other subjects (including those who initiated prescription lipid lowering therapy after the qualifying ACS hospital admission) were considered to be "lipid-therapy naïve".

values, using a Cox proportional-hazards model with covariates of treatment and stratification factors.

Treatment with ezetimibe/simvastatin resulted in a 6.4% relative risk reduction in the primary efficacy endpoint compared to treatment with simvastatin alone (HR 0.936, 95% CI 0.89; 0.99 *p*=0.016), Figure 3. The primary endpoint occurred in 2,572 of 9,067 subjects (7-year Kaplan-Meier [KM] rate 32.72%) in the ezetimibe/simvastatin group and 2,742 of 9,077 subjects (7-year KM rate 34.67%) in the simvastatin only group in the protocol-defined ITT population.

Figure 3 Cumulative Incidence Rate of Primary Composite Endpoint: Cardiovascular Death, Major Coronary Event[†], or Non-fatal Stroke (Protocol-defined ITT Population)



[†]Major Coronary Event = Non-fatal MI, documented UA requiring hospitalization, or coronary revascularization with PCI or CABG ≥ 30 days after randomization.

The consistency of the treatment effect across over 20 pre-specified subgroups was assessed for the primary endpoint. It should be noted that the study was not powered to adequately assess subgroup differences, and no adjustment for multiplicity for the subgroup analyses was applied. The effect of ezetimibe/simvastatin relative to simvastatin alone on

the primary composite endpoint was generally consistent across the subgroups including gender, age, ethnicity, and comorbidities, however the benefit appeared to be particularly pronounced in patients with diabetes mellitus and those 75 years or older.

The three secondary composite endpoints and tertiary individual CV endpoints are documented in Appendix 3.

Safety and tolerability

The overall safety and tolerability of ezetimibe/simvastatin in IMPROVE-IT, as assessed by evaluation of adverse experiences, revealed no new safety findings related to study therapy, and was consistent with current ezetimibe/simvastatin product labeling. There were no meaningful differences between the treatment groups in clinical adverse events, including those leading to discontinuation of study drug, those reported as serious, and those deemed by the blinded investigators to be related causally to study drug. There were no clinically meaningful differences in the protocol specified adverse events of special interest such as myopathy/rhabdomyolysis, hepatic safety, and malignancy. In addition, analyses of adverse events such as new-onset of diabetes, pancreatitis, acute renal failure, interstitial lung disease and hypersensitivity reactions revealed no clinically meaningful differences between treatment groups. No meaningful differences were noted between the treatment groups in CV Death or Non-CV-Death.

LDL-c changes

The mean LDL-c at the time of the qualifying event was 2.4 mmol/L in both treatment groups. LDL-c lowering was observed at 1 month, and generally was sustained over the duration of follow-up. The corresponding mean LDL-c levels at 1 year were 1.42 mmol/L in the ezetimibe/simvastatin group vs. 1.86 mmol/L in the simvastatin group. The between-group difference remained relatively similar at all time-points, reflecting a consistency of the treatment effect of the study medication and the fact that lipids were generally measured only on subjects continuing on study drug.

At one year and with inclusion of all available lipid values (ITT), the ezetimibe/simvastatin treatment group achieved an additional mean reduction in LDL-c of 0.43 mmol/L or 16.75% (95% CI 17.5;16.0, $p<0.001$) relative to the simvastatin treatment group LDL-c. This difference represented a 24% further lowering of LDL-c when ezetimibe was combined with simvastatin than with simvastatin alone.

Linking LDL-c to CV events

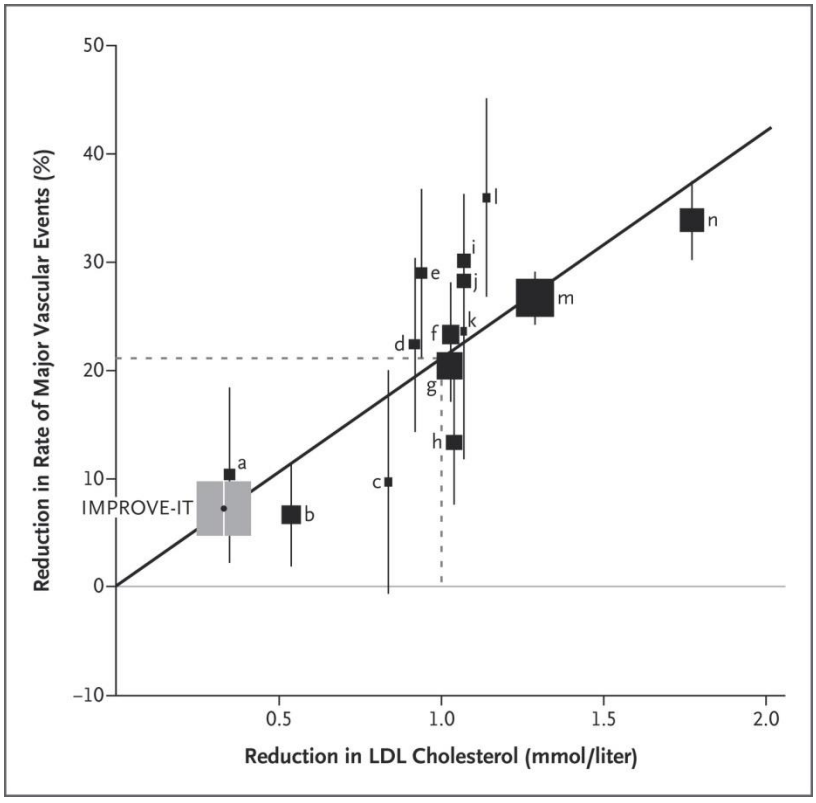
The relationship between LDL-c reduction and outcomes treatment benefit for IMPROVE-IT was assessed through analysis of observed reductions in CV events per 1.0 mmol/L

reduction in LDL-c. This assessment facilitates comparison with observations from the 2010 CTTC meta-analysis where lowering LDL-c (assessed at 1 year in each trial) by 1 mmol/L with statin therapy reduced the incidence of major vascular events by 22%.[9]

In order to perform these analyses, a composite endpoint for IMPROVE-IT that was consistent with the CTTC major vascular event endpoint (CTT-MVE: namely CHD death, non-fatal MI, coronary revascularization that occurred ≥ 30 days after randomization and stroke; [the primary endpoint of IMPROVE IT excluding unstable angina]) was identified and assessed. Additionally, to maintain consistency with the approach used in the CTTC, imputation of baseline LDL-c values was performed for subjects with missing LDL-c values at 1-year.

The Hazard Ratio (HR) for clinical benefit per mmol of LDL-c reduction with ezetimibe in IMPROVE IT was 0.80 (95% CI [0.68; 0.94]), which is consistent with the HR 0.78 (95% CI [0.76; 0.80], p<0.0001) observed with statins in the meta-analysis performed by the CTTC in 2010.[9] Plotting IMPROVE-IT against data from other trials of statins that assessed the association between change in LDL and clinical benefit is shown in Figure 4.[11]

Figure 4 Plot of the IMPROVE-IT trial data and statin trials for change in LDL-c versus clinical benefit.[11]



Interpretation

The IMPROVE-IT trial has demonstrated the clinical benefit of adding ezetimibe to statin therapy and established for the first time that a lipid lowering therapy other than a statin significantly reduces CV events. Additionally, as can be seen in Figure 3 the LDL-c/ CV event reduction relationship obtained by the addition of ezetimibe to simvastatin conforms to that from the CTTC meta-analysis of all the major statin studies.[11]

Whilst IMPROVE-IT is a landmark trial and provides evidence that ezetimibe reduces clinical endpoints, the study was conducted in a sub-population of the wider ezetimibe license. The IMPROVE-IT participants had low baseline LDL-c, were a well-controlled group, and 66.5% received no lipid lowering therapy at time of ACS event indicating they were not considered high risk prior to having the event. In UK clinical practice the treatment choice for these patients is not ezetimibe + simvastatin 40 mg or simvastatin 40 mg, but atorvastatin 80 mg if tolerated (according to current UK guidance) .[52] As such, extrapolation of the CV event reduction from the IMPROVE-IT population to the wider ezetimibe co-administered with a statin population is challenging as baseline characteristics, CV risk and the patient pathway would be significantly different to the other populations, e.g. primary prevention and treatment of high risk primary hypercholesterolaemia patients with diabetes and CKD, as well as monotherapy. IMPROVE-IT has demonstrated the clinical benefit of ezetimibe when added to a statin, as well as a further LDL-c reduction of 24%, which is a level consistent with other ezetimibe/statin combination trials, allowing extrapolation to other populations. This allows the modelling of the effect of ezetimibe on LDL-c with linkage to CV outcomes via the CTTC meta-analysis.

Both IMPROVE-IT and SHARP have demonstrated that ezetimibe containing regimens reduce CV events in two distinctive populations. Additionally, the relationship between LDL-c lowering and the reduction of CV events demonstrated in these two trials is equivalent to and consistent with that seen in the CTTC meta-analysis.

SEAS trial [17]

SEAS was a multicentre, randomised, double-blind, placebo-control study in patients with mild-to-moderate, asymptomatic aortic stenosis. Exploratory studies had demonstrated the potential for Ezetimibe to reduce intimal wall thickening related to plaque deposition, with a subsequent hypothesis being that this reduction would lead to a lowering of CV events. All subjects entering the study were assigned to randomised, double-blind treatment in a 1:1 ratio to either ezetimibe/simvastatin combination 10/40 mg once daily (n=944) or placebo once daily (n=929). The trial was specified to end after all subjects had been followed for a

minimum of 4 years. Demographic and baseline disease characteristics were similar between the two treatment groups. Mean age at baseline was 67.5 years, and 40% of subjects randomised into the trial were female. The median duration of follow-up was 52.2 months.

The primary composite efficacy endpoint outcome measured major cardiovascular events, including death from CV causes, aortic-valve replacement, nonfatal MI, hospitalisation for unstable angina pectoris, heart failure, coronary-artery bypass grafting, percutaneous coronary intervention, and non-haemorrhagic stroke. The outcome occurred in 333 patients (35.3%) patients in the ezetimibe/simvastatin group and in 355 patients (38.2%) in the placebo group (HR 0.96, 95% CI 0.83; 1.12, *p*=0.59).

Ference *et al.* the biological effect of lowering LDL-c [53]

Before IMPROVE-IT considerable uncertainty existed as to whether lowering low-density lipoprotein cholesterol (LDL-c) by inhibiting the Niemann-Pick C1-Like 1 (NPC1L1) receptor with ezetimibe, either alone or in combination with a 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) inhibitor (statin), will reduce the risk of coronary heart disease (CHD).

Despite the established causal association between LDL-c and the risk of CHD, several randomised trials have failed to consistently show an incremental clinical benefit from further lowering LDL-c by adding niacin or a fibrate to treatment with a statin, creating uncertainty as to whether lowering LDL-c by a mechanism other than inhibiting HMGCR with a statin will reduce the risk of CHD. Ezetimibe inhibits intestinal absorption of cholesterol by binding to the NPC1L1 protein, which leads to up regulation of hepatic LDL-c receptors and increased clearance of circulating LDL-c. Statins reduce hepatic cholesterol synthesis by inhibiting HMGCR, which also leads to up-regulation of hepatic LDL-c receptors and increased clearance of circulating LDL-c. Because both ezetimibe and statins reduce LDL-c through the same final common pathway, it is intuitive to hypothesise that lowering LDL-c by inhibiting NPC1L1 with ezetimibe may also reduce the risk of CHD and other major vascular events as seen in statin trials. Ference *et al*. recently undertook a study to compare the biological effect of lower LDL-c mediated by inhibition of NCP1L1, HMGCR, or both on the risk of CHD, and sought to compare the effect of naturally random allocation to lower LDL-c on the risk of CHD mediated by genetic polymorphisms in the NPC1L1 gene (as a proxy for ezetimibe treatment), the HMGCR gene (as a proxy for statin treatment), or both (as a proxy for combination treatment) using a novel 2 x 2 factorial mendelian randomisation study design.

Participants were randomised into 4 groups: reference, lower LDL-c mediated by NPC1L1 polymorphisms, lower LDL-c mediated by HMGCR polymorphisms, or lower LDL-c mediated

by polymorphisms in both NPC1L1 and HMGCR. The comparison was the risk of CHD (fatal or nonfatal MI) among each group. A total of 108,376 persons (10,464 CHD events) from 14 studies were included. There were no significant differences in baseline characteristics among the 4 groups. Compared to the reference group, the NPC1L1 group had 2.4 mg/dl lower LDL-c and 4.8% lower risk of CHD (OR] 0.952, 95% CI: 0.920; 0.985, p=0.0044); whereas the HMGCR group had 2.9 mg/dl lower LDL-c and a similar 5.3% lower risk of CHD (OR: 0.947, 95% CI: 0.909; 0.986, p=0.0091). The group with lower LDL-c mediated by both NPC1L1 and HMGCR polymorphisms had 5.8 mg/dl additively lower LDL-c and a 10.8% log-linearly additive lower risk of CHD (OR: 0.892, 95% CI: 0.854; 0.932, p<0.0001). The effect of lower LDL-c on the risk of CHD mediated by polymorphisms in NPC1L1, HMGCR, or both is approximately the same per unit lower LDL-c and log-linearly proportional to the absolute exposure to lower LDL-c.

This genetic approach assessing natural variation in populations and linking it to polymorphisms in the NPC1L1 gene, which encodes the target of ezetimibe supports the validity of this mechanism of action in lowering LDL-c. Furthermore it supports the combination approach to the use of ezetimibe in addition or on top of a statin as the study shows an additive effect of lowering LDL-c through both HMGCR and NPC1L1.

4.1 Identification and selection of relevant studies

A review of the evidence for the clinical effectiveness of ezetimibe was undertaken by systematically searching the literature following the general principles from Systematic reviews: CRD's guidance for undertaking reviews in health care.

Searches were carried out in order to:

- Identify studies to include in the clinical effectiveness review for LDL-c change
- Identify studies to include in the cost effectiveness review

The aim of the following section is to document the search for RCTs of ezetimibe for the treatment of primary hypercholesterolemia. The evidence for two distinct populations was reviewed:

- Ezetimibe monotherapy
- Ezetimibe in combination with a statin

Search strategy

A comprehensive search strategy was conducted to identify RCTs that included ezetimibe for the treatment of primary hypercholesterolemia. Medline, EMBASE, and the Cochrane

Register of Controlled Trials were searched. Medline and EMBASE were accessed through the OVID portal. The three search strategies are presented in

Appendix *4*

Study selection

4.1.2 Description of the inclusion and exclusion selection criteria, language restrictions, and the study selection process

After removal of duplicate publications, titles and abstracts from citations retrieved from the three searches were screened independently by two reviewers. For all abstracts deemed relevant, full text reports were obtained and evaluated by the same two reviewers based on all predefined selection criteria. Any disagreements between the two reviewers were resolved through discussion. The population, interventions, comparisons, outcomes, and study design (PICOS) criteria used to select studies for the populations under review and are presented in Table 13 and Table 14. RCTs with a treatment period of 12 weeks or greater were included. This is to allow time for the efficacy measure to take effect and is consistent with previous TA's and guidelines addressing the efficacy of LMT.

Table 13 Eligibility criteria used in the search strategy – Ezetimibe monotherapy

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Adults >18 years with primary hypercholesterolaemia	Adults with homozygous familial hypercholesterolaemia Adults with homozygous sitosterolaemia Secondary hypercholesterolaemia Paediatric populations
Intervention	Ezetimibe 10 mg (ezetimibe, ezetrol, zetia, vytorin, inegy)	Other LMT (nicotinic acid, bile acid sequestrants, fibrates, omega-3 fatty acids)
Comparators	Placebo	
Outcomes	LDL-c reduction (mean % change from baseline) TC reduction (mean % change from baseline) Apolipoprotein B Lipoprotein a Adverse Events (AEs and serious AEs)	
Study design	RCTs > 12 weeks	Non-RCTs
Language restrictions	English	
Other	Studies from 1990 onwards	

Table 14 Eligibility criteria used in the search strategy – Ezetimibe in combination with a statin

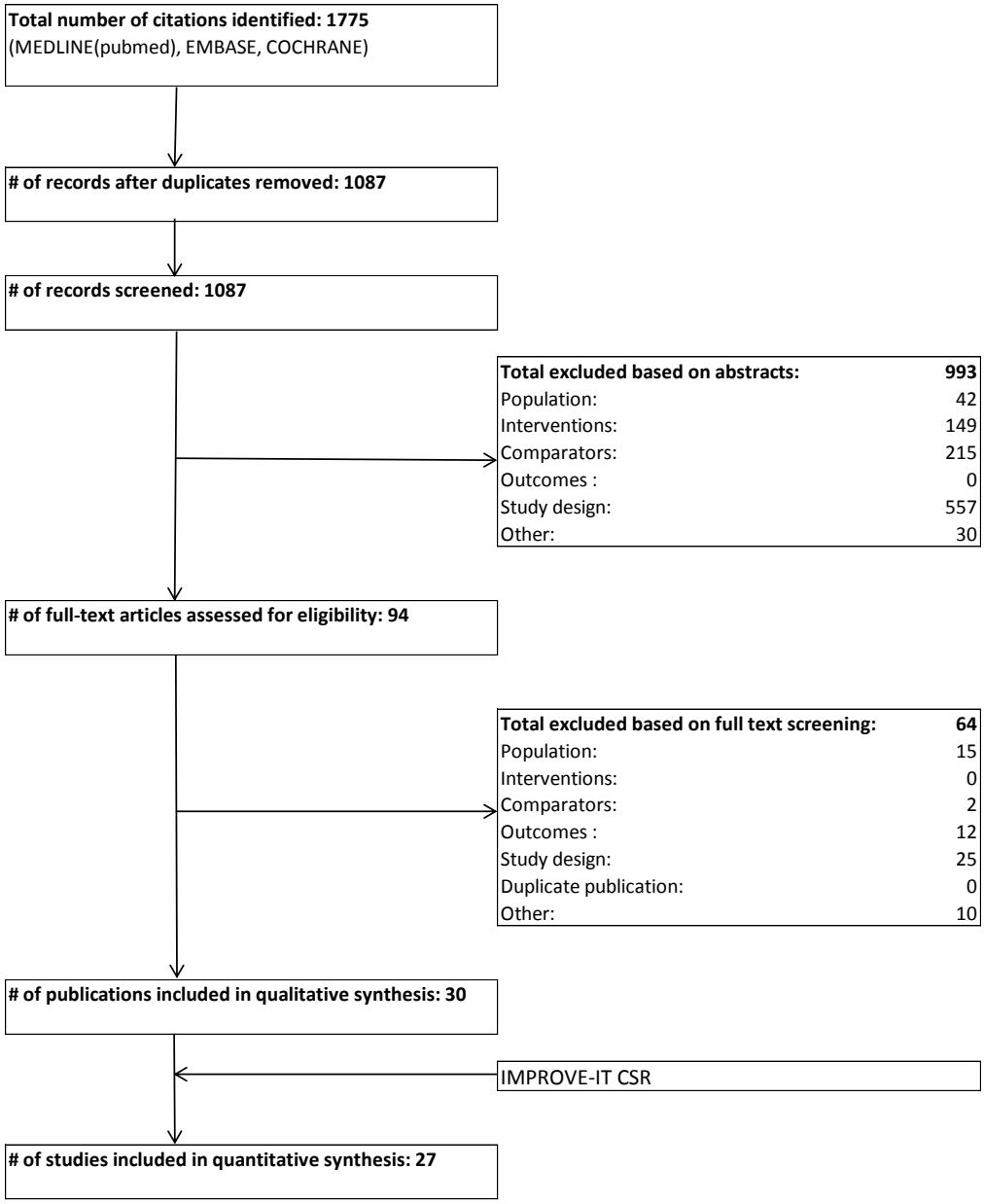
Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Adults >18 years with primary hypercholesterolaemia	Adults with homozygous familial hypercholesterolaemia Adults with homozygous sitosterolaemia Secondary hypercholesterolaemia Pediatric populations
Intervention	Ezetimibe 10 mg + atorvastatin 10 -80 mg Ezetimibe 10 mg + simvastatin 10-80 mg Ezetimibe 10 mg + pravastatin 10-40 mg Ezetimibe 10 mg + fluvastatin 20-80 mg Ezetimibe 10 mg + rosuvastatin 5-40 mg	Other LMT (nicotinic acid, bile acid sequestrants, fibrates, omega-3 fatty acids)
Comparators	Matching statin dose: Atorvastatin 10 - 80 mg Simvastatin 10 - 80 mg Pravastatin 10 - 40 mg Fluvastatin 20 - 80 mg Rosuvastatin 5 - 40 mg	
Outcomes	LDL-c reduction (mean % CFB) TC reduction (mean % CFB) Apolipoprotein B Lipoprotein a Adverse Events (AEs and serious AEs)	
Study design	RCTs > 12 weeks	Non-RCTs
Language restrictions	English	
Other	Studies from 1990 onwards	

4.1.3 Flow diagram of the numbers of studies included and excluded at each stage

A total of 1,775 citations were retrieved from the three searches. The flow of study selection according to PRISMA guidelines is presented in Figure 5**.** Ninety-four full-text publications were screened; 63 of these were found to be ineligible and are listed in

Appendix *4***.** After screening, 30 publications describing 26 RCTs were selected. The clinical trial report from the IMPROVE-IT trial was added to the selected set of trials to complete the evidence base for this study.

Figure 5 Flow diagram of included and excluded publications



4.1.4 Complete reference list for excluded studies

A total of 64 studies were excluded during full-text review; a complete list is given in Appendix *4.* Many trials were excluded due to study length of fewer than 12 weeks.

4.2 List of relevant randomised controlled trials

4.2.1 Relevant RCTs involving the intervention of interest

Of the 27 included studies, fifteen studies[54-68] compared ezetimibe monotherapy to placebo. Fourteen studies[11;56;58;61;64-66;68-74] compared combinations of ezetimibe and simvastatin to matched simvastatin doses. One study[54] compared combinations of ezetimibe and atorvastatin to matching atorvastatin dose. Five studies[75-79] compared combinations of ezetimibe and fluvastatin to matching fluvastatin dose. One study[67] compared ezetimibe and pravastatin to matching pravastatin dose.

Four included publications[80-83] were found to be extension studies or supplementary information to other included trials and, after review, were not considered further.

Table 15 presents a summary list of included trials; each consists of ezetimibe 10 mg vs placebo (or no treatment) added to either placebo or statin. Studies are arranged by statin; note that some trials contribute arms to multiple comparisons. A detailed list of relevant RCTs can be found in Appendix 5

Table 15 Summary list of relevant RCTs

Author, year	Background drug/dose
Placebo	
Ballantyne *et al.* 2003[54;80]	Placebo
Bays *et al.* 2001[55]	Placebo
Bays *et al.* 2004[56;82]	Placebo

Clement *et al.* 2014[57]	Placebo
Davidson *et al.* 2002[58]	Placebo
Dujovne *et al.* 2002[59]	Placebo
Farnier *et al.* 2005[60]	Placebo
Goldberg *et al.* 2004[61]	Placebo
Knopp *et al.* 2001[62]	Placebo
Knopp *et al.* 2003[63]	Placebo
Krysiak *et al.* 2011[65]	Placebo
Krysiak *et al.* 2012a[64]	Placebo
Krysiak *et al.* 2012b[66;82]	Placebo
Melani *et al.* 2003[67]	Placebo
Sager *et al.* 2003[68]	Placebo
Atorvastatin	
Ballantyne *et al.* 2003[54]	Atorvastatin 10, 20, 40, or 80 mg
Fluvastatin	
Alvarez-Sala *et al.* 2008[75]	Fluvastatin XL 80 mg
Habara *et al.* 2014[76]	Fluvastatin 30 mg
Kinouchi *et al.* 2013[77]	Fluvastatin 20 mg
Stein *et al.* 2008[78]	Fluvastatin XL 80 mg
Stojakovic *et al.* 2010[79]	Fluvastatin 80 mg
Pravastatin	
Melani *et al.* 2003[67]	Pravastatin 10, 20, or 40 mg
Simvastatin	
Bays *et al.* 2004[56]	Simvastatin 10, 20, 40, or 80 mg
Davidson *et al.* 2002[58]	Simvastatin 10, 20, 40, or 80 mg
Goldberg *et al.* 2004[61]	Simvastatin 10, 20, 40, or 80 mg
IMPROVE-IT 2015[11]	Simvastatin 40 mg
Kastelein *et al.* 2008[69;81]	Simvastatin 80 mg
Krysiak *et al.* 2011[65]	Simvastatin 40 mg
Krysiak *et al.* 2012a[64]	Simvastatin 40 mg
Krysiak *et al.* 2012b[66]	Simvastatin 40 mg
Krysiak *et al.* 2014[70]	Simvastatin 40 mg
Masana *et al.* 2005[71]	Simvastatin 10, 20, 40, or 80 mg
Rodney *et al.* 2006[72]	Simvastatin 20 mg
Sager *et al.* 2003[68]	Simvastatin 10, 20, 40, or 80 mg
Shankar *et al.* 2007[73]	Simvastatin 10 mg
Zinellu *et al.* 2012[74;83]	Simvastatin 40 mg

4.2.2 RCTs excluded from further discussion

Not applicable

4.3 Summary of methodology of the relevant randomised controlled trials

A description of the methodology of the RCTs is presented in Appendix 6.

4.4 Statistical analysis and definition of study groups in the relevant randomised controlled trials

The statistical analyses of the relevant RCTs can be found in Appendix 7

4.5 Participant flow in the relevant randomised controlled trials

All RCTs included in the review of TA132 are published and the participant flow figures can be found in the manuscripts. The patient demographics and baseline characteristics are detailed in Appendix 8. The trials included in the review enrolled a variety of patients across a range of patient characteristics including gender, age, BMI, smoking status, ethnicity and comorbidities.

4.6 Quality assessment of the relevant randomised controlled trials

A quality assessment for each RCT is presented in Appendix 9.

4.7 Clinical effectiveness results of the relevant randomised controlled trials

A summary of the results of the individual trials can be found in the

Appendix *10*.

Notes regarding the evidence base for ezetimibe add-on to statin population systematic review

- Short duration studies (i.e. those of 6-8 weeks) randomised patients that were stable on a baseline statin (Figure A). The analysis of change in LDL-c for these studies is multiplicative (calculation of LDL-c reduction from baseline based on stable statin).
- Studies ≥12 weeks duration (Figure B), require that patients discontinue LMT therapy prior to randomisation to either ezetimibe + statin or statin alone. The analysis of change in LDL-c for these studies is additive (calculation of LDL-c reduction from baseline based on no treatment).

In order to use the widest available evidence base to support the submission, only studies of 12 weeks or greater have been included. This approach is consistent with previous TA's and guidelines addressing the efficacy of LMT.

It should be noted that the clinical efficacy for ezetimibe in combination with a statin is traditionally reported as a percentage value from a multiplicative analysis (approximately 23-25% reduction in LDL-c).

Figure A

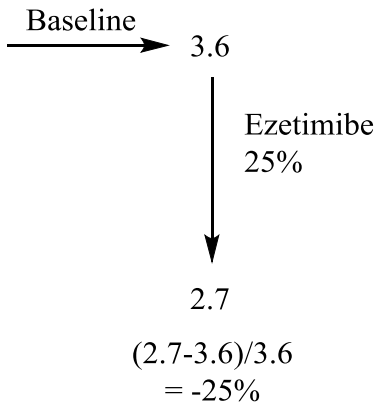
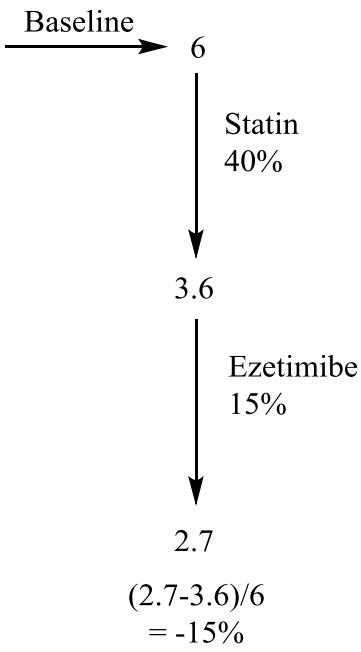


Figure B



4.8 Subgroup analysis

The subgroups described in Table 16 have been explored.

Table 16 Subgroups analysed

Subgroup explored	Pre-planned or post-hoc	Comments
Primary prevention in people with diabetes	Pre-planned	Data available from three trials for add-on to statin and one trial in monotherapy
People with CKD	Pre-planned	Data available in one trial for add-on to statin
People with HeFH	Pre-planned	Data available in one trial for add-on to statin

Primary prevention in people with diabetes

Whilst a large number of the included RCTs enrolled people with diabetes, only three studies reported on the LDL-c differences for people with and without diabetes (pre-specified analyses).[56;61;72] The patient demographics across the groups were similar. The % CFB in LDL-c for Bays 2004 and Goldberg 2004 across the two arms can be found in the Table 17 below. Rodney 2006 reported between treatment mean % LDL-c reduction for the ezetimibe + statin versus statin arms with a -18% difference for those people with diabetes and -16% difference for those without diabetes.

Table 17 % CFB in LDL-c

People with diabetes	Arms	Study	
		Bays *et al.* 2004	Goldberg *et al.* 2004
Yes	Ezetimibe + Statin	LDL-c -56% CFB	LDL-c -56% CFB
	Statin	LDL-c -38% CFB	LDL-c -35% CFB
No	Ezetimibe + Statin	LDL-c -53% CFB	LDL-c -54% CFB
	Statin	LDL-c -39% CFB	LDL-c -39% CFB

A single study, Knopp 2003, reported between treatment mean % LDL-c reduction for ezetimibe versus placebo arms with a -26% difference for those people with diabetes and -17.5% difference for those without diabetes.[63]

People with CKD

A single study reported on the use of ezetimibe in combination with a statin in patients with CKD.[74] Thirty patients with a mean baseline LDL-c of 4.26 mmol/L received either simvastatin 40 mg, ezetimibe + simvastatin 20 mg or ezetimibe + simvastatin 40 mg for 52 weeks. The kidney profiles in the arms were creatinine 1.63 – 1.92 mg/dL, GFR 52 – 61 ml/min per 1.73 m^2 and proteinuria 0.81 – 1.25 g/24 h. The simvastatin 40 mg group reduced LDL-c by a mean 42.8% and the ezetimibe + simvastatin 40 mg arm by a mean 64.0%. This gave an additional mean difference of 16.5%, or a further lowering in LDL-c of 36.6%. No meta-analysis was performed on this sub-group. Whilst this study was the only one identified to fit the populations for this appraisal, the SHARP study has demonstrated the clinical benefit for the use of ezetimibe + simvastatin 20 mg in patients with CKD.[10]

People with HeFH

A single study reported on the use of ezetimibe in combination with a statin in patients with HeFH.[69] 720 patients with a mean baseline LDL-c of 8.22 mmol/L received either double-blind simvastatin 80 mg + ezetimibe 10 mg or simvastatin 80 mg + placebo for 24 months. The baseline characteristics were similar between the groups, with mean age of 46 years, approximately 50% were male, and a mixture of co-morbidities including diabetes (2%), hypertension (14-19%) history of MI 4-7%) and a history of statin use (>80%). The simvastatin group reduced LDL-c by a mean 39.1% and the ezetimibe + simvastatin arm by a mean 55.6%. This gave an additional mean difference of 16.5%, or a further lowering in LDL-c of 26.9%. No meta-analysis was performed on this sub-group.

4.9 Meta-analysis

Outcomes

Meta-analyses were performed for mean percent change from baseline in LDL-c and TC. For studies that did not report mean percent change from baseline, we used the baseline and endpoint values to calculate the mean percent change, using a conservative correlation coefficient of 0.50 to estimate the standard error of the mean percent change.

Analyses conducted

The following primary meta-analyses were conducted for change from baseline in LDL-c and TC:

- Ezetimibe 10 mg monotherapy vs placebo
- Ezetimibe 10 mg plus statin vs matching statin dose

In addition, we performed subgroup analyses by each background statin with more than one available RCT (simvastatin, fluvastatin, and atorvastatin), and also by specific dose of simvastatin (10 mg, 20 mg, 40 mg or 80 mg).

Among studies that reported change from baseline in LDL-c in subgroups with and without diabetes, we performed a subgroup analysis in each group and additionally performed an analysis with presence of diabetes as a covariate in order to estimate the effect of diabetes on the treatment effect of ezetimibe in combination versus matching statin dose.

Sensitivity analyses

We conducted a sensitivity analysis removing the three studies involving 100% Japanese or Indian patients.[73;76;77] This analysis was used in the base case for the cost effectiveness analysis.

Assessment of heterogeneity

We tested for heterogeneity within each analysis using the I^2 statistic; this statistic gives the proportion of overall variation that can be attributed to between-study heterogeneity. Large I^2 values are indicative of heterogeneity.[84] Where heterogeneity was found, we investigated differences in trial and patient characteristics to identify sources of variability in treatment effects between trials.

Statistical models

For each outcome, pairwise meta-analysis was performed using a DerSimonian-Laird[85] random effects model, which assumes that the true treatment effects of the included studies are assumed to follow a distribution around an overall mean, and estimates a measure of between-study heterogeneity.

For each analysis, we present the relative treatment effect (MD and 95% CI) of ezetimibe vs placebo for each study, pooled MD and 95% CI for each subgroup, and corresponding forest plots.

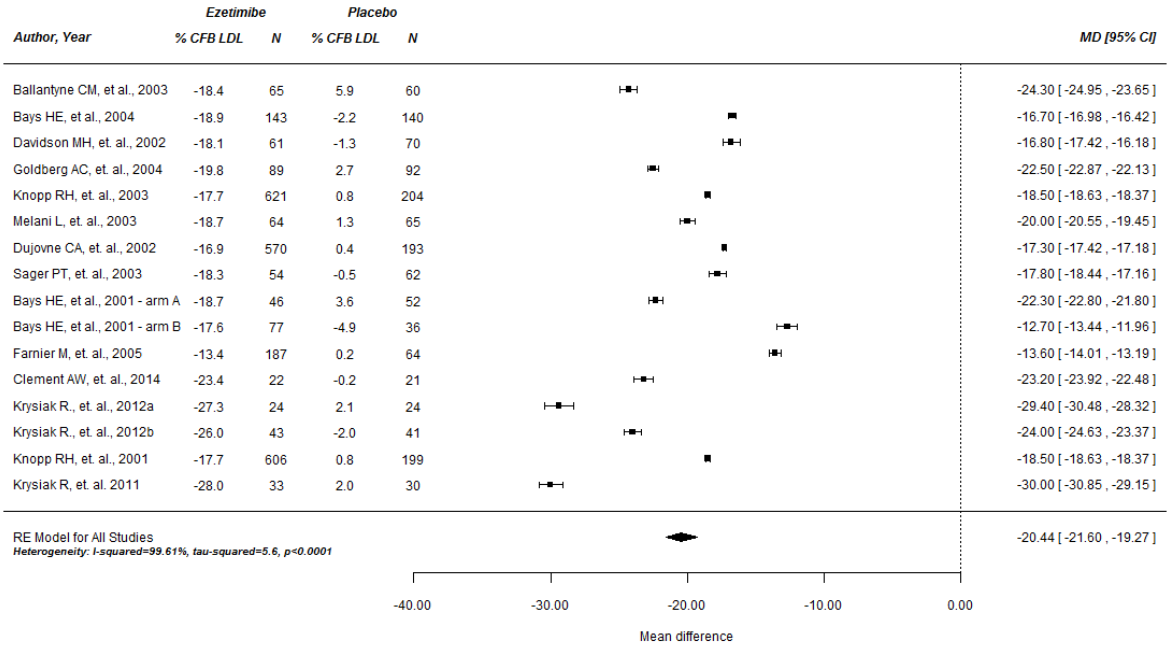
Analysis was performed in R (version 3.1.3) using the metaphor package.

Outcomes and evidence synthesis

Ezetimibe vs placebo – LDL-c

Fifteen studies (N=4,058) studies assessing ezetimibe monotherapy vs placebo reported %CFB in LDL-c and TC. Figure 6 summarises these studies with respect to LDL-c. The random-effects meta-analysis demonstrated that ezetimibe monotherapy resulted in a significantly greater reduction of LDL-c compared to placebo (MD -20.4%, 95% CI -21.6 to -19.3). The relative treatment effect in the individual studies ranged from -30.0% to -12.7%. There was a large degree of heterogeneity present (I^2=99.61 for all studies combined).

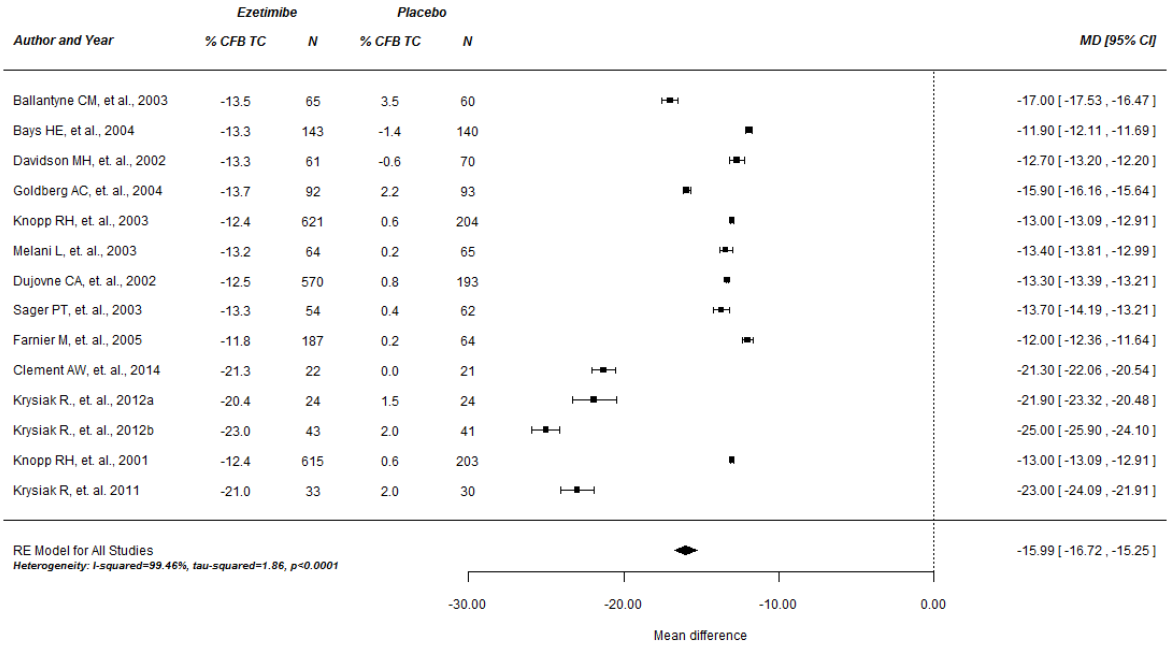
Figure 6 Percent change in LDL-c (mmol/L) among studies comparing ezetimibe monotherapy to placebo



Ezetimibe vs placebo - TC

Figure 7 summarises % CFB in TC among the studies (N=3,864) assessing ezetimibe monotherapy vs placebo. The mean difference between ezetimibe monotherapy and placebo was -16.0% (95% CI -16.7 to -15.3); individual study treatment effect ranged from -25.0% to -11.9%. The I^2 value was 99.46, which indicates a very large degree of heterogeneity.

Figure 7 Percent change in total cholesterol among studies comparing ezetimibe monotherapy to placebo



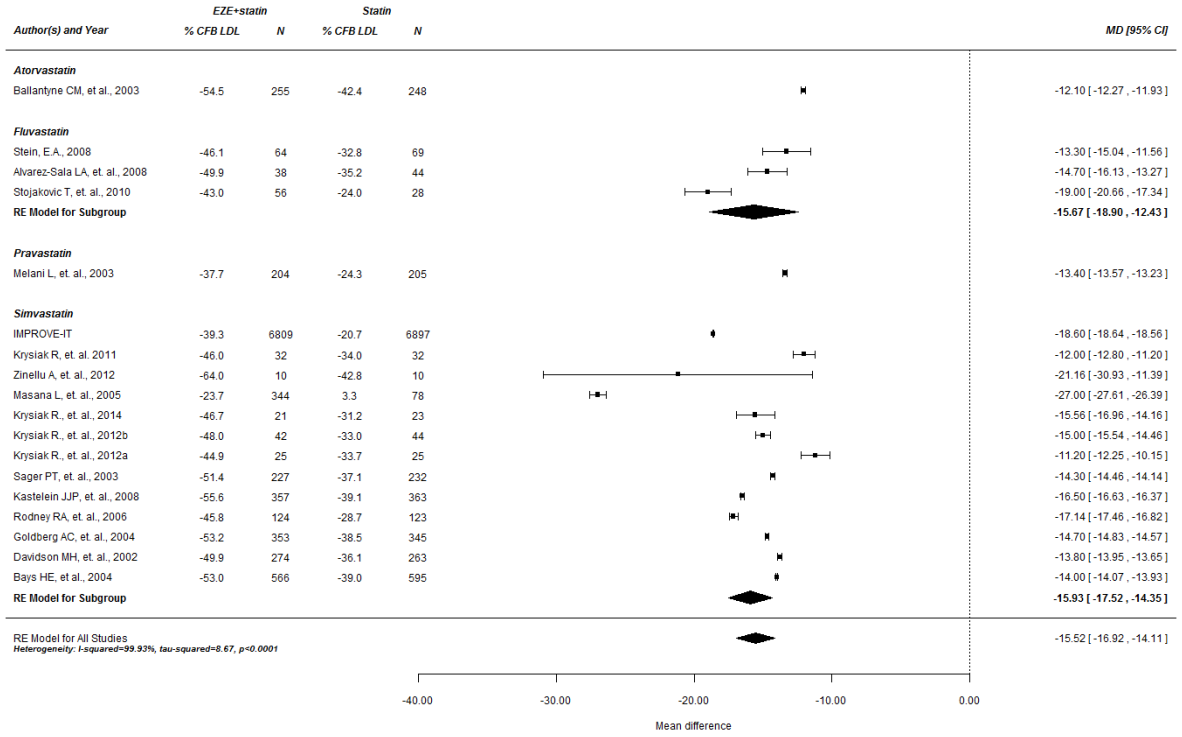
Ezetimibe vs matching statin dose – LDL-c

- Twenty-one studies (N=21,496) assessing combinations of ezetimibe and matching statin dose reported %CFB in LDL-c and TC, see Appendix 11 for this analysis. Three studies that included 100% Japanese or Indian patients were removed from the analysis for the purposes of this appraisal. These populations metabolise a number of drugs differently. Therefore, Eighteen studies (N=19,425) assessing combinations of ezetimibe and statins versus matching statin dose reported %CFB in LDL-c and TC.
-
-

Figure 8 presents a summary of these studies with respect to LDL-c, overall and by statin. The MD of ezetimibe plus fluvastatin versus fluvastatin monotherapy was -15.7% (95% CI -18.9 to -12.4). The MD of ezetimibe plus simvastatin to simvastatin monotherapy was -15.9% (95% CI -17.5 to -14.4). Combinations of ezetimibe and atorvastatin and pravastatin

were only reported by one study each; for these studies no meta-analysis was performed. For all statins combined, the MD of ezetimibe in combination versus matching statin dose was -15.5% (95% CI -16.9 to -14.1). Overall, there was a large degree of heterogeneity present (I^2=99.93 for all studies combined).

Figure 8 Percent mean difference in LDL-c (mmol/L) among studies comparing ezetimibe + statin to matching statin dose

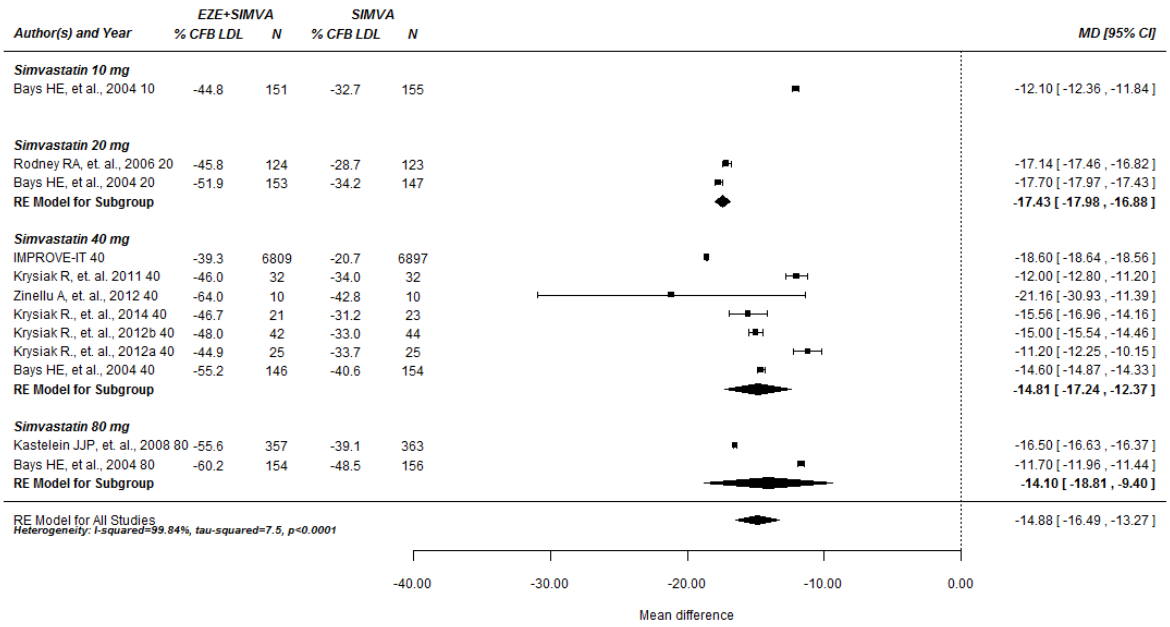


As described at the beginning of section 4, the trials included in this review required washout of LMT prior to randomisation, and so the LDL-c change is reported as mean % change from baseline using the additive approach. The more meaningful representation of the clinical efficacy of ezetimibe is to present LDL-c as a change from baseline on stable statin, the multiplicative approach. This has been calculated from the studies included in the meta-analysis, Appendix 12. By using a weighted average ezetimibe provides a further LDL-c lowering of 23.5%.

Sufficient evidence was available to perform meta-analysis by specific doses of simvastatin; these results are summarized in Figure 9. Only one study reported on ezetimibe plus simvastatin 10 mg vs simvastatin 10 mg, so no meta-analysis was performed for this dose.

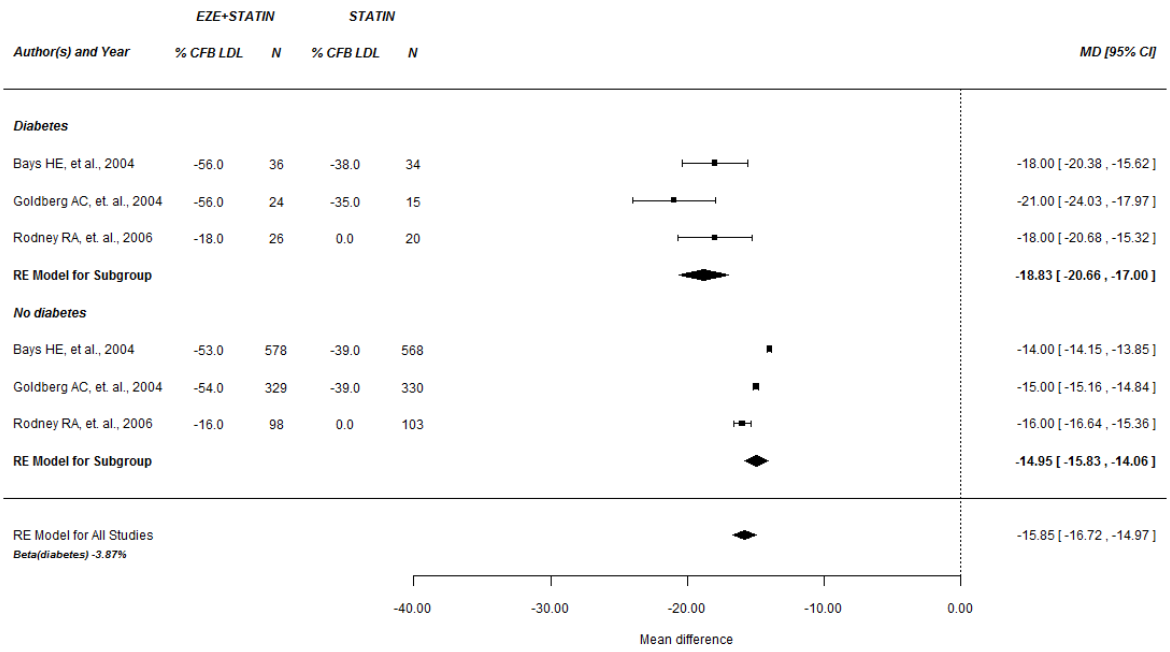
Ezetimibe plus simvastatin 20 mg showed a MD of -17.4% (95% CI -18.0 to -16.9), ezetimibe plus simvastatin 40 mg produced a MD of -14.8% (95% CI -17.2 to -12.4), ezetimibe plus simvastatin 80 mg produced a MD of -14.1% (95% CI -18.8 to -9.4). All combinations were compared to the matching simvastatin dose.

Figure 9 Percent mean difference in LDL-c (mmol/L) among studies comparing ezetimibe + simvastatin to matching simvastatin dose



Three studies reported percent change from baseline in LDL-c for patients with and without diabetes. These results are shown in Figure 10. Among patients with diabetes, the mean difference for ezetimibe plus statin vs statin monotherapy was -18.8% (95% CI -20.7 to -17.0). Among patients without diabetes, the mean difference was -15.0% (95% CI -15.8 to -14.1). The estimated difference in treatment effect between patients with diabetes and those without was -3.87% (95% CI -5.85 to -1.90).

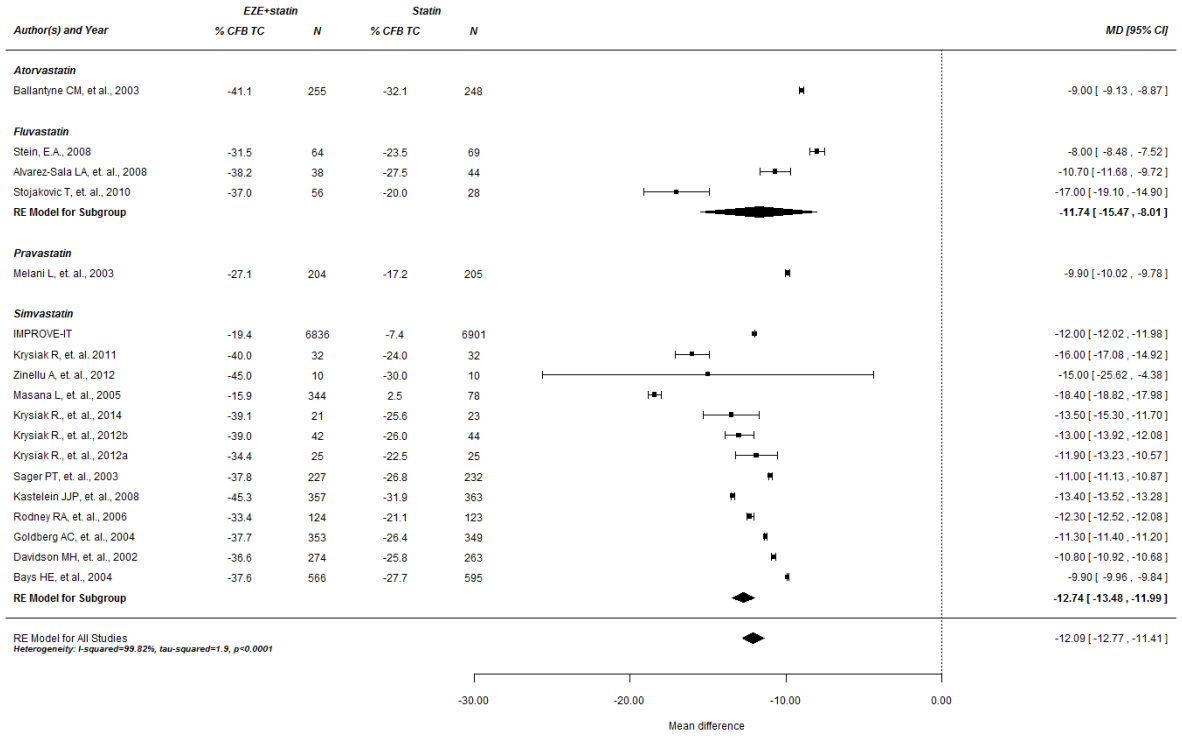
Figure 10 Percent mean difference in LDL-c (mmol/L) among studies comparing ezetimibe + simvastatin to matching simvastatin dose – diabetes subgroups



Ezetimibe vs matching statin dose - TC

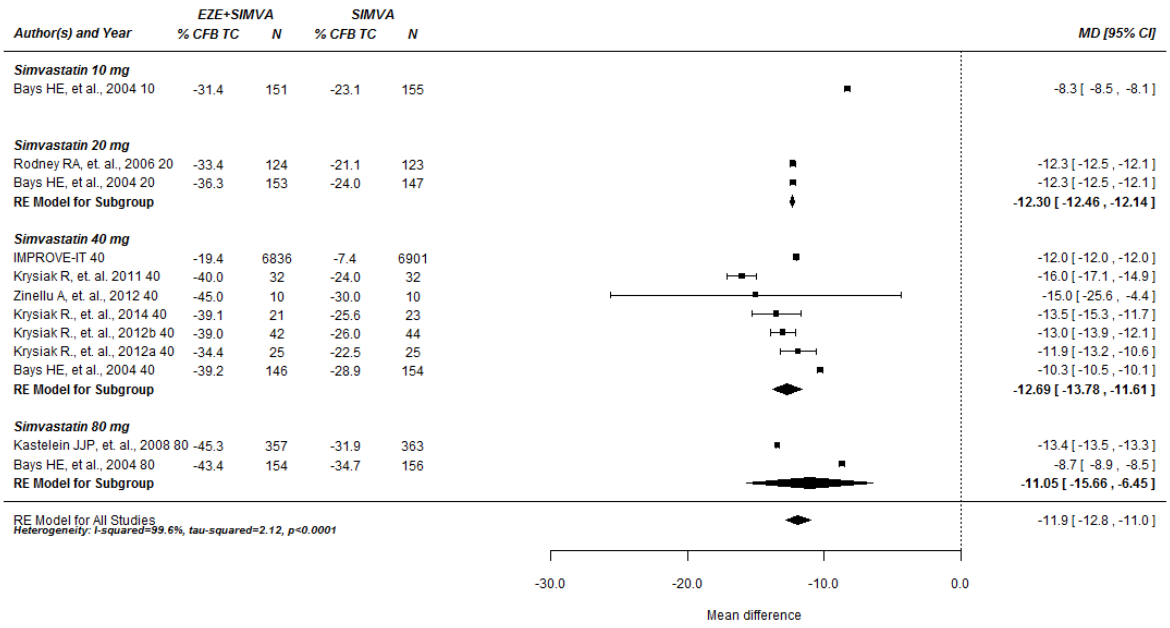
Figure 11 summarises % CFB in TC among the studies assessing ezetimibe in combination with statins vs matching statin monotherapy (for the full meta-analysis including 100% Japanese and Indian studies please refer to Appendix 11). The MD in TC between ezetimibe in combination with a statin and matching statin dose was -12.1% (95% CI -12.8 to -11.4); treatment effect in the individual studies ranged from -18.4% to -8.0%. The I^2 value was 99.82, which indicates a large degree of heterogeneity between the trials.

Figure 11 Percent mean difference in TC among studies comparing ezetimibe + statin to matching statin dose



A meta-analysis of percent change from baseline in TC stratified by specific doses of simvastatin was performed; these results are summarized in Figure 12. Ezetimibe plus simvastatin 10 mg produced a MD of -8.3% (95% CI -8.5 to -8.1) compared to the matching simvastatin dose. Ezetimibe plus simvastatin 20 mg showed a MD of -12.3% (95% CI -12.5 to -12.1), ezetimibe plus simvastatin 40 mg produced a MD of -12.7% (95% CI -13.8 to -11.6), ezetimibe plus simvastatin 80 mg produced a MD of -11.1% (95% CI -15.7 to -6.5). All combinations were compared to the matching simvastatin dose.

Figure 12 Percent change in TC among studies comparing ezetimibe + simvastatin to matching simvastatin dose



4.10 Indirect and mixed treatment comparisons

Not applicable.

4.11 Non-randomised and non-controlled evidence

Not applicable.

4.12 Adverse reactions

The adverse events reported in each of the included studies have been summarised in Appendix 13.

Ezetimibe monotherapy was found to have a similar adverse event profile to placebo. The most commonly reported adverse events were gastrointestinal (5–10%), musculoskeletal disorders (2–5%) and upper respiratory infections (7–11%). It was found that treatment-related adverse events ranged from 6% to 61% in the ezetimibe monotherapy arm and from 8% to 65% in the placebo arm. The number of people that discontinued treatment because of treatment-related adverse events was similar across both treatment groups (1% to 3% in the ezetimibe plus statin arm and 1% to 3% in the statin-only arm).

Therapy with ezetimibe co-administered with a statin was found to have a similar adverse event profile to that of statin therapy alone. The most commonly reported adverse events were gastrointestinal (2–18%) and musculoskeletal disorders (2–17%). It was found that treatment-related adverse events ranged from 7% to 23% in the ezetimibe plus statin arm and from 13% to 19% in the statin-only arm. The number of people that discontinued

treatment because of treatment-related adverse events was similar across both treatment groups (2% to 4% in the ezetimibe plus statin arm and 1% to 4% in the statin-only arm).

There is no known association between ezetimibe and new onset diabetes, and historically RCTs have not evaluated this outcome. However, because of an apparent association between statins and new onset diabetes, such an analysis was performed using the IMPROVE-IT trial database. For the purpose of this assessment, new onset of diabetes was defined at the individual level as any individual with no recorded prior history of diabetes who had a diabetes-related adverse event reported during IMPROVE-IT and/or received antidiabetic medication post-randomisation when such medication was not reported at baseline. Overall, approximately 7.2% of individuals were either reported or deduced to have developed diabetes over the course of the trial. No clinically meaningful differences between treatment groups were noted; there were 650 (7.2%) individuals with New Onset Diabetes in the ezetimibe/simvastatin group and 659 (7.3%) in the simvastatin group.[11]

4.13 Interpretation of clinical effectiveness and safety evidence

The evidence presented here demonstrates that ezetimibe provides a valuable treatment option for patients that require cholesterol lowering in order to reduce their risk of developing CVD or a CV related event.

The IMPROVE-IT and SHARP trials provide evidence demonstrating the clinical benefit of ezetimibe. Additionally, both trials provide support for the LDL hypothesis from the CTTC meta-analysis which shows that a reduction in LDL-c of 1 mmol/L reduces the incidence of major vascular events by 22%.[9] This analysis enabled the use of a large body of RCT evidence for ezetimibe that demonstrated the consistent LDL-c lowering in a wide population.

For the two populations in this submission:

- Where ezetimibe is used as monotherapy, a meta-analysis of 15 RCTs revealed that ezetimibe provides a significant 20.4% reduction in LDL-c.
- Where ezetimibe is used in combination with a statin, a meta-analysis of 18 RCTs revealed that ezetimibe provides a percentage mean difference of 15.5% (a further 23.5% lowering in LDL-c) when combined with a statin versus statin alone.

The overall safety and tolerability of ezetimibe, as assessed by evaluation of adverse experiences from the included RCTs, revealed no new safety findings related to study therapy.

The clinical effectiveness and safety of ezetimibe was demonstrated during TA132, and based on the additional clinical evidence presented in this submission, ezetimibe continues to provide the only valuable treatment option other than a statin that can lower LDL-c and provide clinical benefit to patients where significant unmet need remains.

End-of-life criteria

Not applicable

4.14 Ongoing studies

There are no ongoing studies that would be relevant for the current appraisal.

5 Cost effectiveness

Summary of cost-effectiveness section

- The updated cost-effectiveness analyses confirm the original findings from NICE MTA in 2007 that ezetimibe is cost-effective in high-risk groups where dose titration of the statin is inappropriate and/or limited by intolerance (such as people with CKD), or in monotherapy for those that are intolerant or contraindicated to statins.
- A Markov model over a lifetime time horizon has been developed. The model considers the benefits of ezetimibe treatment on the reduction of major CV events (unstable angina, myocardial infarction and stroke).
- In the base case analysis for the primary prevention population at a 10-year CV risk of 20%, the ICER is £29,286 for monotherapy and £56,394 for add-on to statin. In the secondary prevention population, the ICER is £17,553 for monotherapy and £30,940 for ezetimibe co-administered with statin treatment.
- There are three relevant sub-groups due to the differences in the baseline CV risk and the lipid-modification management strategies appropriate for these sub-groups:
    - for the primary prevention population with diabetes, at a 10-year CV risk of 20%, the ICER is £19,852 for monotherapy and £30,503 for add-on to statin. No specific analyses were possible for people with type 1 diabetes, however, the elevated risk associated with these patients is reflected by the type 2 diabetes analyses.
    - An analysis reflecting a maximum atorvastatin dose of atorvastatin 20mg has been evaluated for the secondary prevention population with CKD, with an estimated ICER of £30,953.
    - Patients with HeFH have extremely high LDL-c levels, and while no specific analyses for this subgroup was possible due to lack of baseline risk data, increased LDL-c levels to such high levels, has shown that ezetimibe is a cost-effective option in the analyses.
- At higher baseline LDL-levels for all poulations examined and higher 10-year risk levels for the primary prevention population, the cost-effectiveness of ezetimibe increases

5.1 Published cost-effectiveness studies

Identification of studies

5.1.1 Strategies used to retrieve cost-effectiveness studies relevant to decision-making in England

An updated systematic review of the literature was performed to identify all published cost-utility studies in hypercholesterolaemia in the UK since TA132[7]. The systematic searches were conducted using the following electronic databases:

- *MEDLINE and MEDLINE in-process (Ovid)*
- *Embase (Ovid)*
- *Cochrane Library*
- *CRD (Centre for Review and Dissemination) databases* (i.e. *DARE (Database of Abstracts of Reviews of Effects)*, *HTA (Health Technology Assessment)*, *NHS-EED (NHS-Economic Evaluation Database*).

The search terms were defined based on the disease area, population (adult patients with primary hypercholesterolaemia), outcomes of interest (e.g. LYs gained, QALYs, and ICERs), study type (e.g., cost-utility analyses), and relevant publication types (e.g., HTAs and economic evaluations). Search terms for the outcomes of interest were defined broadly to obtain the maximum number of relevant articles.

In addition, the following congresses were searched for relevant abstracts:

- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) [EU and US]
- European Atherosclerosis Society (EAS)
- American College of Cardiology (ACC)
- European Society of Cardiology (ESC)

Congress meeting abstracts were searched via their respective websites for the preceding three years (2013-2015[3]). Relevant studies were identified, retrieved, and categorised

[3] At the time of the search, no 2015 conferences had taken place

according to topic (e.g., cost-utility results, utility results, or both). Each congress maintains a different website structure that allows users to search manually for abstracts using free-text terms which were tailored to the hypercholesterolaemia population. All included abstracts and posters were compared to the published literature retrieved from the primary literature search to identify what had been published since the congress in question was held, and what has yet to be published. This ensured that the most recent data were identified and highlighted any potential duplicates for removal. Congress abstracts were only included when no full-text article was available. This decision is based on the assumption that full-text publications provide more robust data. Details on the keyword searches for the conferences are included in Appendix 14.

For Embase, MEDLINE, and MEDLINE in-process, the searches were carried out using the OVID search platform using a global search string developed specifically for this review. Search terms were defined using a combination of Medical Subject Heading (MeSH) terms and single keywords associated with the disease area, topics of interest, and any associated diagnostic procedures or interventions of interest. When applicable, wildcards (i.e., characters such as * or $ used in a search term to represent one or more other characters) were used to increase the sensitivity to various forms or spellings of search terms (e.g. randomised vs. randomized; study vs. studies).

The searches were developed to be in line with those which were conducted by School of Health and Related Research (ScHARR) as part of the original HTA assessment of ezetimibe by NICE (TA132).[86]

As the previous review of ezetimibe published in 2008 was carried out in 2007, the current literature review will be limited to publications dated from January 2006 to the present. Although the searches were conducted between April and June 2006, this search included articles published in January of the same year to ensure full overlap with the original search.

In addition, the searches in Ovid (Embase and MEDLINE) were limited to studies with adult patients (18 years or older) and English language publications only.

The scope of the review was defined in terms of PICOS criteria - population, interventions, comparators, outcomes, and study design.[87] PICOS is a stepwise process developed to answer several questions; the PICOS scope for this review is described below (

Table 18).

Table 18 Eligibility criteria for cost-effectiveness studies

Population	Adults aged 18 years and older with primary hypercholesterolaemia (heterozygous-familial and non-familial)
Intervention	Ezetimibe Statins (atorvastatin, fluvastatin, pravastatin, rosuvastatin, simvastatin) Other lipid-lowering drugs (fibrates, nicotinic acid, bile acid sequestrants, omega-3 fatty acid)
Comparator	Ezetimibe Statins (atorvastatin, fluvastatin, pravastatin, rosuvastatin, simvastatin) Other lipid-lowering drugs (fibrates, nicotinic acid, bile acid sequestrants, omega-3 fatty acid)
Outcomes	Inputs and outcomes reported in economic evaluations
Study design	CEA, CUA

CEA: Cost-effectiveness analysis; CUA: Cost-utility analysis

Following the searches in the aforementioned databases, all potentially eligible references were imported into the *Reference Manager* software and any duplicates were removed. The titles and abstracts of the remaining references were reviewed by two independent reviewers based on the inclusion and exclusion criteria that were defined by the PICOS criteria. In the instance of discrepancies between the two decisions, arbitration was carried out by an independent reviewer.The inclusion and exclusion criteria are outlined in

Table 19 and

Table 20, respectively.

Table 19 Inclusion criteria for the economic evaluation searches

Parameter	Criteria
Population	Adults ≥18 years with primary hypercholesterolaemia (heterozygous familial and non-familial)
Intervention	Ezetimibe Statins (atorvastatin, fluvastatin, pravastatin, rosuvastatin, simvastatin) Other lipid-lowering drugs (fibrates, nicotinic acid, bile acid sequestrants, omega-3 fatty acid)
Comparators	Ezetimibe Statins (atorvastatin, fluvastatin, pravastatin, rosuvastatin, simvastatin) Other lipid-lowering drugs (fibrates, nicotinic acid, bile acid sequestrants, omega-3 fatty acid) No treatment
Outcomes	Costs: Total costs, cost breakdown HRQoL: Utilities, utility sources Other data inputs: Health states, baseline risks / transition probabilities Effectiveness: QALYs, LYs, incremental costs, incremental QALYs, ICERs
Time Limit	January 2006 – present
Country	UK
Language	English only
Study type	CEA, CUA

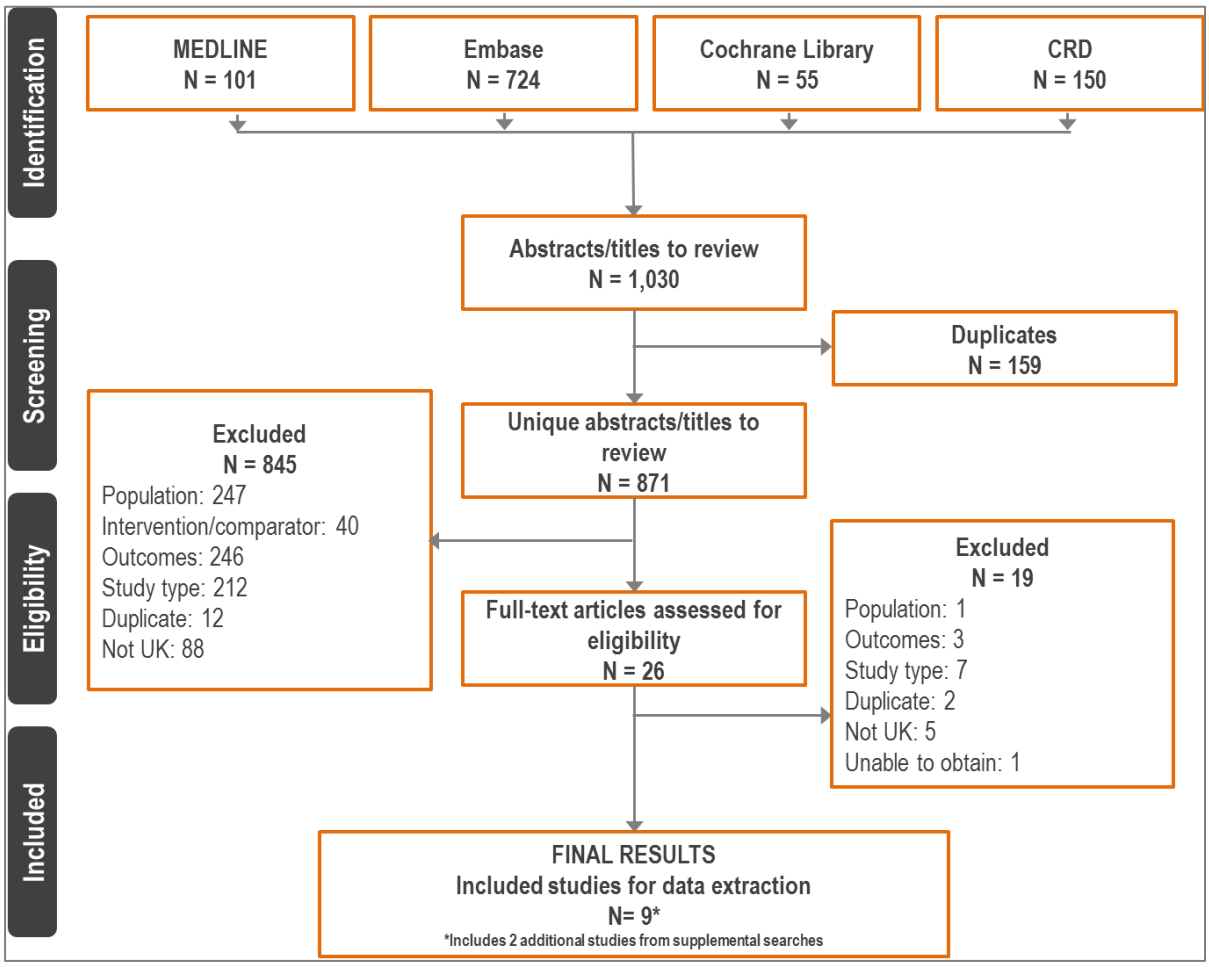
Table 20 Exclusion criteria for economic evaluation searches

	Criteria
Population	Not adults ≥18 years with primary hypercholesterolaemia (heterozygous familial and non-familial)
Intervention	Not ezetimibe, statins or other lipid-lowering drugs
Comparators	Not ezetimibe, statins or other lipid-lowering drugs
Outcomes	Not reporting results from cost-effectiveness models (please see outcomes listed in Table 19 above)
Time Limit	Before January 2006
Country	Countries outside the UK
Language	Non-English
Study type	Animals studies Randomised Clinical Trials (RCTs) Cost minimisation studies Cost analyses Meta-analyses and systematic reviews Other: letters, notes, reports, short surveys, trade journal, conference abstract[4], conference paper, conference proceeding, conference review, or editorials

[4] Conference proceedings have been excluded from the primary literature review as congress abstracts were reviewed specifically from the relevant congress websites

The full publication of any articles that were deemed relevant for full-text review was obtained. As before, two independent researchers reviewed each full-text article and, in the instance of any disagreement, a third party was consulted. The flowchart of the review is illustrated in Figure 13.

Figure 13 Flow-chart for economic systematic review



A total of 1,030 articles were retrieved by the search. After the duplicates were removed 871 abstracts were available to be reviewed against the criteria outlined in

Table 19 and

Table 20, and 845 papers were excluded. After the abstracts were reviewed, 26 papers were ordered for full publication review. A total of seven full-text papers met the inclusion criteria and data were extracted. No conference abstracts fitting the inclusion criteria were identified for this search.

The seven studies that met the criteria based on the full-text review were extracted in a data extraction sheet. Data that were extracted included those pertaining to costs (e.g., total costs, cost breakdown), HRQoL (e.g., utilities, utility sources), cost-effectiveness outcomes (e.g., QALYs, LYs, incremental costs, incremental QALYs, as well as model inputs (e.g., health states, transition probabilities).

In addition, a supplemental search of relevant studies that fell outside of the original scope was conducted. This included a search for clinical guidelines and technology appraisal conducted or published by NICE since TA132[7] for relevant de novo cost-effectiveness models and a hand search of references of included economic evaluations for relevant models. As a result, two additional studies were included (Ward et al. 2007[12] [TA94] and NICE de novo cost-effectiveness analysis for CG181[88]). These studies originally fell outside of the scope of the review as they do not focus specifically on patients with hypercholesterolemia or ezetimibe as a primary intervention; however, as they present relevant inputs and model structures that were utilised by included models they were deemed relevant for final inclusion. These studies have been included in the description below.

Description of identified studies

5.1.2 Brief overview of each cost-effectiveness study only if it is relevant to decision-making in England

All seven studies identified in the systematic review were cost-utility analyses conducted for the UK. In addition, all models applied a discount rate 3.5% for both costs and benefits, in line with recommendations by NICE.[89] The Cook model[90] was adapted in two of the studies,[91,92] and modified versions of the original model developed by Ward *et al.*[12] was applied in two studies[91;93]. The three remaining studies developed new models. Summaries of the included studies are provided below.

The two additional studies, Ward et al. 2007[12] and CG181[88], are also included in the summaries below they provided details on modelling approaches and relevant inputs used in the models above.

Davies and colleagues. Cost-effectiveness of rosuvastatin, atorvastatin, simvastatin, pravastatin and fluvastatin for the primary prevention of CHD in the UK. Br J Cardiol 2006;13:196-202 [94]

A UK study from 2006 by Davies and colleagues aimed to develop a cost-utility model to calculate the cost-effectiveness of lipid-lowering therapy for the primary prevention of CHD. The model estimated the cost-effectiveness of five different statins (rosuvastatin, atorvastatin, simvastatin, pravastatin and fluvastatin) versus no treatment.

A Markov model was developed to extrapolate beyond short-term trial evidence for a cohort of 1,000 male and female patients with a starting age of 55. Model inputs for efficacy - using

mean change in total cholesterol and HDL - were taken from the six-week STELLAR trial[95] where patients were randomised across dose ranges to the different statins. These data were used to derive short-term dosing and risk reduction profiles that were extrapolated through lifetime CHD prevention by applying risk equations from the Framingham Heart Study.[96] Specifically, primary total CHD, stroke and other CVD risk were determined using the Framingham risk equations[96]; however, as these do not estimate secondary CHD risk, this was modelled from D'Agostino *et al.* (2000)[97], which estimates both. This was done by using d'Agostino's primary and secondary CHD risk predictions to determine odds ratios for secondary CHD and applying these to the primary CHD probability calculated from Framingham.

Costs were derived from the Prospective Registry of Acute Ischaemic Syndromes in the UK (PRAIS-UK) as reported in Palmer *et al.* (2004)[98] along with NHS and UK reference costs.[99] The modelled results demonstrated that all statins were found to be cost-effective in comparison to no treatment. The baseline results showed that rosuvastatin was the most effective statin for reducing short-term cholesterol levels. A probabilistic sensitivity analysis was performed to address the uncertainty of the costs associated with the treatment of different cardiovascular events. The results from these analyses showed that the cost-effectiveness of the modelled treatment were consistent and did not differ significantly.

Manufacturer's model for TA132. NICE.[100] Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia. *NICE technology appraisal guidance 132*. November 2007[7]

The original 2007 NICE MTA for ezetimibe reported the results from the manufacturer's submission model. This model was based on the aforementioned Cook model[90], and was developed to evaluate the cost-effectiveness of ezetimibe plus statin therapy in patients with primary hypercholesterolaemia. Only the inputs and results from the manufacturer's submission are reported here, as the ERG model is reported in detail in Ara et al.[86] The manufacturer submitted two models: the 'Cook' model, an adaptation of a previous model, and the 'Basic' model, a simple decision tree model developed to validate the results of the Cook model. This section will focus on the Cook model; it should be noted, however, that the 'Basic' model provided similar results to those calculated using the Cook model, which used published evidence from a meta-analysis conducted by the CTT Collaboration on the relationship between reductions in LDL cholesterol and the corresponding reduction in the incidence.

In contrast, the treatment effect in the Cook model was estimated using changes in total and HDL cholesterol concentrations derived from a meta-analysis of short-term RCTs along with algorithms from the Framingham study[96] to predict future cardiovascular events, and algorithms from the UK Prospective Diabetes Study for people with diabetes who have a history of CVD.[101;102]

Model inputs for costs and utilities were derived from those reported in the Statins Assessment Report from TA94, 2004.[103] Drug costs were generally based on the July 2006 NHS drug tariff. A UK NHS perspective was adopted.

Ara and colleagues. Ezetimibe for the treatment of hypercholesterolaemia: A systematic review and economic evaluation. *Health Technology Assessment* 2008;12(21):1-92[86]

In an ERG report from 2008, Ara *et al.* (2008) conducted a systematic literature review and meta-analysis, and developed a de novo cost-utility model to evaluate the clinical and cost-effectiveness of ezetimibe treatment as monotherapy or as an add-on to statin therapy in patients with primary hypercholesterolaemia in the UK as part of the NICE MTA for ezetimibe.

This de novo model was populated for two specific subgroups: (1) those who tolerate statin treatment, (2) patients where statin treatment is contraindicated and / or in patients who do not tolerate statins. Model inputs used to assess the costs and benefits associated with treatment were derived from literature reviews and focussed searches, as well as the ScHARR economic analysis of statin therapy[103], expert opinion and reference sources such as the British National Formulary. Transition probabilities and baseline risks were derived from Nottingham Heart Attack Data[104], South London Stroke data[105] and from the Health Survey for England.[106]

Effectiveness of treatments is modelled using a reported link between chemically induced LDL-c reductions and CV events from the CTT Collaboration. 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 and translating these changes into CVD events based on the linear relationship between absolute LDL-c reduction and proportional reduction in CV event.[16]

The study explored the cost-effectiveness of ezetimibe across several different treatment scenarios. These are outlined in Table 21 below.

Table 21 Cost-effectiveness of ezetimibe across scenarios modelled by the Assessment Group

Scenario	ICER (cost per QALY)
Scenario 1: Ezetimibe co-administered with current strategy vs. current statin therapy titrated to the next dose (simvastatin)	£24,000–£43,000
Scenario 2: Ezetimibe monotherapy vs. no treatment	£24,000–£42,000
Scenario 3: Ezetimibe co-administered with non-proprietary simvastatin vs. atorvastatin	£1,500–£4,600
Scenario 4: Ezetimibe co-administered with current statin therapy vs. current statin therapy alone	£19,000–£47,000
Scenario 5: Ezetimibe co-administered with rosuvastatin monotherapy	£19,000–£47,000

Ara and colleagues. Cost effectiveness of ezetimibe in patients with cardiovascular disease and statin intolerance or contraindications: a Markov model. *American Journal of Cardiovascular Drugs*. 2008;8(6):419-27[91]

In 2008, Ara and colleagues also published the results from a cost-utility model based on a modified a Markov model initially constructed by Ward *et al.*[12] The model was developed to estimate the cost-effectiveness of long-term ezetimibe monotherapy. The effect of treatment was compared to no treatment.

The model was developed for a population of 1,000 male patients aged 55 years with established cardiovascular disease who do not tolerate statins or in whom they are contraindicated. Prevalence data from the British Heart Foundation were used in order to designate patients to initial health states. Efficacy data for the treatment of ezetimibe monotherapy were taken from a meta-analysis conducted by the authors which comprised seven placebo-controlled trials that measured the intermediate outcome LDL-c in patients with CVD. This was then used to predict cardiovascular events using the published CTT Collaboration relationship that links changes in LDL-c to CVD events.[16]

Model inputs for health state costs and quality of life were derived from published literature, and baseline risks / transition probabilities were derived from the Nottingham Heart Attack Register[104] and the South London Stroke Register[105]. The authors reported that, for this population, ezetimibe monotherapy compared with no treatment is cost-effective. Further, univariate sensitivity analyses demonstrated that the modelled results were robust in a majority of cases towards changes in individual parameter values, keeping most results below the threshold of £30,000 per QALY.

Ara and colleagues. Estimating the health benefits and costs associated with ezetimibe co-administered with statin therapy compared with higher dose statin monotherapy in patients with established cardiovascular disease: results of a Markov model for UK costs using data registries. *Clinical Therapeutics*. 2008 August;30(8):1508-23.[93]

In 2008, Ara and colleagues published a study estimating the cost-effectiveness of ezetimibe treatment in combination with statin therapy and its long-term impact on health status in patients with established cardiovascular disease. As in the above mentioned study, costs and benefits were modelled for a hypothetical cohort of 1,000 male patients at the age of 55 using a Markov model adapted from an original model by Ward *et al.*[12]

Results from a meta-analysis by Ara and colleagues[91] reporting clinical evidence were used to compare the effect of treatment to the effect of statin monotherapy. The relative risks of events were estimated using a published relationship linking LDL-c to CVD events.[16] The model was developed using inputs from UK registries for transition probabilities, and findings from published literature were used for health-state costs and HRQoL data.

The authors observed that, in some cases, ezetimibe treatment in combination with statin therapy was cost-effective compared with statin monotherapy. This study utilised the established relationship between the reduction of low-density lipoprotein cholesterol and the reduction in cardiovascular events.

Nherera and colleagues. Cost-effectiveness analysis of the use of a high-intensity statin compared to a low-intensity statin in the management of patients with familial hypercholesterolaemia. *Current Medical Research and Opinion*. 2010;26(3):529-36[107]

Nherera et al. developed a lifetime Markov model to estimate the cost-effectiveness of treating patients with familial hypercholesterolaemia with high-intensity statins compared with low-intensity statins. The model was populated for a hypothetical cohort of 1,000 patients between 20 and 70 years of age.

Model inputs for the effectiveness of treatment were derived from a meta-analysis conducted by the authors which was based on published trials. A linear relationship between absolute LDL-c reduction and reduction in CVD outcomes was assumed based on a published relationship linking this surrogate outcome to CVD events.[16] Cost and quality of life data

were collected from published literature, UK Prescription Pricing Authority, NICE TA94[103], and Department of Health reference costs.

In this model, high-intensity statins were found to be cost-effective for patients with familial hypercholesterolaemia between the ages 18 and 59 years. Above the age of 60, the cost-effectiveness rose above the £20,000 threshold. Results from the sensitivity analyses suggest that the results were most sensitive to changes in treatment effect on mortality and the cost of high-intensity statins.

Reckless and colleagues. Projected cost-effectiveness of ezetimibe/simvastatin compared with doubling the statin dose in the United Kingdom: findings from the INFORCE study. *Value in Health*. 2010 September;13(6):726-34[92]

The Cook model was also used in the study by Reckless *et al*. In this study, the model was adapted to evaluated the lifetime costs and benefits of switching to ezetimibe/simvastatin in comparison to doubling the submaximal statin doses.

Efficacy data were derived from the INFORCE study;[108] reduction in LDL-c after 12 weeks was linked to reductions in CVD events using changes in lipid components from the Framingham risk equations.[96;97] In addition the model was populated using UK-specific mortality data, and costs based on published literature. The patients included in the INFORCE study had been hospitalised for acute coronary syndrome events and had also been using a submaximal dose of a statin for six weeks before admission.

The authors reported that, compared to doubling the submaximal statin dose, switching to ezetimibe/simvastatin is a cost-effective treatment for reducing low-density lipoprotein cholesterol.

Ward and colleagues. A systematic review and economic evaluation of statins for the prevention of coronary events. *Health Technol Assess*. 2007;11(14):1-160[12]

The model by Ward *et al.* has been adapted in two of the relevant included economic evaluations previously discussed. The aim of this study was to evaluate the clinical and cost-effectiveness of groups of statins (atorvastatin, fluvastatin, pravastatin, rosuvastatin and simvastatin), for the primary and secondary prevention of cardiovascular events in adults with, or at risk of CHD. This de novo model was developed as part of NICE TA94, which was conducted prior to NICE TA132[7].

A Markov model was developed to explore the costs and health outcomes associated with a lifetime of statin treatment using a UK NHS perspective. Data from UK epidemiological

studies were used to inform event rates, and were combined with results from the meta-analysis of RCT evidence on the effectiveness of statins to model the relative risk reductions of event rates for patients on statin therapy.

Costs of health states (first-year costs and subsequent year) were based on a review of published evidence to obtain the most recent and appropriate costs; they were at 2004 prices and a discount rate of 6% was applied. The annual cost of statins comprised a weighted average cost of statins (weighted by the trial evidence), for different statins at different dosage. Utility estimates for health states within the model were identified by a literature review. A 1.5% discount rate was applied to health benefits. Input parameters were assigned probability distributions to reflect their imprecision, and Monte Carlo simulations were performed to reproduce this uncertainty in the results.

The authors concluded that statin therapy in secondary prevention is likely to be considered cost-effective when compared with other current standard treatments available to the NHS. However, in primary prevention, the cost-effectiveness ratios are dependent on the level of CHD risk and age.

NICE. Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. *NICE clinical guideline 181*. July 2014[88]

The NICE CG181[88] is a partial update of the 2008 guidelines. This update focussed on the latest evidence on lipid modification management and CVD risk assessment for the primary and secondary prevention of CVD. While the guidelines considered many treatments, this section focusses on the de novo cost-effectiveness model evaluating statins for primary and secondary prevention of CVD.

The cost-effectiveness was assessed using a cost-utility model, and is based on the models developed by Ward *et al*.[12;103] A Markov model with annual cycles was used and was composed of two parts. The first component of the model was designed to investigate the secondary prevention of CVD, and the second added an initial primary prevention phase using the same structure. These models followed the NICE reference case.[89]

For clinical inputs, the risk ratios from the meta-analyses performed for the clinical review in the same guidance document were applied to baseline event rates, which were primarily taken from Ward *et al.* 2005 and re-adjusted to reflect the QRISK2 risk assessment tool for primary prevention people without diabetes and UKPDS for primary prevention people with

diabetes. Utility multipliers for each health state were also taken from these previous models. The costs of each health state were calculated based on assumed typical resource use.

The results of these models investigated the following cost-effectiveness scenarios:

- Secondary prevention for people with existing CVD, using the secondary model.
- Primary prevention for people without existing CVD and without diabetes, using the primary model, calibrated to relate to CV risk as predicted by the QRISK2 tool (5-30% levels).
- Primary prevention for people without existing CVD but with type 2 diabetes, using the primary model, calibrated to relate to CV risk as predicted by the UKPDS tool (5-30% levels)

For secondary prevention, the analysis found that high-intensity statin treatment using atorvastatin 20 mg, 40 mg or 80 mg is cost-effective compared to medium- and low-intensity statin treatment and compared to no treatment for people who already have CVD (ICER: £2,959 per QALY gained for atorvastatin 20 mg compared to no treatment; £3,275 per QALY gained for atorvastatin 80 mg compared to no treatment). These results were robust to the sensitivity analyses conducted and for all subgroups by age and sex.

For primary prevention, the analysis found that high-intensity statin treatment using atorvastatin 20 mg is cost-effective compared to medium-intensity statin treatment using simvastatin 20 mg at a cost-effectiveness threshold of £20,000 per QALY gained for men aged 60 who do not have CVD and who have a QRISK2 CV risk score above 6.8%. Atorvastatin 80 mg is cost-effective compared to medium-intensity statins for those men aged 60 who have a QRISK2 score above 8.7%. Medium-intensity treatment is cost-effective or dominant compared to no treatment or low-intensity treatment at all risk levels of interest.

For diabetes, the analysis found that high-intensity statin treatment using atorvastatin 20 mg is cost-effective compared to medium-intensity statin treatment at a cost-effectiveness threshold of £20,000 per QALY gained for people who have type 2 diabetes but do not have CVD and who have a UKPDS CV risk score above 3.9%. Atorvastatin 80 mg is cost-effective compared to medium-intensity statins for those who have a UKPDS score above 5.0%. Medium-intensity treatment is cost effective or dominant compared to no treatment or low-intensity treatment at all risk levels of interest.

Table 22 provides and overview of the nine included cost-effectiveness studies and baseline results.

Table 22 Summary of included cost-effectiveness studies

Study	Summary of model	Health States	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (cost (£) per QALY gained)
Davies *et al.* 2006[94]	Combination of a titration model and a long-term Markov model with 9 health states and a cycle length of 4 years.	1 CHD free 2 Existing CHD 3 Angina 4 MI – year 1 5 Post-MI 6 Other CVD: Stroke (mild, 7 moderate, severe), CHF, PVD 8 Secondary CHD 9 Dead	NR	NR	NR	ICER (men/ women) Rosuvastatin/ vs. Simvastatin: 9,735/ 15,184 Atorvastatin/ vs. Rosuvastatin: Dominated/dominated Simvastatin/ vs. Pravastatin: 6,883/10,790 Fluvastatin/ vs. Simvastatin: Dominated/dominated Pravastatin/ vs. No treatment: 296/779

NICE TA132 2007 Manufacturer's submission (Cook model)[91]	Cook Markov model including 9 health states. Cycle length is not reported.	1 Event free 2 Primary MI 3 Primary angina 4 Primary stroke 5 Secondary M 6 Secondary angina 7 No event in previous 12 months 8 CHD death 9 Non-CHD death	NR	NR	NR	ICER Ezetimibe plus current statin: range from just under 8,000 to just under 122,000 Ezetimibe monotherapy versus no treatment, ranged from just under 10,000 to just over 131,000
Ara *et al.* 2008[91]	Modified Markov model based on the original model by Ward S *et al.* with a cycle length of 1 year.	1 New unstable angina 2 New nonfatal MI 3 New nonfatal stroke 4 Post-stable angina 5 Post-unstable angina 6 Post-MI 7 Post-TIA 8 Post-stroke 9 Fatal CHD 10 Fatal stroke 11 Death other causes	NR	Lifetime Ezetimibe: 8.400 No treatment: 8.189	£, UK, 2006 Lifetime Ezetimibe: 14,458,088 No treatment: 9,597,278	Lifetime ICER for Ezetimibe in comparison to no treatment: 23,026 (22,979-23,074)

Ara *et al.* 2008[93]	Adapted version of the original Markov model developed by Ward *et al.* with a cycle length of 1 year	1 New unstable angina 2 New nonfatal MI 3 New nonfatal stroke 4 Post-stable angina 5 Post-unstable angina 6 Post-MI 7 Post-TIA 8 Post-stroke 9 Fatal CHD 10 Fatal stroke 11 Death other causes	NR	Lifetime Ezetimibe co-administered with statin: 8.386 Statin monotherapy: 8.252	£, UK, 2006 Lifetime Ezetimibe co-administered with statin: 16,560,000 Statin monotherapy: 12,867,000	ICER for ezetimibe co-administered with statin in comparison to statin monotherapy Mean (95% CI) Lifetime: 27,475 (27,331-27,620)
Ara *et al.* 2008[86]	A new Markov model with a cycle length of 1 year	1 Event free 2 Stable angina 3 Post-stable angina 3 Unstable angina 4 Post-unstable angina 5 Non-fatal MI 6 Post-non-fatal 7 MI 8 TIA 9 Post-TIA 10 Non-fatal stroke 11 Post-non-fatal stroke 12 Fatal CHD event 13 Fatal CVD event 14 Death from other causes	NR	NR	NR	ICER range: Ezetimibe to ongoing statin treatment compared with maintaining statin treatment at the current dose: 19,000 to 48,000 Ezetimibe to ongoing statin treatment compared with a switch to a more potent statin: 1,500 to 116,000

Nherera *et al.* 2010[107]	Lifetime Markov model. Cycle length is not reported.	1 Well 2 MI – year 1 3 MI – subsequent 4 Stroke – year 1 5 Stroke – subsequent 6 PVD – year 1 7 PVD- subsequent 8 HF – year 1 9 HF – subsequent 10 REV – year 1 11 REV – subsequent 12 Unstable angina – year 1 13 Unstable angina – subsequent 14 Death	NR	High-intensity statin: 12.44 Low-intensity statin: 12.02	£, UK, 2008-2009 values High-intensity statin: 14,095 Low-intensity statin: 9,448	ICER for high-intensity statin in comparison to low-intensity statin: 11,103
Reckless *et al.* 2010[92]	Markov- decision-analytic model, based on the Cook model with 5 health states and a cycle length of 1 year.	1 No event 2 MI 3 Angina 4 CHD death 5 Non-CHD death	Ezetimibe/Simvastatin (10/40 mg) group (mean, SD): 63.3 (10.5) Double statin dose group (mean, SD): 63.6 (10.9)	Pooled baseline (mean) Ezetimibe-Simvastatin (10/40 mg): 6.82 Doubling the statin dose: 6.94	£, UK, 2004 values, inflated to 2009 costs Pooled baseline (mean) Ezetimibe-Simvastatin (10/40 mg): 4,602 Doubling the statin dose: 4,763	ICER for Ezetimibe/Simvastatin in comparison to doubling the statin dose: 11,571

Ward *et al.* 2007[12]	Markov model with 10 health states and a cycle length of 1 year.	1 Event free 2 Remain event free 3 Stable angina 4 Unstable angina 5 Non-fatal MI 6 Fatal CHD event 7 TIA 8 Non-fatal stroke 9 Fatal CVD event 10 Death from other causes	Range, starting age: 45 – 85	Discounted incremental QALYs Secondary prevention (M/F) 45 yrs.: 462/493 55 yrs.: 410/452 65 yrs.: 314/387 75 yrs.: 193/248 85 yrs.: 103/132	Discounted incremental costs Secondary prevention (M/F) 45 yrs.: £4,732/£4,966 55 yrs.: £4,109/£4,432 65 yrs.: £3,310/£3,660 75yrs: £2,455/£2,799 85 yrs.: £1,615/£1,853	Discounted ICERs Secondary prevention (M/F, £,000) 45 yrs.: £10.2/£10.1 55 yrs.: £10.0/£9.8 65 yrs.: £10.5/£9.5 75 yrs.: £12.7/£11.3 85 yrs.: £15.7/£14.0
NICE CG181 2014[88]	Markov models based on Ward. including 15 health states and a cycle length of 1 year. Low, medium vs. high intensity statins	1 Well 2 MI 3 Post-MI 4 HF 5 Post-HF 6 TIA 7 Post-TIA 8 Stroke 9 Post-stroke 10 PAD 11 Post-PAD 12 Stable angina 13 Post-stable angina 14 Unstable angina 15 Post-unstable angina 16 CV Death 17 Non-CV Death	Range, starting age: 40 – 70	NR	NR	Discounted ICERs: Secondary prevention: (£,000) 60 yrs., male, Med – Low: dominates 60 yrs., male, High – Medium: £1.4 Primary prevention: (Male, £,000), 60 yrs., 10% QRISK2 S20 vs NT: £4.3 A20 vs S20: £3.2 A80 vs S20: £13.3

CHD: coronary heart disease; MI: myocardial infarction; TIA: transient ischaemic attack; CVD: cardiovascular disease; CHF: congestive heart failure; PVD: peripheral vascular disease; PVD: peripheral arterial disease; HF: heart failure; REV: Revascularisation; S20, simvastatin 20mg; A20, atorvastatin 20mg; A80, atorvastatin 80mg

5.1.3 Complete quality assessment for each relevant cost-effectiveness study identified

All included economic models were quality assessed using the quality checklist for cost-effectiveness studies by Drummond *et al.* (1996). The results from these assessments are *reported in Appendix 15.*

5.2 De novo analysis

Patient population

The patient population considered in the cost-effectiveness analyses are patients with primary hypercholesterolaemia in a primary prevention (without established CVD) or a secondary prevention population (with established CVD), using ezetimibe either:

- as a monotherapy in patients where a statin is considered inappropriate or is contraindicated or not tolerated (referred to as 'monotherapy' in the following sections);
- or, co-administered with a statin (interchangeably referred to as 'add-on to statin') in people whose condition is not appropriately controlled with a statin alone, either after appropriate dose titration of initial statin therapy or because dose titration is inappropriate or not tolerated.

There are three further subgroups that are relevant:

- Primary prevention for people with diabetes
- People with CKD
- People with heterozygous-familial hypercholesterolaemia (HeFH)

Section 5.9 provides details of the cost-effectiveness approach adopted for these sub-groups.

Primary Prevention

For the base case, a 20% 10-year risk level has been applied, and is measured using the QRISK2 risk assessment tool recommended in the recent Lipid Modification guideline (CG181, 2014)[8]. Scenario analyses applying alternative 10-year CV risk levels of 30% and 10% for the primary prevention population are evaluated in section 5.8.

The baseline characteristics representative of the primary prevention population that are used in the cost-effectiveness analyses are summarised in Table 23. These have been informed by a CPRD observational study which investigated statin prescribing in the primary prevention population in the UK (n=300,914).

Table 23 Baseline characteristics, primary prevention population

Patient characteristic	Mean	Source
Starting age	60	van Staa et l., 2013[27]
% female	46.4%	

As part of the modelling approach, the baseline LDL-c pre-statin treatment is also required. Van Staa *et al.* reported the mean LDL-c level for the primary prevention population one-year prior to statin initiation.[27] This value (4.32 mmol/L) has been applied in the base case for primary prevention. A scenario analysis evaluating the impact of alternative baseline LDL-c value, pre-statin has been conducted (Section 5.8).

Secondary Prevention (established CVD)

The baseline characteristics representative of the secondary prevention population are presented in Table 24; these come from a UK retrospective observational study. The data is consistent with other UK data sources.[109]

Table 24 Baseline characteristics, secondary prevention population

Patient characteristic	Mean	Source
Starting age	69	Jameson *et al.*, 2014 [30]
% female	34.6%	

The baseline LDL-c values reported in Van Staa *et al.* (4.32 mmol/L) are also utilised for the secondary prevention population analyses, as no data specific data for this population were found.[27] A scenario analysis evaluating the impact of alternative baseline LDL-c value, pre-statin has been conducted (Section 5.8).

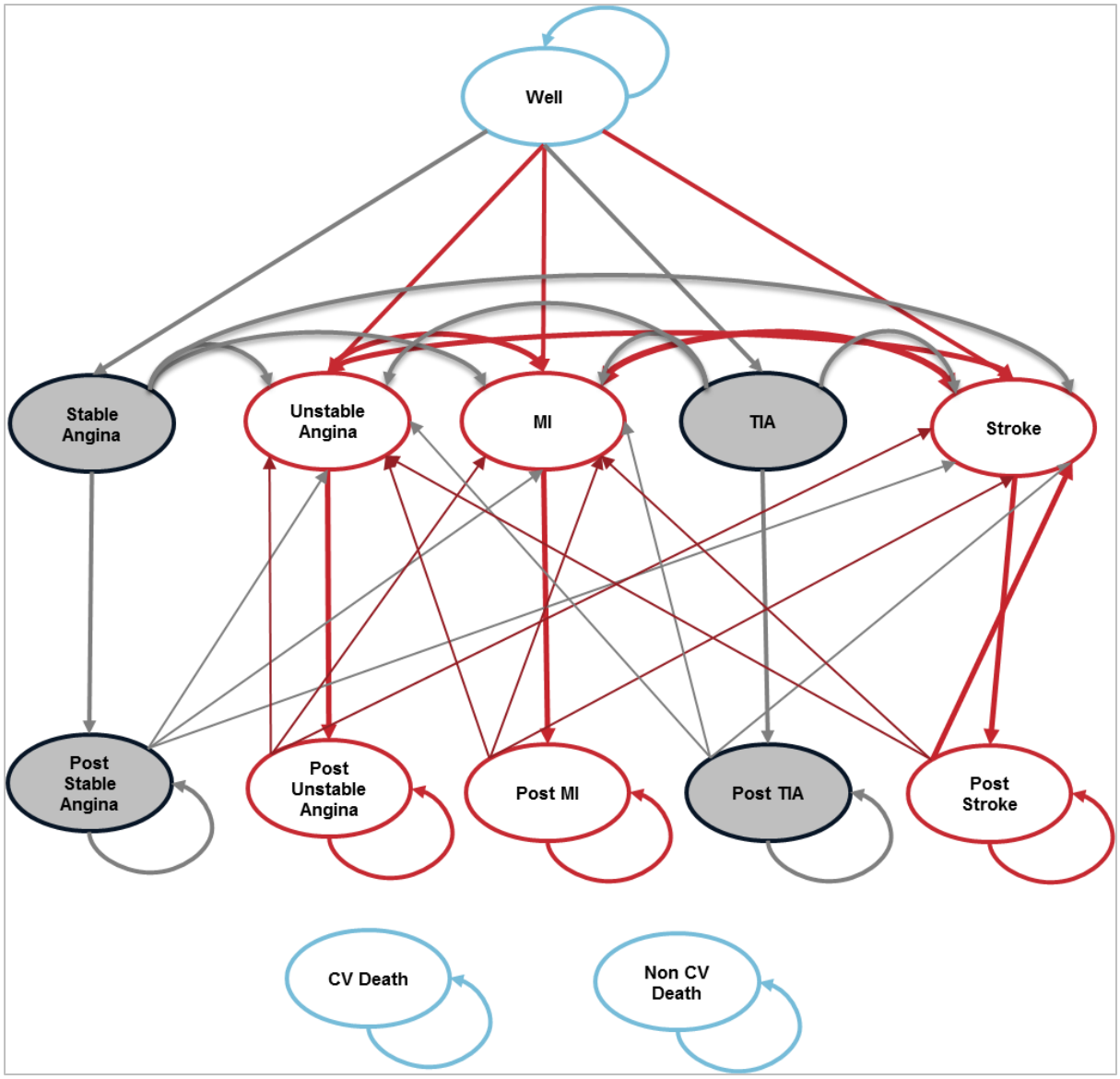
Alternative baseline characteristics are explored in sensitivity analyses (see section 5.8).

Model structure

A Markov model has been developed for the cost-utility analyses, which is based on the modelling approaches developed by Ward *et al.* for TA94 and Ara *et al.* for the original

TA132 review. Markov modelling is useful for diseases involving risks that continue or increase over time and where events can occur more than once, such as hypercholesterolaemia. The methodology provides flexibility for tracking costs and utilities over numerous health states. The proportion of patients in each of the mutually exclusive health states is governed by age-dependent time-variant transition matrices which describe the annual probability of moving to an alternative health state. Figure 14 provides a schematic representation of the model structure used.

Figure 14 Schematic of model structure



NB. Stable angina and TIA health states (grey coloured) are additional health states explored in scenario analyses . All non-fatal health states can transition at any point in the absorbing fatal health states, CV death and Non-CV death.

CV events modelled focus on the three major CV events, unstable angina, MI and stroke, which aligns with the evidence base between lipid-lowering therapies and CV event reduction. Unstable angina and myocardial infarction are often referred to as acute coronary

syndrome, which covers a spectrum of severity of events from unstable angina, NSTEMI to STEMI (most severe). Revascularisation has been reflected in the cost data for the health states, and therefore this has not been modelled as a separate health state. Prior models by Ward *et al.* and Ara *et al.*, modelled treatment benefits associated with the use of lipid-lowering therapy for stable angina and transient ischemic attack (TIA), which are not included in the base case cost-utility analysis. A scenario analysis has been performed to explore the impact of including these health states (section 5.8).

The secondary prevention structure follows people who have established CVD and therefore have experienced a non-fatal CV event. Patients are categorised as to whether they have experienced unstable angina, MI or a stroke. Patients within these states can incur any of the other CV events in the next cycle. Alternatively they can die (due to CV-related or non-CV-related death). If patients do not experience any of these events, they move into the respective post-event state. Similar to the cost-effectiveness modelling approached by Ward *et al.* and Ara *et al.*, time dependency has been incorporated into the model by cross referencing age as a risk factor for mortality and an increasing CV risk over time. Baseline utility is also time dependent in the cost-effectiveness model and falls as the cohort ages. Mortality is incorporated into the model via two transitions: the transition to the CV death health state and the transition to the non-CV death state. Patients can transition to these two states at the end of each model cycle.

Primary prevention considers an additional health state; the 'well' state, where all patients begin the model. Patients in this state are assumed not to have experienced any CV event. A proportion of patients transition from this health state to the CV events health states (including non-CV death and CV death) based upon the risk associated with incurring each CV event, while the remaining patients remain in the 'well' state.

Within both primary and secondary prevention each non-fatal CV event is modelled in two stages. The first stage accounts for cost and HRQoL impact in the first year following the event, the second stage accounts for long-term outcomes post-event. This approach is required due to the memoryless nature of Markov models (i.e. all patients are assumed to have the same risk of future events) in order to capture different risk levels, utility impacts and costs in the first 12 months after an event compared to the longer term management of the disease. Patients modelled can incur one event per annual cycle. In clinical practice, patients may experience more than one type of non-fatal CV event over a lifetime, for example, a patient experiences a stroke, followed by a MI subsequently. Due to the memoryless feature of Markov models, the most recent CV event occurred is used to model

the future costs and QALY impact of the patients. This is a conservative assumption and thus the cost-effectiveness estimates are expected to be an underestimate.

Quality-adjusted life years for the cohort are computed for each annual cycle by multiplying the proportion of the cohort in each state by the age adjusted utility multiplier for that state. Consistent with the NICE reference case, the QALYs were then discounted by 3.5% to reflect time preference; QALYS accumulated during the first cycle were not discounted. The total discounted QALYs were the sum of the discounted QALYs per annual cycle.

Costs per cycle were summed using the same approach as was used for the QALYs. Higher monitoring and appointment costs were applied to all individuals undergoing treatment in the first year of both primary and secondary treatment. Lower costs were applied to all subsequent years. Costs were discounted to reflect time preference in the same way as QALYS (discount rate = 3.5%).

A half cycle correction was applied to both costs and outcomes in line with NICE guidance to take into account the 1 year cycle length implemented in the model. Table 25 summarises the key features of the de novo cost-effectiveness analysis.

Table 25 Features of the de novo cost-effectiveness analysis

Factor	Chosen values	Justification
Time horizon	Max 100 years	Lifetime (max mean age of 100); number of years evaluated varies dependent upon the starting age of the population chosen
Cycle length	1 year	In line with available information from data sources & sufficient to model the patterns of CV events
Half-cycle correction	Applied to costs and health effects[5]	NICE reference case
Were health effects measured in QALYs; if not, what was used?	QALYs	NICE reference case
Discount of 3.5% for utilities and costs	3.5% per annum	NICE reference case
Perspective (NHS/PSS)	NHS/PSS	NICE reference case
Key: CV, cardiovascular; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, personal social services; QALYs, quality-adjusted life years		

Intervention technology and comparators

The intervention (i.e. ezetimibe) has been implemented in the cost-effectiveness model for patients with primary hypercholesterolemia in a manner that is consistent with the license (Section 2.2.1).

The comparator for the monotherapy analyses is 'no treatment'. The assumption is that patients have received appropriate diet and lifestyle advice, and are still deemed in need of treatment.

For the add-on analyses, the comparator is the maximum tolerated dose of statin alone. Atorvastatin has been presented as the main statin under consideration in the base case to reflect the updated recommendations in the NICE Lipid Modification Guideline (2014) and clinical practice[8]. For primary prevention, add-on to statin analyses, atorvastatin 20 mg has been used in the base case because the relevant population is those that cannot be up-titrated further. For secondary prevention, add-on to statin analyses, atorvastatin 40 mg is used as the relevant dose. The NICE Lipid Modification Clinical Guideline recommends patients are offered atorvastatin 80 mg, and while in clinical practice, the majority of patients are initiated on this dose post-event and prior to discharge from hospital, it is common place for the dose to be down-titrated subsequently by GPs who are responsible for the long-term management of these patients because of widespread tolerability issue of high dose statins. Additionally, the cholesterol of those patients that can tolerate atorvastatin 80 mg for primary or secondary prevention are likely to be appropriately controlled at this dose, and not require the add-on of ezetimibe.

A comparison to simvastatin 40 mg has been included in a scenario analysis to evaluate the cost-effectiveness of ezetimibe in the IMPROVE-IT population.

Treatment with both statins and ezetimibe is assumed to continue for a patients' lifetime in line with product SPCs.

5.3 Clinical parameters and variables

Baseline event rates – first CV events

The baseline transition probabilities for the primary prevention cohort are based on combining the baseline 10-year CVD-risk with the distribution of specific CVD events observed in UK disease registries, by age and gender.

The primary prevention cohort enters the model based on a specified 10-year CVD risk (e.g. 30%, 10% or 20%) as defined by QRISK2. QRISK2 is a cardiovascular risk assessment tool recommended by NICE in the 2014 Lipid Modification Guideline[8] that has been developed

by Hippisley-Cox *et al.* using GP data from the QRESEARCH database[110]. It estimates an individual's risk of experiencing a CV event, defined as fatal or non-fatal angina, MI, stroke or TIA, in the next 10 years. The selected 10-year CVD risk based are converted into 1-year probabilities to reflect the cycle length used.

The distributions to primary CV events summarised in Table 26 have been based on the data originally analysed by Ward *et al.* 2007 and included in the Ara *et al.* 2008 analyses. These were based on incidence angina and MI data from the Bromley Coronary Heart Disease Register[111] and incidence stroke and TIA data from the Oxfordshire Community Stroke Project[112;113]. It has been assumed that the distributions for the 45-54 age group are the same for the 40-44 age group, which is consistent with the approach adopted in the CG181 cost-effectiveness analysis[88].

Table 26 Distribution of patients to primary CVD event health states, originally sourced from Ward *et al.*, 2007[12]

Gender	Age (years)	Stable angina	Unstable angina	MI	TIA	Stroke	CVD Death
Male	40-54*	30.7%	10.7%	29.5%	6.0%	12.9%	10.1%
	55-64	32.8%	7.1%	17.2%	8.9%	20.6%	13.4%
	65-74	21.4%	8.3%	17.3%	10.0%	27.0%	16.0%
	75-84	19.1%	8.1%	16.1%	8.0%	34.3%	14.3%
	85-100	21.4%	9.6%	18.6%	1.6%	35.1%	13.7%
Female	40-54*	32.5%	11.7%	8.0%	16.0%	22.9%	9.1%
	55-64	34.6%	7.3%	9.2%	9.5%	28.8%	10.6%
	65-74	20.2%	5.2%	12.1%	7.3%	38.2%	17.1%
	75-84	14.9%	3.4%	10.2%	9.8%	46.4%	15.2%
	85-100	13.6%	2.9%	10.0%	8.7%	50.1%	14.7%

* It has been assumed that the annual incidence rates and distributions for the 45-54 age group are the same for the 40-44 age group

The incidence rates of CV events are multiplied by the 1-year CV probabilities to obtain a yearly baseline risk of each CV event (i.e. the transition probabilities from the 'Well' state to the first CV event). In the base case, stable angina and TIA health states have not been included in the model and therefore the risks for these events are set to 0. The impact of this is explored in scenario analyses.

As the risk of CVD increases with age, the baseline risks have been adjusted to reflect this. The age-related risk data has been sourced from an analysis of Health Survey for England 1998 data conducted by Ward *et al.*[12], which found an approximately linear relationship

between age and the annual CHD (angina and MI) risk. The rate of increase per year was 0.03% for men and 0.008% for women. A proportionately equal risk is assumed for all CV events modelled and implemented into the model. The annual rate of increase is applied for the full time horizon.

Secondary prevention

For the secondary prevention analyses, the cohort is distributed to the first non-fatal CV event that they have experienced in the model. The distribution data has been sourced from the analysis conducted by Ward *et al.*[12] (Table 27), which utilised data from the British Heart Foundation[114] and Bots *et al*[115]. These proportions were used to allocate the secondary prevention cohort to the starting CV health states in the model. As the reported values were categorised by gender, the model weights these values according to the defined baseline gender distribution of patients.

Table 27 Distribution of patients to initial health states in secondary prevention analyses

Age group	Unstable angina	MI	Stroke
Male			
40-54	15.6%	58.4%	25.9%
55-64	13.7%	62.0%	24.3%
65-74	19.6%	52.4%	28.1%
75+	18.7%	46.1%	35.2%
Female			
40-54	19.4%	43.0%	37.6%
55-64	17.6%	43.0%	39.4%
65-74	20.8%	41.5%	37.7%
75+	24.9%	31.9%	43.3%

Adapted from Ward *et al.*, 2007[12]

Baseline event rates – subsequent event

The secondary event transition probabilities have been sourced from CG181,[88] as this includes the relevant transitions for the health states modelled in the base case and the scenario analyses. These are summarised in Table 28. The data has been sourced from the original Ward *et al.* model[12] that included data from the Nottingham Heart Attack Register[104] and the South London Stroke Register[105] It has been assumed that the same transitions for the 45-54 age group originally reported are the same for patients in the age group 40-44.

Table 28 Baseline transition probabilities for secondary CV events

Age	Transition from/to	Unstable angina	MI	Stroke	CV death
40-54	Unstable angina	0	0.0495	0.0140	0.0378
	MI	0.0075	0.1280	0.0015	0.0174
	Stroke	0.0016	0.0016	0.0431	0.0092
	CV Death	0	0	0	1
	Post Unstable angina	0.0000	0.0186	0.0140	0.0085
	Post MI	0.0075	0.0162	0.0004	0.0054
	Post Stroke	0.0016	0.0016	0.0144	0.0042
55-64	Unstable angina	0	0.0497	0.014	0.0644
	MI	0.0075	0.1152	0.0032	0.0333
	Stroke	0.0031	0.0031	0.0459	0.0222
	CV Death	0	0	0	1
	Post Unstable angina	0	0.0348	0.014	0.0104
	Post MI	0.0075	0.0179	0.001	0.0095
	Post Stroke	0.0031	0.0031	0.0186	0.0098
65-74	Unstable angina	0	0.0488	0.014	0.1077
	MI	0.0075	0.1019	0.0068	0.0626
	Stroke	0.0055	0.0055	0.0481	0.052
	CV Death	0	0	0	1
	Post Unstable angina	0	0.0632	0.014	0.0124
	Post MI	0.0075	0.0185	0.0022	0.0159
	Post Stroke	0.0055	0.0055	0.0223	0.0208
75-84	Unstable angina	0	0.0466	0.014	0.1745
	MI	0.0075	0.0874	0.0141	0.1136
	Stroke	0.008	0.008	0.0446	0.1172
	CV Death	0	0	0	1
	Post Unstable angina	0	0.1122	0.014	0.0145
	Post MI	0.0075	0.0178	0.0047	0.0245
	Post Stroke	0.008	0.008	0.0246	0.0412
85+	Unstable angina	0	0.0425	0.014	0.2702
	MI	0.0075	0.0711	0.0278	0.1958
	Stroke	0.0104	0.0104	0.0446	0.243
	CV Death	0	0	0	1
	Post Unstable angina	0	0.1955	0.014	0.0167
	Post MI	0.0075	0.016	0.0091	0.0355
	Post Stroke	0.0104	0.0104	0.0252	0.0375

Adapted from CG181[88] and Ward *et al.*[12]

Background mortality

Background mortality for non-CV related death has been incorporated into the model using 2011–2013 life tables from the Office of National Statistics[116]. Within the model RRs were

calculated based upon age and gender. The proportion of living patients who are male and female is tracked within the mortality calculations to most accurately predict the number of patients dying each year. The life table data were adjusted to exclude CV-related deaths using the ONS mortality data by cause for deaths attributed to diseases of the circulatory disease coding (I00-I99) because as CV death is modelled as a distinct health state.[3;117]

Clinical data incorporated in the model

As described in the beginning of Section 4, the association between lowering LDL-c and the reduction in the risk of CV events has been established. In the original cost-effectiveness analyses for the NICE review of ezetimibe in 2007[7], the meta-analysis conducted by CTTC was used to model the treatment effect of ezetimibe and the comparators, linking the absolute reduction in LDL-c to the proportional reduction of CV events.[9] The CTTC have performed meta-analyses of statin RCTs to demonstrate the link between lowering LDL-c and reducing coronary events[9;16]. The most recent meta-analysis from 2010 included 26 RCTs (five trials more versus less intensive statin regimens, n=39,612; 21 trials statin versus control, n=129,526) showed that a reduction in LDL-c of 1.0 mmol/L reduced the risk of major vascular events by up to 22%.[9] The reduction in risk across individual endpoints is presented in Table 29.

Table 29 Individual endpoints from the CTTC meta-analysis[9]

Endpoint	RR (96% CI), 1 mmol/L reduction in LDL-c
Non-fatal MI	0.74, 95% CI 0.69; 0.78 *p*<0.0001
Stroke	0.85, 95% CI 0.80;0.90 *p*<0.0001
Any vascular death	0.86, 95% CI 0.82;0.90 *p*<0.0001
All-non vascular deaths	0.97, 95% CI 0.91;1.03 *p*<0.0001

Since the original technology appraisal of ezetimibe (TA132[7]) in 2007, additional RCT data for ezetimibe including the SHARP and IMPROVE-IT trials with CV outcomes have reported (see section 4 for the full details). IMPROVE-IT and SHARP have demonstrated the clinical benefit of adding ezetimibe to statin therapy and established for the first time that a lipid lowering therapy other than a statin significantly reduces CV events. Additionally, the LDL-c/CV event reduction relationship obtained by the addition of ezetmibe to simvastatin conforms to that from the CTTC meta-analysis (Figure 4).[11] Both trials provide evidence that ezetimibe reduces clinical endpoints, however, the studies were conducted in sub-populations of the wider ezetimibe license. Extrapolation of the CV event reduction from the IMPROVE-IT and SHARP populations to the wider ezetimibe co-administered with a statin population is challenging as baseline characteristics, CV risk and the patient pathway would

be significantly different to the other populations, e.g. primary prevention and treatment of high risk primary hypercholesterolaemia patients with diabetes, as well as monotherapy. As such, the effect of ezetimibe on LDL-c with linkage to CV outcomes has been modelled via the CTTC meta-analysis. A scenario analysis for the IMPROVE-IT population (i.e. post-ACS) comparing simvastatin 40 mg plus ezetimibe versus simvastatin alone has also been undertaken and reported in section 5.8.

Relative treatment effects – comparator arm for monotherapy and add-on to statin analyses

The baseline event rates reported above for primary and subsequent events represent those for patients that are untreated. As such, these are used as the transition probabilities in the model for the 'no treatment' comparator arm for the ezetimibe monotherapy analyses.

For the add-on to statin analyses, ezetimibe can be added on for patients who are not appropriately controlled on statin therapy alone at the maximum tolerated dose. To reflect this treatment pathway, the baseline transition probabilities for the first and subsequent events are adjusted to reflect the background statin therapy. To derive RRs to apply to the baseline risk data, we have used RCT data with CV endpoints for the comparator arm. We rejected the approach taken by Ara *et al.*[86] in this instance because the high-intensity statins (defined by NICE as atorvastatin 20 and 80 mg) recommended in updated Lipid Modification Guideline reduce patient's LDL-c by over 2 mmol/L, which exceeds the absolute LDL-c level threshold examined within the CTTC meta-analysis. For example, a patient on atorvastatin 80 mg with a baseline-LDL-c of 4.32 mmol/L pre-statin treatment, achieving a 55% reduction in LDL-c[88], would achieve an absolute LDL-c reduction of 2.4 mmol/L. As such, the LDL-c reductions expected with high-intensity statins do not conform to the main body of the data in CTTC. As such, utilising RCT data with CV endpoints has been applied in the model. The RRs have been sourced from the clinical review analyses conducted as part of CG181. The same RR were used for primary and secondary prevention populations, as although there may be a significant difference none was observed between these group in the CG181 clinical data analyses.

Table 30 summarises the RR for each statin intensity group versus no treatment.[88]

Table 30 Risk ratios (95% CI) for statin vs no treatment

Health state	Risk Ratios		
	Low-intensity	Medium-intensity	High-intensity
Unstable angina (non-fatal)	Same as MI	Same as MI	Same as MI
MI (non-fatal)	0.78 (0.72 to 0.84)	0.61 (0.55 to 0.68)	0.46 (0.37 to 0.59)
Stroke (non-fatal)	0.84 (0.75 to 0.94)	0.73 (0.66 to 0.81)	0.80 (0.70 to 0.91)
CV death	0.84 (0.78 to 0.91)	0.81	0.72
Non-CV death	0.96 (0.90 to 1.02)	0.96 (0.90 to 1.02)	0.96 (0.90 to 1.02)
Low-, medium- and high-intensity category definitions sourced from NICE CG181 Lipid Modification Guideline: Low-intensity statins include simvastatin 10 mg Medium-intensity statins include simvastatin 20 mg, simvastatin 40 mg & atorvastatin 10 mg High-intensity statins include simvastatin 80 mg, atorvastatin 20 mg, atorvastatin 40 mg & atorvastatin 80 mg			

Both clinical guidelines for lipid modification and clinical practice demonstrate that individual patients may require and tolerate different doses of statin, reflecting both the efficacy required and the tolerability of the statin dose by the patient to manage their hypercholesterolaemia. A limitation of RRs derived from the clinical review in CG181 is that they focus on low, medium and high intensity groups of statins and do not provide specificity related to statin and dose. As such, by applying these RRs, the consequence is that different high-intensity doses of atorvastatin (20mg, 40mg and 80mg) have the same relative risk reduction of CV events, a simplifying assumption that has consequences for some of the analyses.

Relative *treatment effects – ezetimibe, monotherapy and add-on to statin analyses*

Two meta-analyses were conducted to estimate the relative clinical effectiveness of ezetimibe in LDL-c change from baseline for the following two uses of ezetimibe using the RCT identified in the systematic review:

- Ezetimibe 10 mg monotherapy vs placebo, based on 15 RCTs (N=4,058);
- Ezetimibe 10 mg plus statin vs matching statin dose, based on 18 RCTs (N=19,425).

Further details regarding percentage LDL-c reduction for ezetimibe and the meta-analysis can be found in section 4.7 and 4.9, respectively. The results of these meta-analyses were incorporated into the model in order to estimate the LDL-c reduction expected when patients receive ezetimibe monotherapy or when add on to a statin. The meta-analysis results are shown below in Table 31.

Table 31 Meta-analysis results used to inform reduction in LDL-c with ezetimibe

% reduction in LDL-c	Mean	N	SD	SE	95% Confidence interval
Ezetimibe monotherapy*	20.44%	4,058	37.98	0.60	[21.60; 19.27]
Ezetimibe add on to statin	15.52%	19,425	99.82	0.72	[16.92; 14.11]
Key: LDL-c, low-density lipoprotein cholesterol; N, number of patients; SD, standard deviation; SE, standard error.					

As described previously, the meta-analysis published by the CTTC was used to inform the relationship between CV events and LDL-c values within the model. The CTTC 2010 publication reported the RRs of a 1 mmol/L reduction in LDL-c for specific CV events.[9] In the model, each cohort has a defined baseline LDL-c. No specific data was reported for unstable angina in the CTTC analysis, and as per Ward et al.[12] and Ara et al., (2008) in TA94 and TA132, the same RR as non-fatal MI has been applied for the RR for unstable angina. The RRs from CTTC were used to calculate corresponding RRs based upon the overall anticipated, absolute LDL-c reduction in both treatment arms for ezetimibe monotherapy or add-on to statin analyses.

5.4 Measurement and valuation of health effects

Health-related quality-of-life data from clinical trials

[redacted]

[redacted]

Mapping

Not applicable.

Health-related quality-of-life studies

Systematic review for relevant HRQL data

A systematic literature review was carried out to identify studies reporting health related quality of life (HRQoL) data. Searches of the MEDLINE and MEDLINE In-Process, Embase, Cochrane Library, CRD (National Health Service - Economic Evaluation Database [NHS-EED], Database of Abstracts of Reviews of Effects [DARE], and Health technology assessment [HTA]) databases were conducted. Details of the complete search strategy used including all search terms text words (free-text), subject index headings and the relationship between the search terms can be found in Appendix 17. These searches are in line with those which were conducted by ScHARR in the original HTA assessment of ezetimibe by NICE.[86] Consistent with the review of cost-effectiveness studies (Section 5.1), the current literature review was limited to publications dated from January 2006 to present as this search was an update to the previous search conducted for the previous review of ezetimibe. Although the searches were conducted between April and June 2006, this search included articles published in January of the same year to ensure full overlap with the original search. Searches in Ovid (Embase and MEDLINE) were limited to studies with adult patients (18 years or older) and English language publications only.

In addition, the reference lists of the cost-effectiveness analyses retrieved in the economic evaluation review reported in Section 5.1 were reviewed for additional sources for utilities. These studies were screened using the same inclusion and exclusion criteria as the original utility searches defined below.

The search was also supplemented by reviewing congress publications from ISPOR (EU and US), EAS, ACC, and ESC. The process for searching and reviewing these abstracts

was the same that outlined in Section 5.1. As previously noted, the results from this search was then categorised according to topic (e.g., cost-utility results, utility results, or both).

Two researchers independently screened each reference for inclusion based on title and abstract. A third researcher then resolved any conflicts between decisions. All publications that met entry criteria for the review were obtained as full articles and reassessed against the review criteria. Data from selected studies were subsequently used to populate the data extraction tables in *Excel*. All data were fully checked by a second researcher.

To be included in this systematic review, references had to meet the inclusion criteria (and none of the exclusion criteria) as defined by the PICOS criteria. The inclusion and exclusion criteria are outlined in Table 33 and Table 33, respectively. This process was fully compliant with the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[Moher 2009]. Only studies that reported quality of life scores using the EQ-5D questionnaire were eligible for inclusion. The justification for this strict criterion is that it is in line with the recommendations for the NICE reference case.[89] Furthermore, as this is an update of a previous submission, appropriate utilities for all health states modelled (unstable angina, MI and stroke) have already been identified from the previous NICE cost-effectiveness models; thus this review was conducted with the perspective that only utility studies reporting data that improve upon the original figures used, i.e., follow the NICE reference case and are more up-to-date or provide data on a more representative population for the health states in question, will be included.

Table 32 Inclusion criteria for HRQoL searches

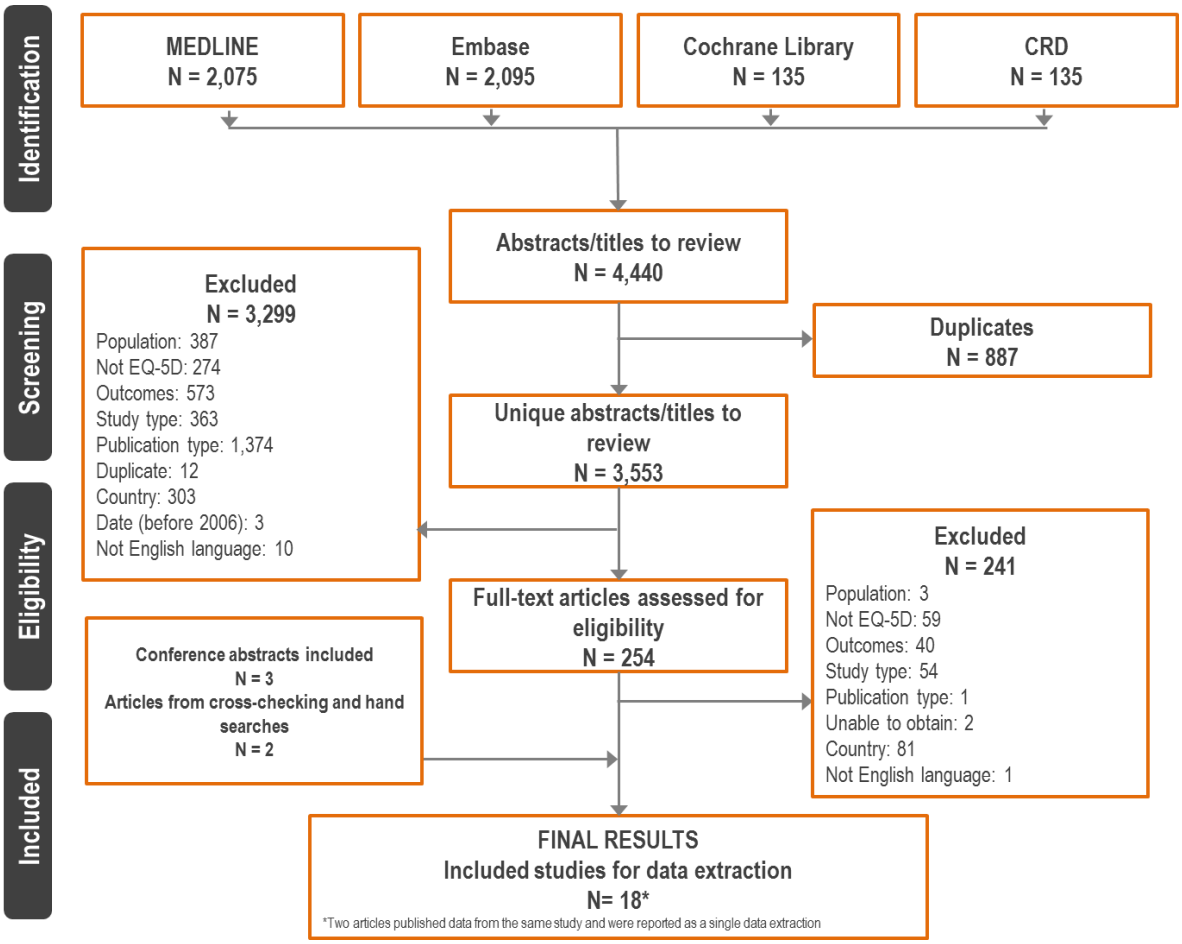
	Criteria
Population	Adults ≥18 years who have experienced a myocardial infarction or stroke, or have unstable angina
Outcomes	Health state utility scores for myocardial infarction, stroke, unstable angina, HRQoL scores using the EQ-5D quality of life questionnaire
Time Limit	January 2006 – present
Country	Studies in populations from UK preferred to non-UK
Language	English only
Study type	CEA, CUA, HRQoL study types not listed in the exclusion criteria

Table 33 Exclusion criteria for HRQoL searches

	Criteria
Population	Not adults ≥18 years who have experienced a myocardial infarction or stroke, or have unstable angina Patients with: peripheral vascular disease, atrial fibrillation, Chronic Heart Failure
Outcomes	Not reporting utilities or HRQoL scores in line with the NICE reference case (i.e., not a UK population or EQ-5D questionnaire)
Time Limit	Before January 2006
Country	Countries outside the UK
Language	Not only
Study type	Animals studies Meta-analyses and Systematic reviews Other: letters, notes, reports, short surveys, trade journal, conference abstract, conference paper, conference proceeding, conference review, or editorials

Following the full-text review, studies that met the criteria based on the full-text review were abstracted into a data extraction sheet in *Excel*. In total, 19 studies were included for data extraction. Figure 15 outlines the results from the search and screening.

Figure 15 Flow chart for HRQoL systematic review



A total of 4,440 articles were retrieved by the search. After the duplicates were removed 3,553 abstracts were available to be reviewed against the criteria outlined in Table 32 and Table 33, and 3,299 publications were excluded. A total of 254 papers were ordered for full publication review, and 18 papers met the inclusion criteria and data were extracted. This includes three conference abstracts identified in the searches of the grey literature and two additional publications identified from the references of studies included in the review of cost-effectiveness studies. Two studies[118;119] reported data from the same study and were data extracted together. For this study, Ankolekar *et al.* was reported as the primary publication.[118]

The 18 studies found to meet the criteria based on the full-text review were extracted in a data extraction sheet. In addition, all included studies were quality assessed using the quality checklist developed based on suggestions in the NICE Decision Support Unit (DSU) technical support document 9.[120] The results from these assessments are reported in Appendix 18.

Tabulation of HRQoL studies

The systematic review identified 18 publications (three abstracts and 15 full-text papers) that reported EQ-5D utility data for observational studies or baseline data for treatment-related studies for patients with hypercholesterolaemia-related symptoms and are summarised in Appendix 19 . As previously stated, two studies[118;119] reported data from the same study and were therefore reported together. This is reflected in the summary tables. Most studies identified were randomised control trials. Other study types identified in the review included prospective observational studies and secondary analyses. For the remaining studies, the study type was not reported. In line with the inclusion criteria, all studies reported data elicited using the EQ-5D questionnaire.

In general, the identified studies corresponded with what was expected for the NICE reference case guidelines. The vast majority of the studies reported a date of publication, sponsor information, a study perspective along with details of the population that was being studied. The country of interest was indicated along with the study design, sample size, study setting, and the inclusion and exclusion criteria for the patients. Concomitant medications and co-interventions that were allowed during the study period along with reported health states were often not reported.

HRQoL studies where the utility values reported for unstable angina, stroke or MI were unclear or not consistent with the NICE reference case were not further considered as relevant sources of utility data to include in the cost-effectiveness model.[118;121-130]

Utilities were also reported in the cost-utility analyses identified in the economic search of cost-effectiveness studies (Section 5.1). Seven cost-utility studies were identified in this review, and two supplemental studies (Ward et al.[12] and NICE CG181[88]) that support a number of the economic evaluations published studies were also included. The utilities from these publications are provided in Appendix 19. The EQ-5D questionnaire was the most frequently used tool to measure utilities. Utility data used for the health states modelled in this cost-effectiveness model, MI, stroke and unstable angina were reported. In addition, some of the studies also reported utilities for other health states such as heart failure, revascularisation, and peripheral artery disease, but these were not reported as there were not relevant to our analysis. A quality assessment was undertaken for these studies also and is described in Appendix 18.

The EQ-5D utility scores from IMPROVE-IT at baseline are consistent with the published literature for unstable angina, although higher than those for myocardial infarction. This may be explained by the higher proportion of patients with complete EQ-5D data in the IMPROVE-IT trial for the lower severities of ACS events.

Adverse reactions

Detailed adverse event data for ezetimibe as an monotherapy and as an add-on to statin is detailed in 4.12. Ezetimibe monotherapy and ezetimibe co-administered with a statin has a similar adverse event profile to placebo and statin therapy alone, respectively. Adverse reactions associated with ezetimibe are expected to have minimal impact on patients' HRQoL. No treatment-related utility decrements have been applied.

Health-related quality-of-life data used in cost-effectiveness analysis

Table 34 below summarises the utility values that have been applied to the health states modelled in the base case analysis, which have been selected based on their consistency with the NICE reference case. The methods guide specifies the following criteria:[89]

- reported directly from patients;
- valuation of HRQoL is based on public preferences using a choice–based methods;
- EQ-5D is the preferred HRQoL instrument.

The utility data have been identified from previous cost-effectiveness analyses conducted by NICE as part of previous technology appraisals and clinical guidelines (specifically TA94, TA132 and CG181[88])[12;86], as well as the updated systematic review outlined previously to identify more recent data. The well and death states are by their definition, 1 and 0.

To reflect the decrease in HRQoL observed in the general population as they age, the baseline utility of the modelled cohort has been adjusted using data from Kind *et al.*, 1998. This multiplier is obtained by applying an algorithm produced by Ara and Brazier.[131] This algorithm is shown below:

$$General\ population\ EQ-5 = 0.9508566 + 0.0212126 * male - 0.0002587 * age - 0.0000332 * age^2$$

In the model, an age-related multiplier is applied to the utilities applied to each health state a patient ages.

Table 34 Summary of utility values for base case cost-effectiveness analyses

State	Utility value: mean	Standard error	Reference in submission	Justification
Well	1	n/a	By definition	By definition
Unstable angina	0.770	0.038	Goodacre *et al.*, 2004[132]	Only published data consistent with reference case
Post-unstable angina	0.80	Not reported	NCCPC 2008[133]; Ara *et al.* [86]	Evidence of small increase in HRQoL over time
MI	0.760	0.018	Goodacre *et al.*, 2004 [132]	Consistent with NICE reference case[89] and previous values used in TA132 and TA94
Post-MI	0.80	Not reported	MI plus Lacey *et al.*, 2003 [134]	Evidence that HRQL improves over time
Stroke	0.50	Not reported	Tengs *et al.* 2003;[135] weighted by stroke severity from Youman *et al.*, 2003 [136]	Evidence of lower HRQoL in 1st 6 months post event; meta-analysis of 20 HRQoL studies; consistent with previous values used in TA94 and TA132
Post-stroke	0.628	Not reported	Tengs *et al.* 2003;[135] weighted by stroke severity from Youman *et al.*, 2003 [136]	Meta-analysis of 20 HRQoL studies; consistent with previous values used in TA94, TA132 and CG181
CV death	0	n/a	By definition	By definition
Non-CV death	0	n/a	By definition	By definition

*calculated from standard deviation weighted by severity

Unstable angina

There are two, relevant published studies, Goodacre *et al.*[132] and Kim *et al.*[137], with relevant utility values that are consistent with NICE's reference case for unstable angina in the first year post-event (Table 35). While the Kim *et al.* study included patients with unstable angina and NSTEMI, separate utility values for unstable angina are not reported. As such, the Goodacre *et al.* study is used, which is consistent with Ara *et al.*[86], Ward *et al.* 2005 and the cost-effectiveness modelling approach in CG181[88].

Table 35 Summary of utility values for unstable angina

Study	Study design / method for elicitation and valuation	Utility values
Goodacre *et al.*,2004[132] [103]	RCT (N=972) in UK & economic evaluation comparing care in a chest pain observation unit compared with routine care for patients with unstable angina & NSTEMI	Unstable angina (at 6 months; n=209): 0.77 (SE 0.038)

	Single centre – North General Hospital, Sheffield (2001-02) EQ-5D questionnaire	
Kim *et al.*, 2005 [137]	RCT (N=915) in UK evaluating interventional (IS) vs. conservative strategy (CS) in patients with unstable angina or NSTEMI 45 centres in England and Scotland (1997-2001) Includes EQ-5D questionnaire at baseline, 4 months & 1 year; valuation: UK Tariff (TTO)	Mean EQ-5D, IS vs CS: 4 months (n = 839 vs. 853): 0.748 (SE 0.009) vs. 0.714 (SE 0.010) 1 year (n = 806 vs. 820): 0.752 (SE 0.009) vs. 0.736 (SE 0.010)

The Mason 2005 study was excluded from consideration as there was insufficient data to assess its consistency against the criteria.

Post-unstable angina

One study, Kim *et al.*[137], provide utility values for patients with unstable angina or NSTEMI, 1 year post event (Table 35). However, separate utility values for unstable angina are not reported. As per the previous approach used by Ara *et al*[86]., the changes in HRQoL between 4 and 12 months were evaluated, which indicate that there may be a small increase in HRQoL over time (the mean EQ-5D in the cohorts increases from 0.748 and 0.714 to 0.752 and 0.736, respectively. As such, it has been assumed that 0.80 represents the long-term HRQoL associated with unstable angina, which is consistent with the approach by Ara *et al.*[86]

MI

Two relevant studies reporting utility values for patients with MI were identified (Table 36). Goodacre *et al.*[132] collected EQ-5D data in an RCT of UK patients with NSTEMI and reported a mean utility value of 0.760 at 6 months after an MI. [134]y and Walters[134] estimated utility values by surveying patients with the EQ-5D questionnaire and reported utilities of 0.683 and 0.718, respectively. To be consistent with the previous approach used by Ara *et al.*[86] and the cycle length used, the Goodacre values have been used in the base case. However, it should be noted that Goodacre *et al.* is likely to underestimate the overall HRQoL of patients will MI, as it excludes patients with STEMI, which is a more severe type of MI.

Table 36 Summary of utility values for myocardial infarction

Study	Study design / method for elicitation and valuation	Utility values
Lacey & Walters, 2003 [134]	Longitudinal survey analyzing the impact of gender and social class on health status post-MI (N=273) North of England (1998-99) Includes EQ-5D	Mean EQ-5D, post MI (n=222) 6 weeks: 0.683 (SD 0.233) 1 year: 0.718 (SD 0.243)
Goodacre *et al.*, 2004[132] [103]	RCT (N=972) in UK & economic evaluation comparing care in a chest pain observation unit compared with routine care for patients with unstable angina & NSTEMI Single centre – North General Hospital, Sheffield (2001-02) EQ-5D questionnaire	MI (at 6 months; n=209): 0.760 (SE 0.018)

In the de novo modelling undertaken as part of CG181[88], Tsevat *et a.l*[138] was identified as a relevant source. This has been excluded from consideration as part of this analysis because it is not consistent with NICE reference case. HRQoL was assessed in patients with MI using a variety of measures, such as Karnofsky and the Specific Scale, and preferences elicited using TTO.

Post-MI

One study[134] has been identified that provide utility values consistent with the NICE reference case for patients at least one year after an MI event (Table 36). Lacey and Walters provides utility values for 6 weeks and one-year post MI. To calculate the expected utility for the post-MI health state, the relative difference between the two values reported in Lacey and Walters has been applied to the MI utility from Goodacre *et al.*[132;134]

The Mason 2005 study was excluded from consideration as there was insufficient data to assess its consistency against the criteria.

Stroke and post-stroke

From previous NICE technology appraisals (TA94 and TA132[7]) and CG181[88], Tengs *et al.*[135] and Leeds *et al.*[139] were identified as a relevant source for stroke utilities. Tengs *et al.*[135] is a meta-analysis using 53 HRQol estimates from 20 studies. The study estimated the utility values of 0.869, 0.682 and 0.517, respectively for minor, moderate and major stroke, and

was weighted by severity in previous NICE appraisals using data from Youman *et al.*,[136]. Leeds *et al.*[139], compared HRQoL in patients with stroke discharges to a care home and found improvements in HRQoL one-year post-discharge.

Five additional studies with relevant utility data for stroke were identified in the updated systematic review. Three of these focused on a specific subset of patients with stroke (e.g. those that are immobile)[140-142] and these were not considered representative of the population under evaluation in the cost-effectiveness analysis. One study conducted by Luengo-Fernandez[143] collected HRQoL data using EQ-5D for up to 5 years in Oxfordshire in approximately 445 patients, while Ali *et al.* conducted an RCT evaluating the impact of oxygen supplementation to those patients with acute stroke.

Table 37 provides a summary of these studies.

We selected Tengs *et al.*, 2003 because of its consistent use in previous NICE technology appraisals and clinical guidelines[12;86;88;144;145], the same approach and values have been used as TA132. As our modelling approach does not distinguish between the severity of stroke, a mean utility of 0.628 has been calculated by weighting the proportions of patients experiencing stroke by severity using Youman *et al.* (0.19 mild, 0.27 moderate, 0.54 severe).[136] A lower utility has been applied in the 1st year post-stroke of 0.50, given the

evidence that there is a significant reduction in HRQoL in the first 6 months post event that improves and is maintained from 1 year up to at least 60 months.[86;139;143]

Table 37 Summary of utility values for stroke and post-stroke

Study	Study design / method for elicitation and valuation	Utility values
Tengs *et al.*, 2003 [135]	Meta-analysis of 53 QoL estimates for stroke, based on a systematic review of literature to identify utility values for stroke; range of assessment methods and respondents used across the studies	Moderate stroke (reference) = 0.682 (95% CI: 0.533-0.830) Utility increment, minor stroke = 0.187 (95% CI: 0.093-0.281) Utility decrement, major stroke = 0.165 (95% CI: 0.263-0.066)
Leeds *et al.*, 2004[139]	Study to examine the impact of discharging patients who have experienced a stroke to a care home (Group 1) (n=65) in comparison to their own home (Group 2) (n=65). HRQoL assessment at discharge and one-year post-discharge	Mean EQ-5D, at discharge (SD): • Group 1 (n=43) = 0.33 (0.26) • Group 2 (n=50) = 0.46 (0.32) Mean EQ-5D, one-year post discharge (SD): • Group 1 (n=43) = 0.35 (0.2) • Group 2 (n=50) = 0.60 (0.30)

Luengo-Fernandez *et al.*, 2013[143]	Population-based study in Oxfordshire for patients with stroke or TIA that were followed-up for up to 5-years; Method of elicitation: EQ-5D collected at 1, 6, 12, 24 and 60 months post-event and valued using the UK preference set (TTO)	Mean utility associated with Stroke (SD): • 1 month (N=445) ▪ All stroke: 0.64 (0.33) ▪ Controls: 0.83 (0.23) ▪ Minor: 0.73 (0.25) ▪ Moderate: 0.50 (0.37) ▪ Severe: 0.13 (0.32) • 6 months (N=339) ▪ All stroke: 0.70 (0.29) ▪ Controls: 0.85 (0.23) ▪ Minor: 0.76 (0.25) ▪ Moderate: 0.62 (0.32) ▪ Severe: 0.38 (0.37 • 12 months (N=418) ▪ All stroke: 0.70 (0.27) ▪ Controls: 0.85 (0.23) ▪ Minor: 0.74 (0.25) ▪ Moderate: 0.65 (0.25) ▪ Severe: 0.41 (0.38) • 24 months (N=263) ▪ All stroke: 0.66 (0.29) ▪ Controls: 0.85 (0.22) ▪ Minor: 0.70 (0.27) ▪ Moderate: 0.60 (0.30) ▪ Severe: 0.45 (0.33) • 60 months (N=269) ▪ All stroke: 0.68 (0.31) ▪ Controls: 0.86 (0.22) ▪ Minor: 0.73 (0.27) ▪ Moderate: 0.56 (0.38) ▪ Severe: 0.38 (0.39)
Ali *et al.*, 2014	RCT in a single centre in the UK, evaluating the impact of oxygen supplementation for patients within 24 hours of admission to hospital with acute stroke. EQ-VAS and EQ-5D administered at 6 months (n=223)	Covariate-adjusted mean EQ-5D utility scores, oxygen vs. control groups: 0.50 vs.0.49, respectively

Additional utility studies were found from previous economic evaluations identified as part of the systematic review. Van Exel and Pickard 2005 were excluded as they were in a non-UK setting. The study used in Davies 2006 was excluded because it is unclear if it is consistent with the NICE reference case as the method of valuation was not reported.

5.5 Cost and healthcare resource use identification, measurement and valuation

5.5.1 Parameters used in the cost effectiveness analysis

Table 38 below summarises the cost data used in the cost-effectiveness model, which have been inflated to the latest cost year (2013/2014). The included costs were based on estimates of resource use that a typical adult experiencing the modelled CV events would expect to receive for the management of the disease over a lifetime. Different first and subsequent year costs were assigned for every CV health state to reflect the higher costs incurred in the first year of an event.

Consistent with NICE reference case, drug acquisition costs were taken from the drug and pharmaceutical electronic market information tool (eMit)[146] and the Monthly Index of Medical Specialities (MIMs)[15], monitoring costs were taken from published literature and GP and healthcare assistant costs were sourced from Personal Social Services Research Unit (PSSRU) (2014)[147]. Health state costs emerged from published literature were inflated to 2013/2014 values using the Pay and Price Indices for Hospital & community health services (HCHS).

Table 38 Cost-related variables applied in the economic model

Cost Inputs	Value	Distribution (CI)	Reference/Source
Drug Costs			
Ezetimibe 28-day pack	£26.31	Fixed Cost	MIMS (March, 2015)[15]
Atorvastatin 10mg 28-day pack	£0.74	Normal (0.732 - 0.748)	eMit (12 months to Dec 2014)[146]
Atorvastatin 20mg 28-day pack	£1.02	Normal (1.012 - 1.028)	eMit (12 months to Dec 2014)[146]
Atorvastatin 40mg 28-day pack	£1.05	Normal (1.049 - 1.051)	eMit (12 months to Dec 2014)[146]
Atorvastatin 80mg 28-day pack	£1.90	Normal (1.898 - 1.902)	eMit (12 months to Dec 2014)[146]
Simvastatin 10mg 28-day pack	£0.17	Normal (0.169 - 0.171)	eMit (12 months to Dec 2014)[146]
Simvastatin 20mg 28-day pack	£0.48	Normal (0.475 - 0.485)	eMit (12 months to Dec 2014)[146]
Simvastatin 40mg 28-day pack	£0.36	Normal (0.36 - 0.36)	eMit (12 months to Dec 2014)[146]
Simvastatin 80mg 28-day pack	£1.90	Fixed Cost	MIMS (March, 2015)[15]

Monitoring costs			
Appointment for blood sample (with health care assistant)	£6.46	Normal (£3.93 - £8.99)	Resource use from CG181[88]; Unit costs from NHS Reference Costs 2013-2014[148]
GP Appointment	£46.00	Normal (£27.97 - £64.03)	PSSRU 2014[147] without qual, inc direct care staff
Cost Total cholesterol	£1.00	Normal (£0.61 - £1.39)	NHS Reference Costs 13/14 [148]Clinical Biochemistry,DAPS04
Cost HDL cholesterol	£1.00	Normal (£0.61 - £1.39)	NHS Reference Costs 13/14 [148]Clinical Biochemistry, DAPS04
Cost Liver transaminase (ALT or AST)	£1.00	Normal (£0.61 - £1.39)	NHS Reference Costs 13/14 [148]Clinical Biochemistry, DAPS04
Monitoring resource use			
Appointment to take blood sample (with health care assistant) - 1st year	2	Normal (1.22 - 2.78)	NICE, CG181[88]
GP appointment - 1st year	2	Normal (1.22 - 2.78)	NICE, CG181[88]
Total cholesterol test - 1st year	2	Normal (1.22 - 2.78)	NICE, CG181[88]
HDL cholesterol test - 1st year	2	Normal (1.22 - 2.78)	NICE, CG181[88]
Liver transaminase test-1st year	2	Normal (1.22 - 2.78)	NICE, CG181[88]
Appointment to take blood sample (with health care assistant) – subsequent years	1	Normal (0.61 - 1.39)	NICE, CG181[88]
GP appointment – subsequent years	2	Normal (1.22 - 2.78)	NICE, CG181[88]
Total cholesterol test – subsequent years	1	Normal (0.61 - 1.39)	NICE, CG181[88]
HDL cholesterol test - subsequent years	1	Normal (0.61 - 1.39)	NICE, CG181[88]
Liver transaminase test-subsequent years	1	Normal (0.61 - 1.39)	NICE, CG181[88]
Health States			
Well	£0.00	N/A	By definition

Stable angina	£242.38	Normal (£147.37 - £337.4)	Ara 2008[86](costs in 2006 prices inflated to 2014)
Post stable angina	£242.38	Normal (£147.37 - £337.4)	Ara 2008[86](costs in 2006 prices inflated to 2014)
Unstable angina	£575.21	Normal (£349.73 - £800.69)	Ara 2008[86](costs in 2006 prices inflated to 2014)
Post unstable angina	£245.06	Normal (£149.00 - £341.12)	NICE CG94[149] (costs in 2010 prices inflated to 2014)
MI	£6,154.50	Normal (£3741.98 - £8567.02)	Palmer et al 2002[98] +primary care and medication costs as UA
Post MI	£625.27	Normal (£380.17 - £870.37)	NICE CG94[149] (costs in 2010 prices inflated to 2014)
TIA	£3,982.31	Normal (£2421.27 - £5543.35)	Luengo-Fernandez et al 2012 [150](costs in 2009 prices inflated to 2014)
Post TIA	£1,386.22	Normal (£842.83 - £1929.61)	Luengo-Fernandez et al 2012[150] (costs in 2009 prices inflated to 2014)
Stroke	£14,151.26	Normal (£8604.07 - £19698.45)	Youman *et al.*2003 [136](costs in 2002 prices inflated to 2014)
Post stroke	£3,927.73	Normal (£2388.09 - £5467.37)	Youman *et al.* 2003[136] (costs in 2002 prices inflated to 2014)
CV death	£5,536.52	Normal (£3366.25 - 7706.80)	Ara 2008[86](costs in 2006 prices inflated to 2014) (costs in 2006 prices inflated to 2014) weighted by fatal CHD and fatal Stroke

5.5.2 Resource identification, measurement and valuation studies

Systematic literature reviews were conducted to identify updated, relevant cost-effectiveness and HRQL studies in the published literature to inform the sections 5.1 and 5.4 of the submission, since the original MTA of ezetimibe (TA132) in 2007.[7] Please refer to the aforementioned sections and the Appendices 14 and 17 for a detailed description of the methods of the systematic reviews which were designed to identify evidence from a UK perspective to inform the health states of the base case analysis i.e. MI, unstable angina, stroke and fatal CV events.

The economic evaluation and utility studies identified were screened for identification of relevant cost and healthcare resource data. In addition, in April 2015 four relevant cost studies were identified for inclusion through hand searching. Time restriction was applied to include only studies published from 2006 onwards as a systematic literature review was conducted in Ara 2008 for the identification of relevant cost studies until 2007.[86] The

majority of the studies identified in the published cost-effectiveness section based their costing methodology on the published TA94 study.[12] Consistent with NICE reference case, only studies from NHS and PSS perspective were included. Table 39 summarises the cost studies that are relevant to the cost-effectiveness model. Original publications identified in economic evaluation studies were considered separately. Economic evaluation studies were included only if at least one health state cost was estimated based on assumptions, clinical expert opinion or specific resource use breakdown.

Table 39 Summary of Cost and Resource use studies identified in the literature

First Author, Year	Currency, country, year	Costing Methods	CV related Costs	Applicability to clinical practice
Clarke, 2003[151]	GBP, UK, 1998/1999	In-patient and out-patient costs were estimated using multiple regression analysis based on costs calculated from the length of admission multiplied by the average specialty cost and a survey of 3,488 diabetic patients' healthcare usage conducted in 1996–1997.	Fatal MI: £1,152 Non-fatal MI: £4,070 Fatal stroke: £3,383 Non-fatal stroke: £2,367 Ischaemic heart disease: £1,959 Heart failure: £2,221 Subsequent years: Non-fatal MI: £464 Non-fatal stroke: £249 Ischaemic heart disease: £493 Heart failure: £631	Applicable to fatal health states only as according to the study, the diabetic population with CV complications may require more hospitalisation than the general population.
Luengo-Fernandez, 2012[150]	USD ($1=£0.64), UK, 2008/2009	Population-based cohort study (Oxford Vascular Study) estimating average hospital care costs during 5 years post TIA and stroke. Hospital resource usage was obtained from patient hospital records.	Stroke (before): $923 Stroke (year 1): $12,972 Stroke (year 2): $2,303 Stroke (year 3): $3,486 Stroke (year 4): $2,527 Stroke (year 5): $3,088 TIA (before): $1,125 TIA (year 1): $5,719 TIA (year 2): $2,942 TIA (year 3): $1,917 TIA (year 4): $1,348 TIA (year 5): $1,756	Applicable to stroke, post stroke, TIA and post TIA health states.

Luengo-Fernandez, 2013[152]	GBP, UK, 2008/2009	Population-based cohort study (Oxford Vascular Study) estimating average cost 1 year pre and post TIA and stroke. Hospital resource use was obtained from patients' individualised Hospital Episode Statistics records. Each hospitalisation was valued by using the HRG English tariff.	Stroke (1 year before): £1,437 Stroke (1 year after): £6,629 TIA (1 year before): £876 TIA (1 year after): £2,410	Applicable to stroke and TIA health states.
NICE, 2006 (CG34)[153]	GBP, UK, 2004/2005	Health state costs were sourced from published literature and based on assumptions.	UA: £2,107 Subsequent UA: £440 MI: £4,448 Post MI: £500 Stroke: £8,046 Post stroke: £2,163	Applicable only to UA and Post MI health states as the original publications sourcing the remaining health states were considered individually.
Ara 2008[86]	GBP, UK, 2005/2006	Monitoring costs were taken from PSSRU and NHS Reference costs Health state costs were taken from published literature and on assumptions from TA94	Monitoring costs (first year): £68.85 Monitoring costs (subs. years): £17.51 SA, Post SA, Post UA and Post MI: £201 UA: £477 MI: £4,934 Fatal MI: £1,261 TIA: £1,104 Post TIA: £274 Stroke: £8,070, Post Stroke: £2,169 Fatal Stroke £7,425	Monitoring costs were applicable to the monitoring costs section used in the economic model. *Health state costs:* Original publications considered separately. Applicable only to SA, post SA, UA, post UA and post MI.

NICE,2010 (CG94)[149]	GBP, UK, 2006/2007	Hospital resource use was based on differential length of stay data from the MINAP analysis and the cost of an excess bed day for patients with suspected or actual MI from the NHS reference costs. Secondary prevention medication doses were based on dosing recommendations and discussion with the pharmacist on the GDG. Costs values were sourced from the BNF	New MI readmission £1,783, Revascularisation – PCI £2,686, Revascularisation – CABG £8,513, Drug costs: Total year 1 £531 Total year 2+ £89 Annual disease related costs post-one year £264	Only costs following one year of the MI/UA events are applicable to the cost-effectiveness model as the cost of the MI event refers specifically to patients with NSTEMI and would underestimate the cost of MI event in the first year.
NICE, 2014 (CG181[88])	GBP, UK 2013/2014	Costs were sourced from the NHS Drug Tariff, NHS Reference costs, PSSRU Unit Costs of Health & Social Care 2013[147], BNF and GDG assumptions. Standard dosages were taken from BNF, May 2014. Costs reported were for a 6-month period for the event state and for 1-year period for post-event states	*Monitoring costs:* First year £120.17 Subs. Years £100.71 *Health states:* SA £7736 Post-SA £240 UA £3,313 Post-UA £385 MI £3,337 Post-MI £788 TIA £578 Post-TIA £124 Stroke £4,092 Post-stroke £155 Heart failure £2,297 Post-HF £2,597 PAD £952 Post-PAD £529 CV death £1,174	Monitoring costs were applicable to the monitoring costs section used in the economic model. *Health state costs:* As no specific breakdown of costs was described, it was not considered appropriate for use in the model.

Palmer, 2002[98]	GBP, UK, 2005/2006	Resource use and costs were based on data from the Nottingham Heart Attack Register. Average annual health state costs, based only on hospital costs, were calculated by aggregating the resources consumed by each patient.	Ischemic Heart Disease (IHD): £1,421 MI: £3,966 Post MI: £1,587	Applicable to MI and Post MI health states used in the cost-effectiveness model
Ward, 2007 (TA94)[12]	GBP, UK, 2003/2004	Treatment costs were sourced from BNF Monitoring costs were taken from PSSRU and NHS Reference costs Health state costs were taken from published literature and on assumptions and clinical expert opinion.	Monitoring costs (first year): £124 Monitoring costs (subs. years): £33.42 SA, Post SA, Post UA and Post MI: £171 UA: £477 MI: £4,448 Fatal MI: £1,161 TIA: £1,064, Post TIA: £264 Stroke: £8,046, Post Stroke: £2,163, Fatal Stroke £7,041	Monitoring costs were applicable to the monitoring costs section used in the economic model. *Health state costs:* Original publications considered separately. Applicable only to SA, post SA, UA, post UA ,post MI, TIA and post TIA
Youman, 2003[136]	GBP, UK, 2001/2002	Cost estimates from a randomised, prospective study comparing alternative strategies of stroke management	Acute moderate stroke: £5,099 Acute moderate stroke: £4,816 Acute severe stroke: £10,555 Fatal stroke: £6,781 Ongoing home care: £326 Ongoing institution care: £3,872	Applicable to stroke and post stroke health states used in the cost-effectiveness model

5.5.3 Use of NHS reference costs or payment-by-results (PbR) tariffs

The NHS reference costs were only used directly for the estimation of monitoring test costs. Costs associated with the modelled health states have been sourced from the literature as these capture the acute and long-term costs associated with managing CV events in primary, secondary and community care. The costs assigned to some health states e.g. MI and UA were taken from studies that estimated the costs based on NHS reference costs along with other relevant costs for the management of the event.

5.5.4 Input from clinical experts

No additional clinical expert validation was performed for the applicability of costs and resource use in clinical practice.

5.5.5 Intervention and comparators' costs and resource use

Drug and monitoring costs were included in the model. No administration costs were included as both the intervention and the comparators are administered orally via one tablet per day.

Based on data availability, acquisition costs were sourced from the drug and pharmaceutical electronic market information tool (eMit)[146] or the Monthly Index of Medical Specialities (MIMs)[15]. Costs were calculated as an annual cost and applied throughout the model.

When primary prevention cost effectiveness was evaluated, patients experiencing a CV event were switched to atorvastatin 80mg in line with clinical guidelines CG181[8]. All drug costs used within our base case analysis are summarised in Table 40.

Table 40 Annual drug costs

Drug	Cost per 28 day pack	Annual cost of treatment	Source
Atorvastatin 20mg	£1.02	£13.31	eMit (12 months to Dec 2014)[146]
Atorvastatin 40mg	£1.05	£13.70	
Atorvastatin 80mg	£1.90	£24.78	
Ezetimibe (current price)	£26.31	£343.20	MIMS (March, 2015)[15]

Key: eMit, electronic market information tool; mg, milligram; MIMS, Monthly Index of Medical Specialties.

Resource use associated with monitoring of treatment was obtained from CG181[88] since it was the most recent study identified reporting extensively these kinds of costs. It was assumed that patients within the first year of treatment would have more increased monitoring requirements to those of patients in subsequent years. Based on Guideline

Development Group (GDG) assumptions, total and HDL cholesterol tests will be performed at 3 months and annually thereafter. An additional consultation in the first year is also assumed to check total and HDL cholesterols. Liver transaminase enzymes test will be performed at 3 and 12 months and annually form second year onwards. Unit costs applied to the monitoring tests were taken from NHS Reference cost 2013-2014[148] (code DAPS04 Clinical Biochemistry).

Patients were assumed to have an annual medication review which was a face-to-face appointment with a GP. It was also conservatively assumed that one additional consultation is possible in the first year of treatment. Additionally, two appointments with a healthcare assistant in the first year and one annually thereafter were included for performance of blood tests. Costs associated with these resources were taken from the Personal Social Services Services Research Unit (PSSRU).[147] Table 41 reports the usage and costs incorporated yearly within the model.

Table 41 Annual monitoring costs, first and subsequent years

Resource use	1st year	Subsequent years	Source	Cost	Source
Routine appointments:					
Appointment to take blood sample (with health care assistant)	2	1	CG181[88]	£6.46	PSSRU (2014)[147]
GP appointment	2	2	CG181[88]	£46.00	
Blood tests:					
Total cholesterol	2	1	CG181[88]	£1.00	NHS Reference costs 2013-2014[148]
HDL cholesterol	2	1	CG181[88]	£1.00	
Liver transaminase (ALT or AST)	2	1	CG181[88]	£1.00	
Total annual monitoring costs, first year				£110.92	
Total annual monitoring costs, subsequent years				£101.46	

Key: ALT, alanine transaminase; AST, aspartate transaminase; HDL, high density lipid; GP, general practitioner; GDG, guideline development group.

5.5.6 Health-state unit costs and resource use

Health state costs were applied depending upon the CV event that the patient is experiencing with the impact of a CV event accounted for within 12 months of the event (the first year health state cost) and the long-term management associated with CV events accounted for in the post event health states. Based on the cost studies that were identified, the costs incurred in the first year following an event were more increased than those in

subsequent years. The values included were generally in line with the costs incorporated in the original TA132 model.

MI and post MI costs

Regarding the costs of MI health state, the CG94 UA and NSTEMI guideline estimated the cost of MI based on NSTEMI events, however, the NSTEMI events are usually of mild severity and assigning this cost value would probably underestimate the cost of the MI health state.[149] The study by Palmer et al 2002 (£3,966) was considered more appropriate as it was calculated based on annual resource use of patients with MI in the Nottingham Heart Attack (NHAR) cohort.[98] Hospital in-patient stays (cardiac and non-cardiac) and associated length of stay, day case and out-patient visits, as well as intervention use (PCI, CABG and angiography) were included in the costs. This study was widely used to inform the MI health states in HTA and clinical guideline activities.[12,86,153]

For the post MI health states, the figure of £1,587 from Palmer et al 2002 based on NHAR was considered extremely high.[98] Also the values of £171 and £201 from TA94 and TA132, respectively, were based only on primary care costs possibly underestimating the true cost in clinical practice. The estimation of annual post event related costs in CG94 UA and NSTEMI were based only on NSTEMI events and considered inappropriate for inclusion.[149] The cost value of £500 was sourced from the CG18 Hypertension guideline[154], the same value was used for the updated versions of the Hypertension guidelines CG34[153] and CG127[155] as well as the CG172[156] regarding the secondary prevention with MI representing the management cost after the first year of the event. Since this value was widely used it was considered appropriate for use in the post MI health state.

Unstable angina costs, post unstable angina

The costs of unstable angina health state were inflated from Ara et al.[86] (similar with TA94) based on three GP appointments, medication costs and hospitalisation costs (£477).[7] No updated cost studies for this health state were identified and specific breakdown in medication doses was not described by Ara et al.[86] or TA94[12] to allow re-calculation using latest drug prices and GP appointment costs.

For the post unstable angina health state, TA94[12] and Ara et al.[86] considered costs only from a primary care perspective possibly underestimating the costs post event. On the other hand, the clinical guideline CG94 UA and NSTEMI estimated the costs associated with the management of unstable angina/NSTEMI post-one year based on hospital admissions, invasive procedures and secondary prevention treatment costs (including lipid-lowering

medication).[149] The cost value of £264 excluding the cost of lipid-lowering medication (£37.41) was inflated to 2013/14 values.

Stroke and post stroke costs

Two recent studies by Luengo-Fernandez *et al.*[150;152] were identified estimating the hospital care costs of TIA and stroke before and after the event, and over a period of 5 years based on the population-based cohort study OXVASC study. However, the hospital resource costs only partially represent the costs of stroke management. Long-term costs incurred by institutionalisation and primary care costs are relevant to the management of stroke and exclusion of these would underestimate the true costs of stroke management to the NHS and Social Services. Thus, the study from Youman et al 2003[136], which was also used in TA94[12], Ara et al[86] and CG34[153], was selected as it gives a holistic view of stroke management, including both primary and secondary care. For the first year following a stroke, the costs of the acute events were included for the initial 3-month period, followed by the 9-month cost of ongoing care by discharge location. These costs were weighted by severity levels of stroke. The costs for the post stroke health state were estimated based on the costs of ongoing care from the same study.

Fatal non-CV and CV event cost

A weighted average of the fatal MI and stroke costs was calculated from Clarke 2003[151] (fatal MI) and Youman et al [136] (fatal stroke to be consistent with the stroke and post stroke health states) and inflated to 2013/2014 values for the estimation of the fatal CV event costs. The studies were selected to be consistent with TA132 costs for fatal events, as no new data was identified.

Table 42 Health state costs

Health state	Annual cost in health state	Reference
Well	£0.00	By definition
Unstable angina	£575.21	Ara et al. [86]
Post unstable angina	£285.52	CG94[149] (costs in 2010 prices inflated to 2014)
MI	£6,154.50	Palmer et al 2002[98] + primary care and medication costs as UA
Post MI	£625.27	CG18[154] (costs in 2005 prices inflated to 2014)
Stroke	£14,151.26	Youman *et al.*2003 [136](costs in 2002 prices inflated to 2014)
Post stroke	£3,927.73	Youman *et al.* 2003[136] (costs in 2002 prices inflated to 2014)
CV death	£5,697.23	Clarke et al 2003[151], Youman et al 2003[136] inflated to 2014 and weighted by fatal CHD and fatal Stroke
Non-CV death	£0.00	By definition
Key: CV, cardiovascular; MI, myocardial infarction; TIA, transient ischaemic attack.		

5.5.7 Adverse reaction unit costs and resource use

Detailed adverse event data for ezetimibe as a monotherapy and as an add-on to statin is detailed in 4.12. Ezetimibe monotherapy and ezetimibe co-administered with a statin have a similar adverse event profile to placebo and statin therapy alone, respectively. As such, no adverse events have been modelled.

5.5.8 Miscellaneous unit costs and resource use

No additional unit costs and resource use were included apart from those mentioned in the sections above.

5.6 Summary of base-case de novo analysis inputs and assumptions

Summary of base-case de novo analysis inputs

5.6.1 Tabulated variables included in the cost-effectiveness analysis

Table 43 summarises the variables applied in the economic model. The base-case cost-effectiveness analysis reflects the NICE reference case as closely as possible.[89]

Table 43 Summary of variables applied in the economic model

Variable	Value	CI (distribution)	Section
Model settings			
Discount rate for costs	3.5%	N/A	5.2
Discount rate for QALYs	3.5%	N/A	5.2
Patient characteristics (Base Case)			
Primary prevention, age	60	Normal distribution 95% CI: 60 – 60	5.2
Secondary prevention, age	69	Normal distribution 95% CI: 69 – 69	5.2
Primary prevention, proportion female	46.4%	Beta distribution: n=300,914 95% CI: 46.2% – 46.6%	5.2
Secondary prevention, proportion female	34.5%	Beta distribution n=1,773 95% CI: 32.3% – 36.7%	5.2
Patient characteristics (sub-group analysis)			
Primary prevention with type 2 diabetes, age	67	Normal distribution 95% CI: 66 – 68	5.9
Primary prevention with type 2 diabetes, proportion female	44.3%	Beta distribution n=1,681 95% CI: 41.9% – 46.7%	5.9
Utilities			
Utility: well	1	Assumed	5.4
Utility: Unstable angina	0.77	Beta distribution n = 355 95% CI: 0.725-0.812	5.4
Utility Post unstable angina	0.8	Beta distribution n = 1626 95% CI: 0.780 – 0.819	5.4
Utility: MI	0.76	Beta distribution n = 355 95% CI: 0.714 – 0.803	5.4
Utility: Lacey Post MI	0.683	Beta distribution n = 222 95% CI: 0.620 – 0.742	5.4
Utility: Lacey	0.718	Beta distribution n = 222 95% CI: 0.657 – 0.775	5.4
Utility: Post MI	0.799	N/A as calculation	5.4
Utility: Stroke	0.5	Beta distribution SE = 20% mean 95% CI: 0.306 – 0.694	5.4
Utility: Post Stroke	0.628	Beta distribution SE = 20% mean 95% CI: 0.369 – 0.852	5.4

Utility: CV death	0	N/A	5.4
Utility: Non cv death	0	N/A	5.4
Drug costs			
Drug cost Atorvastatin 10mg	£0.74	Normal distribution SE = 0.0043 95% CI: 0.732 – 0.748	5.5
Drug cost Atorvastatin 20mg	£1.02	Normal distribution SE = 0.0042 95% CI: 1.012 – 1.028	5.5
Drug cost Atorvastatin 40mg	£1.05	Normal distribution SE = 0.0006 95% CI: 1.049 – 1.051	5.5
Drug cost Atorvastatin 80mg	£1.90	Normal distribution SE = 0.0008 95% CI: 1.898 – 1.902	5.5
Drug cost Ezetimibe 10mg	£26.31	Fixed cost	5.5
Health state costs			
Health state costs Well	£0.00	N/A	5.5
Health state costs Unstable angina	£575.21	Normal distribution SE = 20% of mean 95% CI: £349.73 – £800.69	5.5
Health state costs Post unstable angina	£285.52	Normal distribution SE = 20% of mean 95% CI: £173.6 – £397.45	5.5
Health state costs MI	£6,154.50	Normal distribution SE = 20% of mean 95% CI: £3,741.98 – £8567.02	5.5
Health state costs Post MI	£625.27	Normal distribution SE = 20% of mean 95% CI: £380.17 – £870.37	5.5
Health state costs Stroke	£14,151.26	Normal distribution SE = 20% of mean 95% CI: £8,604.07 - £19,698.45	5.5
Health state costs Post Stroke	£3,927.73	Normal distribution SE = 20% of mean 95% CI: £2,388.09 – £5,467.37	5.5
Health state costs CV death	£5,536.52	Normal distribution SE = 20% of mean 95% CI: £3,366.25 – £7,706.80	5.5
Health state costs Non-CV death	£0	N/A	5.5
Monitoring costs			
Cost appointment to take blood sample (with health care assistant)	£6.46	Normal distribution SE = 20% of mean 95% CI: £3.93 – £8.99	5.5
Cost appointment with GP	£46.00	Normal distribution SE = 20% of mean 95% CI: £27.97 – £64.03	5.5
Cost total cholesterol test	£1.00	Normal distribution SE = 20% of mean 95% CI: £0.61 – £1.39	5.5

Cost HDL cholesterol test	£1.00	Normal distribution SE = 20% of mean 95% CI: £0.61 – £1.39	5.5
Cost Liver transaminase (ALT or AST) test	£1.00	Normal distribution SE = 20% of mean 95% CI: £0.61 – £1.39	5.5
Monitoring resource use			
Monitoring resource use Appointment to take blood sample (with health care assistant)Usage - 1st year	2	Normal distribution SE = 20% of mean 95% CI: 1.22 – 2.78	5.5
Monitoring resource use Appointment with GP Usage - 1st year	2.2	Normal distribution SE = 20% of mean 95% CI: 1.34 – 3.06	5.5
Monitoring resource use Total cholesterol Usage - 1st year	2	Normal distribution SE = 20% of mean 95% CI: 1.22 – 2.78	5.5
Monitoring resource use HDL cholesterol Usage - 1st year	2	Normal distribution SE = 20% of mean 95% CI: 1.22 – 2.78	5.5
Monitoring resource use Liver transaminase (ALT or AST) Usage - 1st year	2	Normal distribution SE = 20% of mean 95% CI: 1.22 – 2.78	5.5
Monitoring resource use Appointment to take blood sample (with health care assistant) Usage further years	1	Normal distribution SE = 20% of mean 95% CI: 0.61 – 1.39	5.5
Monitoring resource use Appointment with GP Usage further years	2	Normal distribution SE = 20% of mean 95% CI: 1.22 – 2.78	5.5
Monitoring resource use Total cholesterol Usage further years	1	Normal distribution SE = 20% of mean 95% CI: 0.61 – 1.39	5.5
Monitoring resource use HDL cholesterol Usage further years	1	Normal distribution SE = 20% of mean 95% CI: 0.61 – 1.39	5.5
Monitoring resource use Liver transaminase (ALT or AST) Usage further years	1	Normal distribution SE = 20% of mean 95% CI: 0.61 – 1.39	5.5
Risk ratios (Base case)			
Risk Ratios: LDL-c Non-fatal MI	0.74	Lognormal distribution SE = 0.0019 95% CI: 0.69 – 0.78	5.3
Risk Ratios: LDL-c Unstable angina	0.74	Lognormal distribution SE = 0.0019 95% CI: 0.69 – 0.78	5.3
Risk Ratios: LDL-c Non-fatal stroke	0.85	Lognormal distribution SE = 0.0018 95% CI: 0.80 – 0.90	5.3
Risk Ratios: LDL-c All Vascular (causes of death)	0.86	Lognormal distribution SE = 0.0011 95% CI: 0.82 – 0.90	5.3
Risk Ratios: LDL-c Other non CVD Death (non-Vascular death)	0.97	Lognormal distribution SE = 0.0016 95% CI: 0.92 – 1.03	5.3
Risk Ratios: LDL-c Non-fatal MI	0.74	Lognormal distribution SE = 0.0019 95% CI: 0.69 – 0.78	5.3

% reduction in LDL-c Ezetimibe monotherapy: Meta-analysis	20.44%	Beta distribution SE = 0.6 95% CI: 19.27% – 21.60%	5.3
% reduction in LDL-c Ezetimibe add on to statin: Meta-analysis	15.52%	Beta distribution SE = 0.87 95% CI: 14.11% - 16.92%	5.3
Risk ratios (Sub-group analysis)			
% reduction in LDL-c Ezetimibe add on to statin: Meta-analysis (diabetes sub-group_	18.83%	Beta distribution SE = 0.87 95% CI: 17.00% – 20.66%	5.9

Assumptions

Table 44 summarises the assumptions used in the economic model.

Table 44 List of assumptions used in the economic model

Section	Assumption	Source	Justification
Comparator	Relevant comparators for target population is 'no treatment' for ezetimibe monotherapy analysis and statin alone for add-on to statin analysis or	CG181[8], TA132[7]	Standard clinical practice, based on original NICE TA132 recommendation[7]
Baseline LDL-c prior to treatment (ezetimibe monotherapy analysis)	Assume LDL-c prior to treatment sourced from UK observational data	Van Staa *et al.*[27]; Jameson *et al.* 2014[30]	Best data available
Effectiveness data	Assume results of the ezetimibe meta-analyses are representative for the target population	Section 4.9	27 RCTs across a range of populations was included in the meta-analysis
	Assume the results of the ezetimibe meta-analyses are valid irrespective of the dose and statin modelled	Section 4.9	Section 4.9
	Assume observed short-term lipid changes will be maintained over a lifetime	Section 4.9	Uncertainty is explored through varying the model time horizon
	Assume ezetimibe-induced changes in lipids translate to reductions in CV events	IMPROVE-IT study[11], CTTC studies[9;16]	The data available supports the assumption (Figure 4)
	Assume the RR for unstable angina = RR for non-fatal MI	TA132[7]	Impact of assumption explored through scenario analyses
Utility	Utility decreases over time with increasing patient age	Ara and Brazier 2010	Conservative/realistic assumption
	Assume post-event health state utility values are either stable or increase	TA132[7]	Supported by the data available from the literature review
	Assume no disutility associated with treatments modelled	Section 4.12	Ezetimibe monotherapy and ezetimibe co-administered with a statin have a similar adverse event profile to placebo and statin therapy alone, respectively
Compliance	Assume full compliance with treatment	TA132[7]	Simplifying assumption
Statin dose	When primary prevention cost effectiveness is evaluated patients experiencing a CV event are switched to atorvastatin 80mg in line with clinical guideline	CG181[8]	In line with guidance

Section	Assumption	Source	Justification
Adverse events	Adverse events not included within the model	TA132; Section 4.12[7]	Ezetimibe monotherapy and ezetimibe co-administered with a statin has a similar adverse event profile to placebo and statin therapy alone, respectively For simplicity in line with the original modelling work for TA132 adverse events have therefore not been included in the model.
Sub-group analysis			
LDL-c prior to treatment	Assume LDL-c prior to treatment is the same for diabetic and non-diabetic patients but higher for HeFH subgroup	TA132[7] and Kastelein 2008	Best data available

5.7 Base-case results

Analyses were performed for a lifetime horizon and have been presented in terms of discounted incremental cost per QALYs. Results were tabulated for primary and secondary prevention by treatment combination for patients with 20% 10-year CV risk. Overall, ezetimibe consistently incurs additional benefit ranging from (0.096 QALYs in primary prevention as add-on to 0.221 QALYs in secondary prevention as monotherapy). This is achieved by an additional cost ranging from £3,885 (secondary prevention – monotherapy) to £5,429 (primary prevention – add-on statin).

Base-case incremental cost effectiveness analysis results

Primary Prevention

Table 45 and Table 46 below summarise the cost-effectiveness results for monotherapy and add-on to statin in primary prevention, respectively. For patients that statin treatment is considered inappropriate, ezetimibe therapy provides 0.177 incremental QALYs at an additional cost of £5,169. Ezetimibe co-administered with atorvastatin 20 mg results in incremental QALYs of 0.096 at an increased cost of £5,429.

Table 45 Base-case results for primary prevention - monotherapy

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
No Treatment	£7,827	23.89	11.88	-	-	-	-
Ezetimibe 10mg	£12,997	24.36	12.05	£5,169	0.474	0.177	£29,286

Table 46 Base-case results for primary prevention – add-on to Atorvastatin 20mg

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
Atorvastatin 20mg	£7,891	24.73	12.18	-	-	-	-
Ezetimibe 10mg + Atorvastatin 20mg	£13,320	24.99	12.27	£5,429	0.268	0.096	£56,394

Secondary Prevention

Patients who had experienced a CV event and ezetimibe is the only appropriate treatment, accrued additional QALYs of 0.221 at an additional cost of £3,885, deriving a cost-effective ICER of £17,553. Ezetimibe plus atorvastatin 40mg result in additional 0.133 QALYs when compared to the same statin dose by incurring an additional cost of £4,113, Table 47 and

Table 48.

Table 47 Base-case results for secondary prevention – monotherapy

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
No Treatment	£31,072	13.80	5.76	-	-	-	-
Ezetimibe 10mg	£34,957	14.49	5.98	£3,885	0.683	0.221	£17,553

Table 48 *Base-case results for secondary prevention – add-on to Atorvastatin 40mg*

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Atorvastatin 40mg	£31,699	6.24	15.30	-	-	-	-
Ezetimibe 10mg + Atorvastatin 40mg	£35,811	6.37	15.73	£4,113	0.422	0.133	£30,940

Clinical outcomes from the model

Please refer to 5.10 Validation section for a comparison between the economic model outcomes and those observed in the IMPROVE-IT study.[11]

Markov traces

The graphs below show the proportion of patients in each health state at every model cycle, illustrating the flow of patients through the model for each comparator. The markov traces in secondary prevention differ considerably from those in primary prevention as patients have already experienced a CV event.

Primary prevention

Monotherapy

Figure 16 Markov Trace: Ezetimibe for patients with 20% CV risk

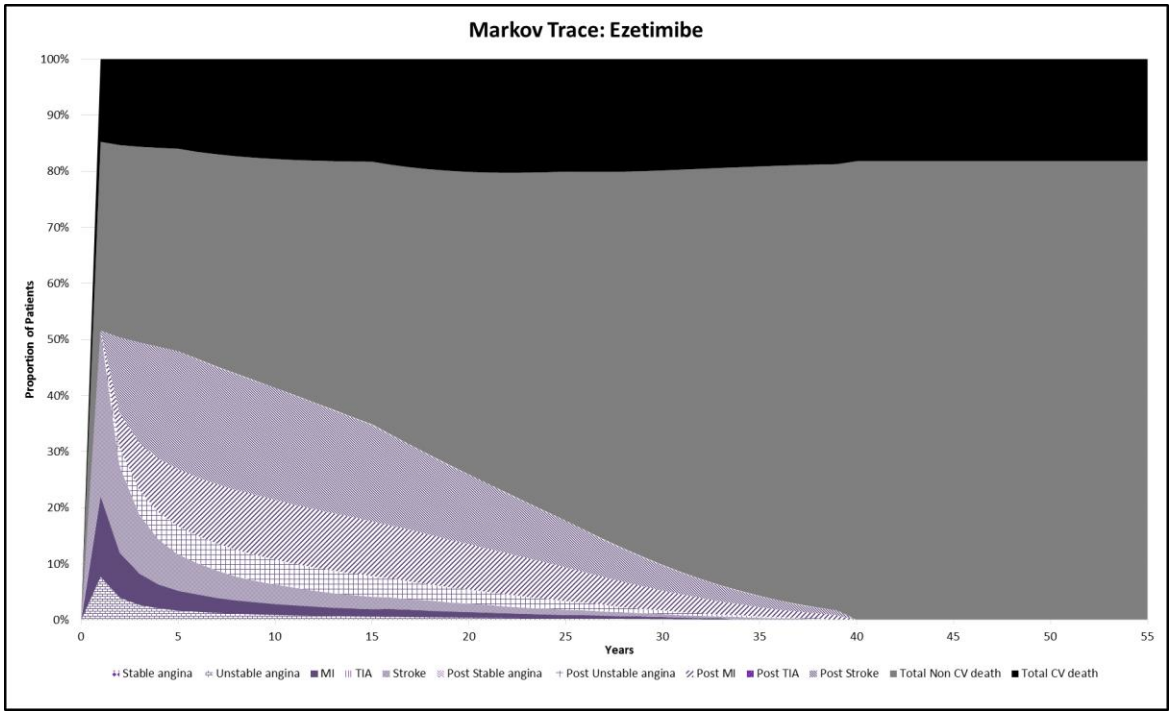
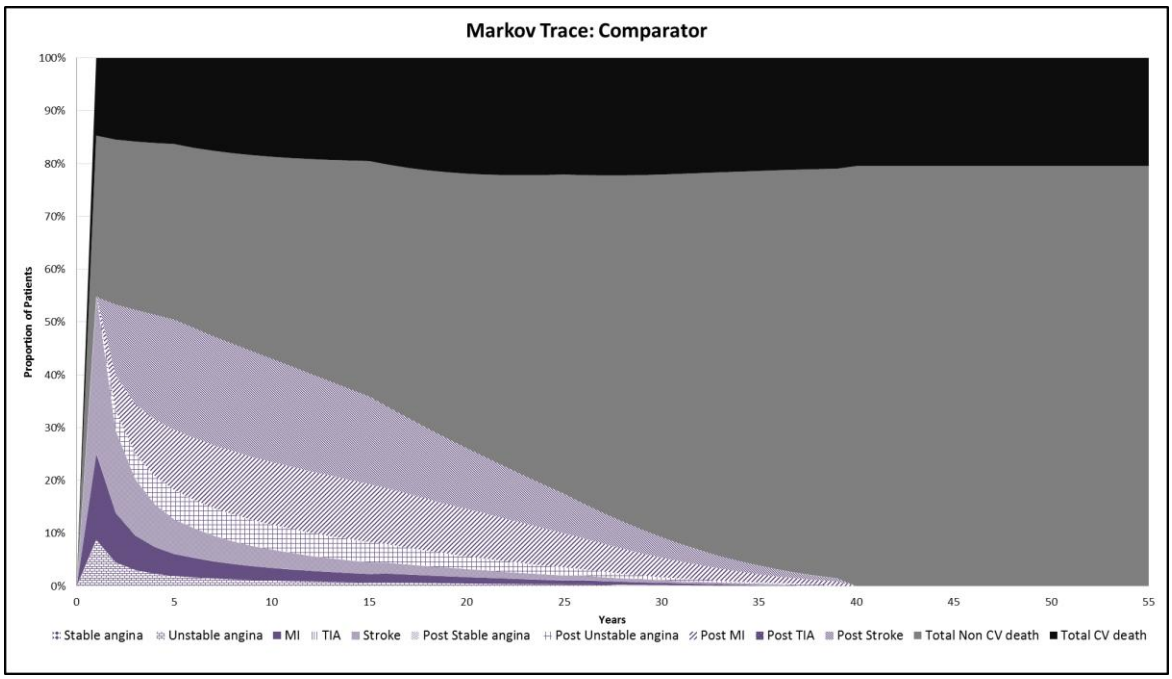


Figure 17 Markov Trace: No treatment for patients with 20% CV risk



Add-on to statin

Figure 18 Markov Trace: Ezetimibe co-administered with Atorvastatin 20mg in patients with (20% CV Risk)

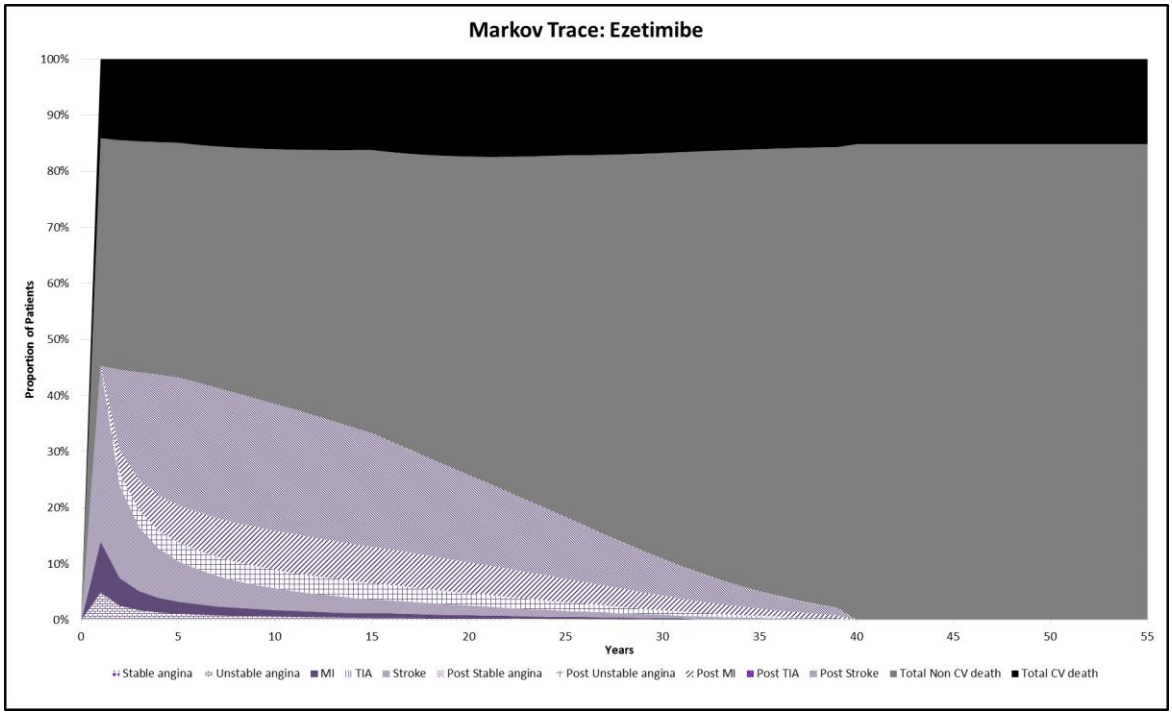
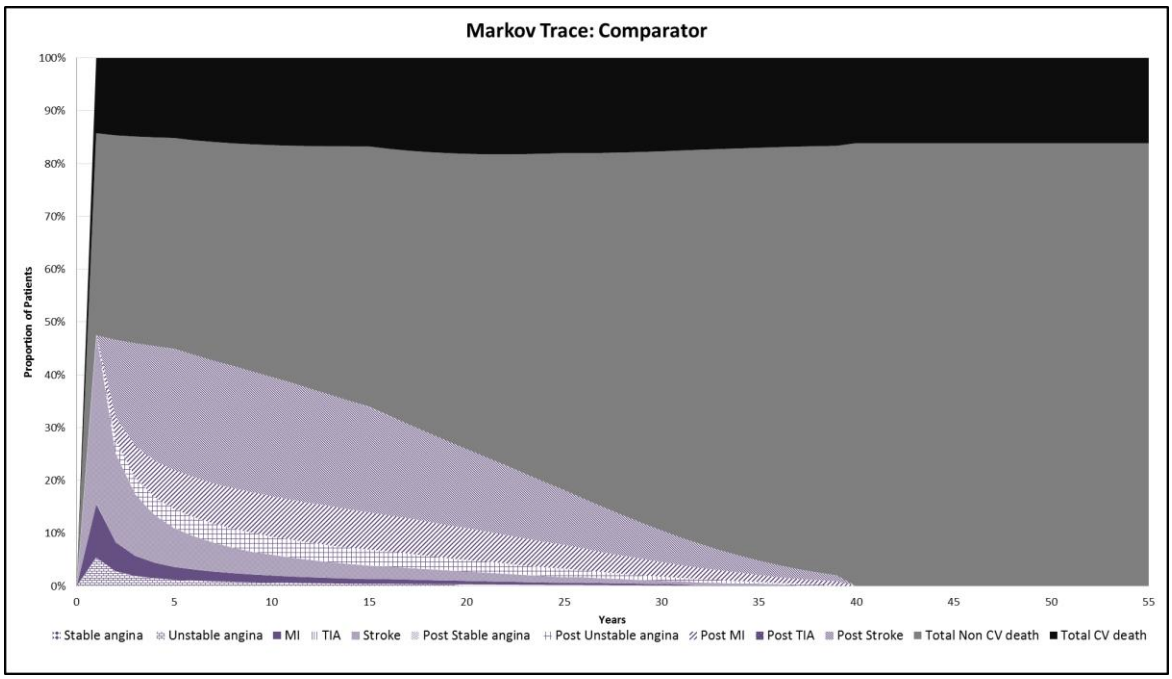


Figure 19 Markov Trace: Atorvastatin 20mg in patients with (20% CV Risk)



Secondary prevention

Monotherapy

Figure 20 Markov Trace for ezetimibe in secondary prevention

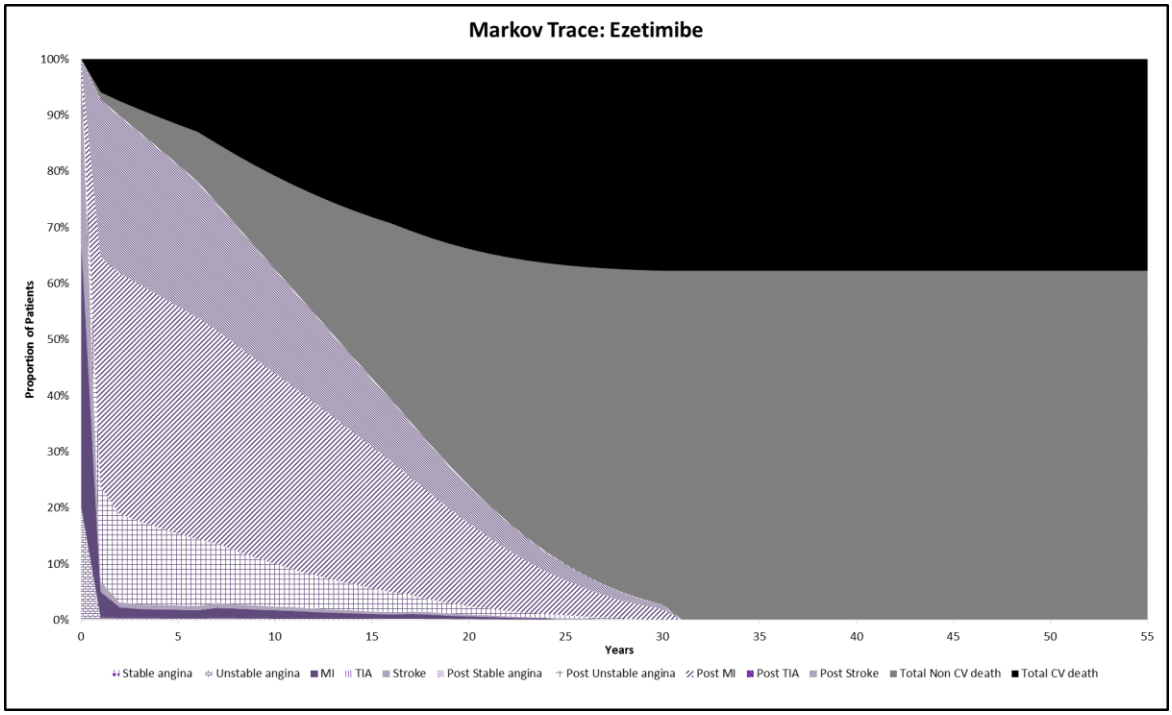
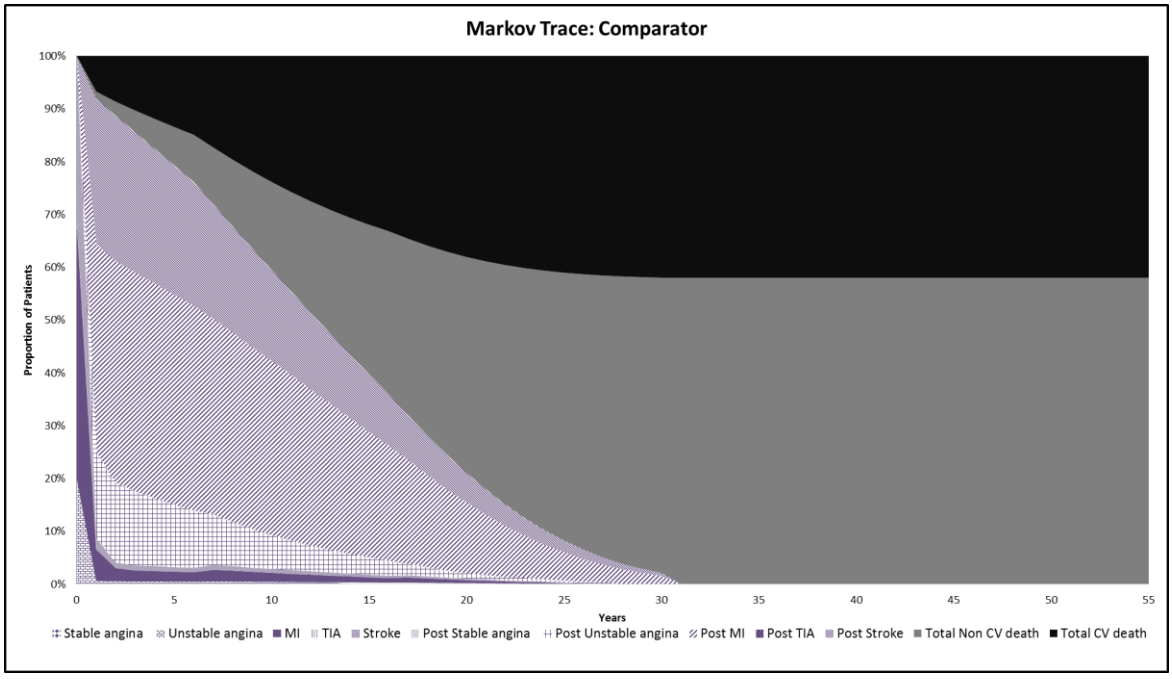


Figure 21 Markov Trace for no treatment in secondary prevention



Add-on to statin

Figure 22 Markov Trace for ezetimibe co-administered with atorvastatin 40mg

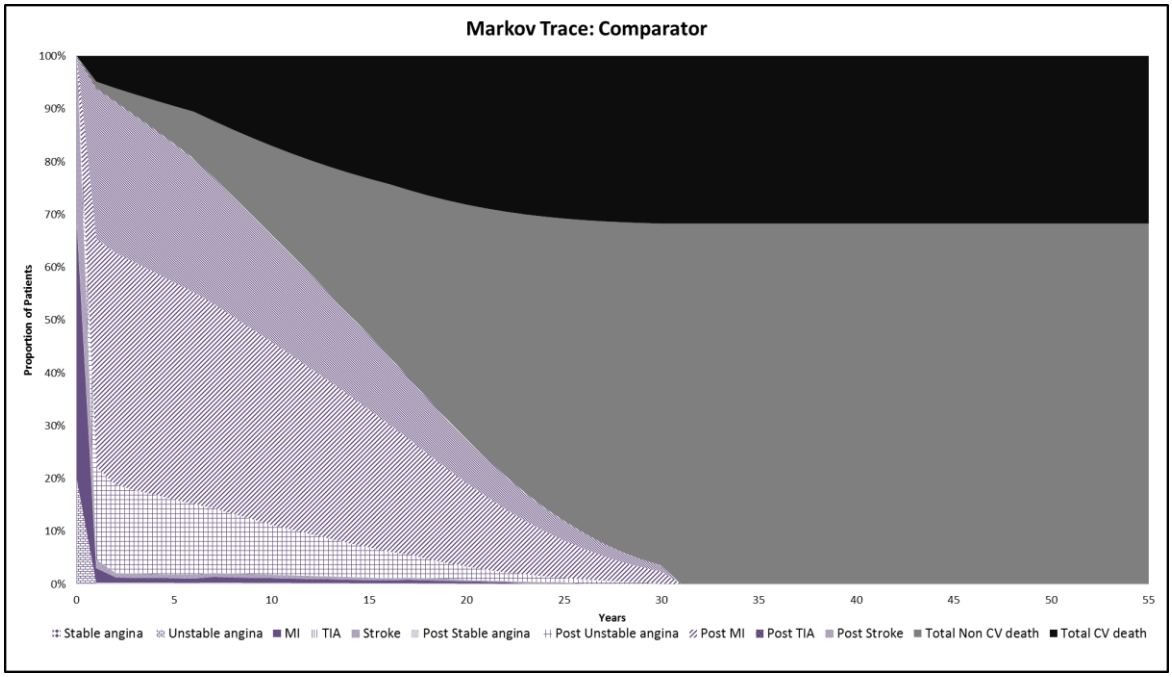
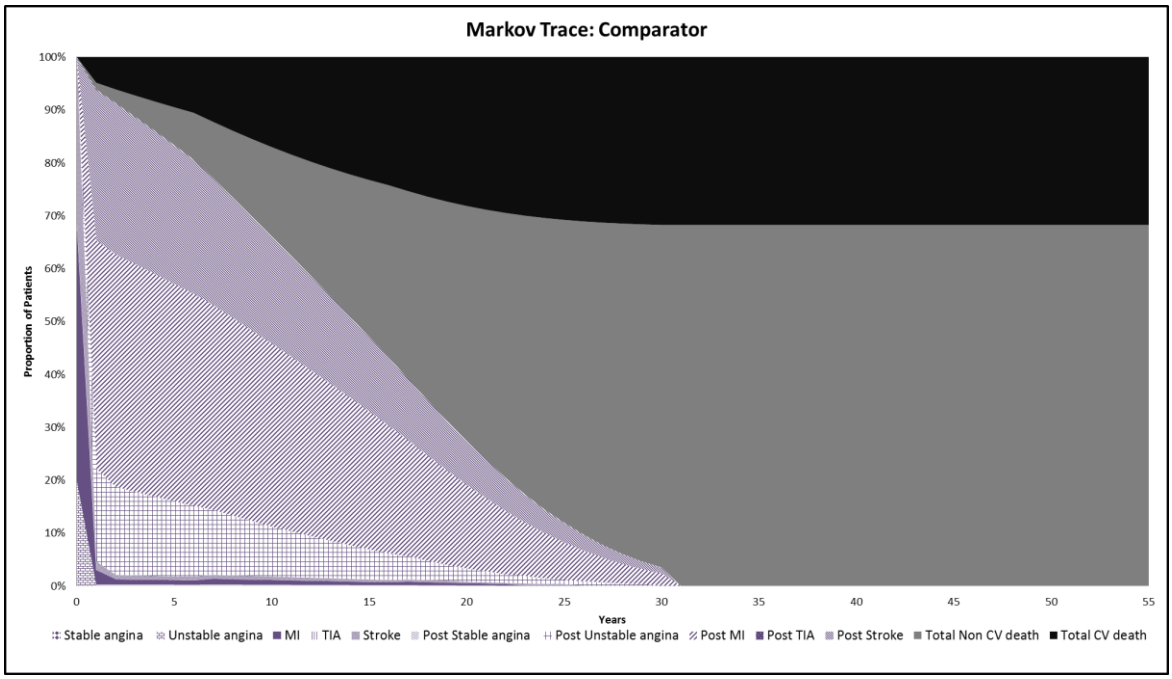


Figure 23 Markov Trace for Atorvastatin 40mg



Accruement of QALYs over time

Primary prevention

Figure 24 -

Figure 27 below illustrate the cumulative QALYs accrued over time in the cost-effectiveness model for ezetimibe monotherapy and add-on to statin, respectively, for patients in primary prevention with 20% risk of experiencing a CV event. QALYs are accrued over time based on the number of CV events they have during their lifetime. As described in section 5.4, patients experiencing CV events have lower QoL than those patients post event.

Figure 24 Cumulative QALYs over time for monotherapy

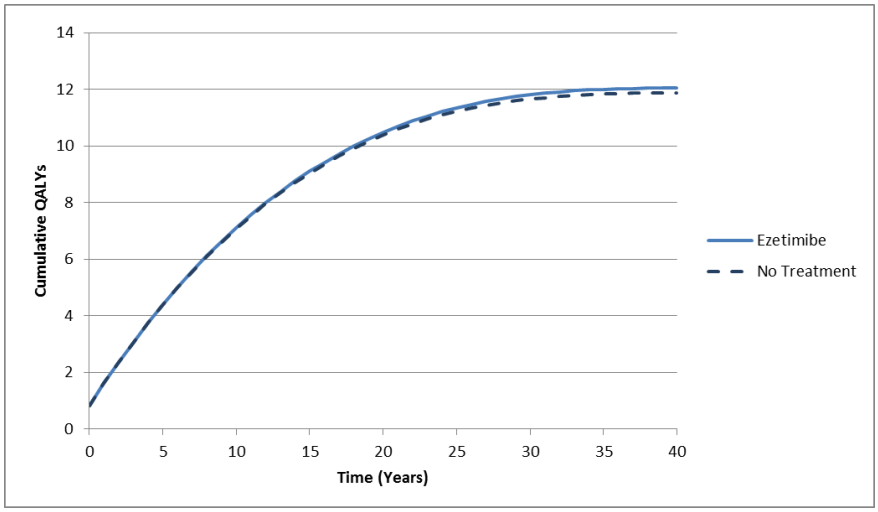
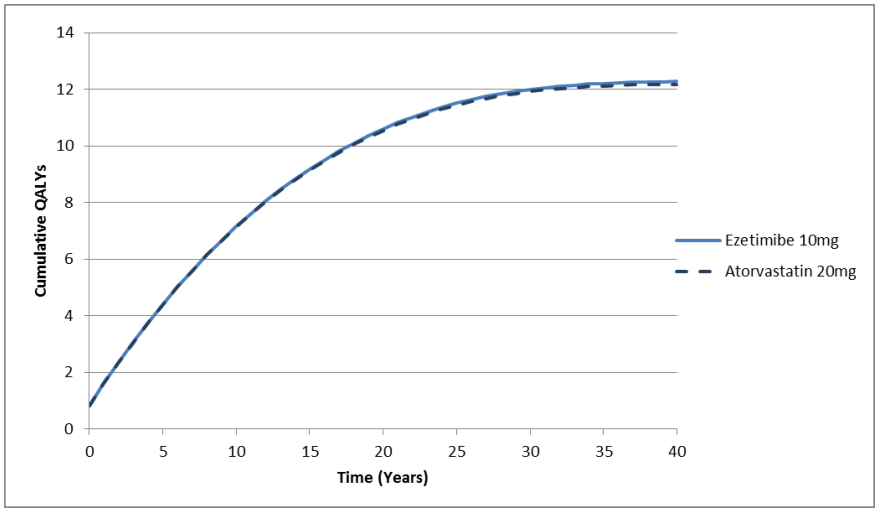


Figure 25 Cumulative QALYs over time for add-on



Secondary prevention

Figure 26 Cumulative QALYs over time for monotherapy

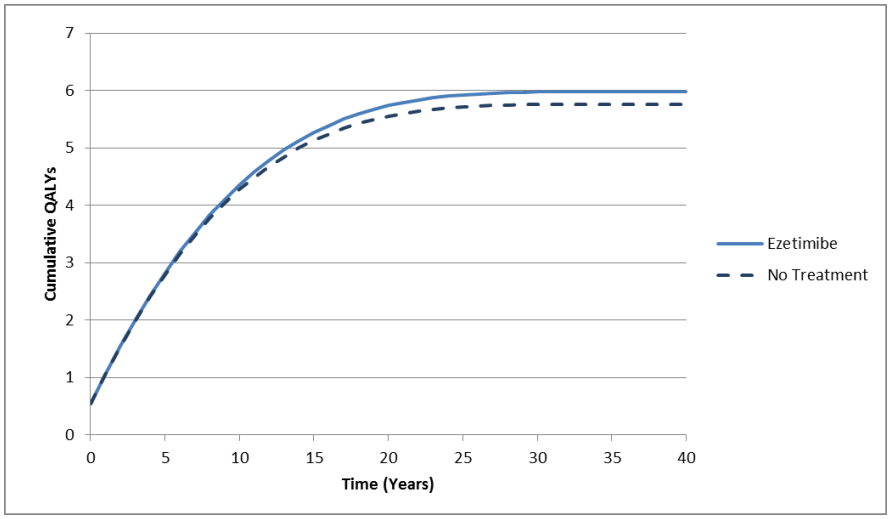
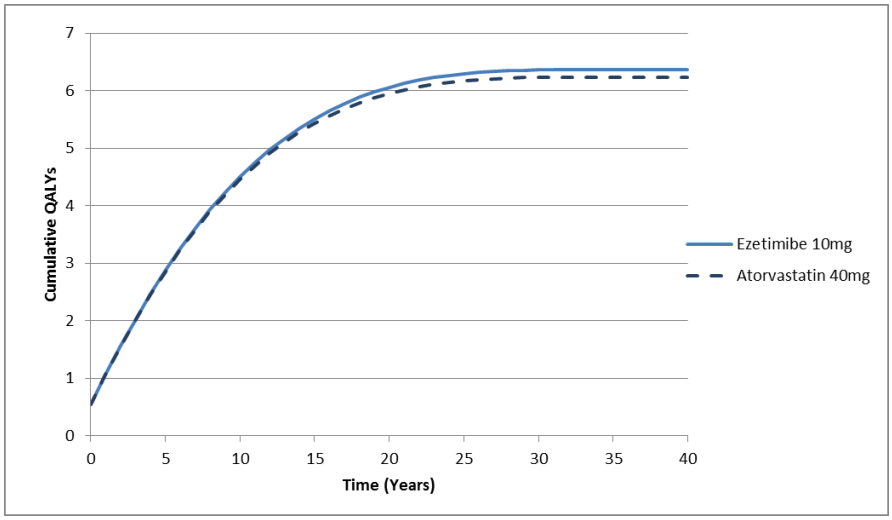


Figure 27 Cumulative QALYs over time for add-on



Disaggregated results of the base case incremental cost effectiveness analysis

Table 49 -

Table 56 below display the disaggregated QALYs and costs in primary and secondary prevention for both monotherapy and add-on to statin treatment options. In primary prevention, patients on ezetimibe treatment arm accrue more QALYs in the 'Well' health state, whereas in secondary prevention patients on ezetimibe treatment accrue additional QALYs on the 'Post MI' health state. Across primary and secondary prevention, the majority of the costs are associated with treatment.

Primary prevention

Monotherapy

Table 49 Summary of QALY gain by health state

Health state	Ezetimibe	No Treatment	Increment	Absolute increment	% absolute increment
Health State Well	11.268	11.020	0.248	0.248	77.66%
Health State Unstable angina	0.019	0.023	-0.004	0.004	1.33%
Health State MI	0.042	0.054	-0.012	0.012	3.61%
Health State Stroke	0.045	0.048	-0.004	0.004	1.11%
Health State Post Unstable angina	0.087	0.094	-0.006	0.006	1.97%
Health State Post MI	0.262	0.305	-0.043	0.043	13.40%
Health State Post Stroke	0.332	0.335	-0.003	0.003	0.92%
Total	12.055	11.878	0.177	0.319	100.00%

Table 50 Summary of costs by health state

Health state	Ezetimibe	No Treatment	Increment	Absolute increment	% absolute increment
Drug Costs	£5,532.54	£0.00	£5,532.54	£5,532.54	93.15%
Health State Well	£0.00	£0.00	£0.00	£0.00	0.00%
Health State Unstable angina	£18.51	£22.66	-£4.15	£4.15	0.07%
Health State MI	£453.81	£576.63	-£122.83	£122.83	2.07%
Health State Stroke	£1,675.36	£1,802.70	-£127.34	£127.34	2.14%
Health State CV Death	£537.77	£609.21	-£71.44	£71.44	1.20%
Health State Post Unstable angina	£35.96	£38.33	-£2.37	£2.37	0.04%
Health State Post MI	£280.79	£325.46	-£44.67	£44.67	0.75%
Health State Post Stroke	£2,818.98	£2,831.21	-£12.23	£12.23	0.21%
Health State non-CV Death	£0.00	£0.00	£0.00	£0.00	0.00%
Monitoring Costs	£1,642.95	£1,621.15	£21.80	£21.80	0.37%
Total	£12,996.67	£7,827.35	£5,169.31	£5,939.38	100.00%

Add-on to statin

Table 51 Summary of QALY gain by health state

Health state	Ezetimibe	Atorvastatin 20mg	Increment	Absolute increment	% absolute increment
Health State Well	11.587	11.458	0.130	0.130	79.47%
Health State Unstable angina	0.011	0.013	-0.002	0.002	0.95%
Health State MI	0.023	0.026	-0.004	0.004	2.24%
Health State Stroke	0.046	0.048	-0.002	0.002	1.22%
Health State Post Unstable angina	0.067	0.071	-0.005	0.005	2.80%
Health State Post MI	0.165	0.185	-0.019	0.019	11.81%
Health State Post Stroke	0.374	0.377	-0.002	0.002	1.52%
Total	12.273	12.176	0.096	0.163	100.00%

Table 52 Summary of costs by health state

Health state	Ezetimibe	Atorvastatin 20mg	Increment	Absolute increment	% absolute increment
Drug Costs	£5,825.41	£231.88	£5,593.53	£5,593.53	96.74%
Health State Well	£0.00	£0.00	£0.00	£0.00	0.00%
Health State Unstable angina	£11.04	£12.56	-£1.52	£1.52	0.03%
Health State MI	£246.49	£285.70	-£39.22	£39.22	0.68%
Health State Stroke	£1,715.31	£1,786.67	-£71.36	£71.36	1.23%
Health State CV Death	£442.61	£472.98	-£30.37	£30.37	0.53%
Health State Post Unstable angina	£27.79	£29.59	-£1.80	£1.80	0.03%
Health State Post MI	£178.25	£198.62	-£20.37	£20.37	0.35%
Health State Post Stroke	£3,200.93	£3,212.81	-£11.89	£11.89	0.21%
Health State non-CV Death	£0.00	£0.00	£0.00	£0.00	0.00%
Monitoring Costs	£1,671.97	£1,659.86	£12.11	£12.11	0.21%
Total	£13,319.80	£7,890.69	£5,429.11	£5,782.16	100.00%

Secondary prevention

Monotherapy

Table 53 Summary of QALY gain by health state

Health state	Ezetimibe	No Treatment	Increment	Absolute increment	% absolute increment
Health State Well	0.000	0.000	0.000	0.000	0.00%
Health State Unstable angina	0.206	0.213	-0.007	0.007	2.21%
Health State MI	0.558	0.588	-0.031	0.031	10.04%
Health State Stroke	0.224	0.228	-0.004	0.004	1.43%
Health State Post Unstable angina	0.773	0.693	0.080	0.080	26.23%
Health State Post MI	2.905	2.795	0.110	0.110	36.12%
Health State Post Stroke	1.314	1.241	0.073	0.073	23.97%
Total	5.981	5.760	0.221	0.305	100.00%

Table 54 Summary of costs by health state

Health state	Ezetimibe	No Treatment	Increment	Absolute increment	% absolute increment
Drug Costs	£3,733.52	£0.00	£3,733.52	£3,733.52	71.15%
Health State Well	£0.00	£0.00	£0.00	£0.00	0.00%
Health State Unstable angina	£197.35	£204.08	-£6.74	£6.74	0.13%
Health State MI	£5,810.03	£6,137.34	-£327.31	£327.31	6.24%
Health State Stroke	£8,142.73	£8,305.33	-£162.60	£162.60	3.10%
Health State CV Death	£1,511.31	£1,695.71	-£184.41	£184.41	3.51%
Health State Post Unstable angina	£314.95	£281.56	£33.39	£33.39	0.64%
Health State Post MI	£3,074.64	£2,954.26	£120.39	£120.39	2.29%
Health State Post Stroke	£11,050.33	£10,413.31	£637.01	£637.01	12.14%
Health State non-CV Death	£0.00	£0.00	£0.00	£0.00	0.00%
Monitoring Costs	£1,122.38	£1,080.32	£42.06	£42.06	0.80%
Total	£34,957.24	£31,071.92	£3,885.32	£5,247.42	100.00%

Add-on to statin

Table 55 Summary of QALY gain by health state

Health state	Ezetimibe	Atorvastatin 40mg	Increment	Absolute increment	% absolute increment
Health State Well	0.000	0.000	0.000	0.000	0.00%
Health State Unstable angina	0.194	0.196	-0.003	0.003	1.54%
Health State MI	0.500	0.512	-0.012	0.012	7.04%
Health State Stroke	0.220	0.223	-0.003	0.003	1.90%
Health State Post Unstable angina	0.949	0.896	0.053	0.053	31.45%
Health State Post MI	3.047	2.991	0.056	0.056	33.29%
Health State Post Stroke	1.461	1.420	0.042	0.042	24.78%
Total	6.370	6.237	0.133	0.168	100.00%

Table 56 Summary of costs by health state

Health state	Ezetimibe	Atorvastatin 40mg	Increment	Absolute increment	% absolute increment
Drug Costs	£4,147.59	£155.76	£3,991.84	£3,991.84	82.78%
Health State Well	£0.00	£0.00	£0.00	£0.00	0.00%
Health State Unstable angina	£184.55	£187.17	-£2.62	£2.62	0.05%
Health State MI	£5,184.86	£5,312.30	-£127.45	£127.45	2.64%
Health State Stroke	£7,986.17	£8,106.18	-£120.01	£120.01	2.49%
Health State CV Death	£1,155.06	£1,259.75	-£104.69	£104.69	2.17%
Health State Post Unstable angina	£389.32	£366.90	£22.42	£22.42	0.47%
Health State Post MI	£3,228.78	£3,167.22	£61.56	£61.56	1.28%
Health State Post Stroke	£12,337.03	£11,970.81	£366.22	£366.22	7.59%
Health State non-CV Death	£0.00	£0.00	£0.00	£0.00	0.00%
Monitoring Costs	£1,197.74	£1,172.43	£25.31	£25.31	0.52%
Total	£35,811.10	£31,698.51	£4,112.59	£4,822.11	100.00%

5.8 Sensitivity analyses

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was performed to account for parameter uncertainty in the cost-effectiveness model. Parameters were varied simultaneously, based upon their distributional information 1,000 times, and the results of every set of iterations were recorded. Results are presented in cost-effectiveness planes (showing the incremental QALYs and costs), and cost-effectiveness acceptability curves (CEACs), showing the likelihood of cost-effectiveness across a range of willingness-to-pay thresholds between £20,000 to £30,000.

Table 57 presents a summary of the distributions used in probabilistic sensitivity analysis. A more detailed presentation of the mean values, distributions around the means and sources used to vary the parameters can be found in section 5.6.

Table 57 Summary of distributions used for sensitivity analysis

Parameter	Distribution
Age	Normal with SE informed by literature
Gender	Beta with number of patients informed from literature
Utilities	Beta with number of patients informed from literature or SE assumed 20% of the mean where no distribution information available
Drug costs available in eMIT	Normal with SE taken from eMIT
Health state and monitoring costs	Normal with SE assumed 20% of the mean
Resource use	Normal with SE assumed 20% of the mean
% reduction in LDL-C for statins	Beta with SD derived from published 95% Cis
% reduction in LDL-C with ezetimibe	Beta using 95% CIs and SD from meta-analysis

The probabilistic sensitivity analyses results presented in the tables below confirm the robustness of the results presented in section 5.7. Additionally, the CEACs highlight that at a WTP threshold of £20,000, ezetimibe has approximately 93% probability of being cost effective in secondary prevention as monotherapy.

Primary prevention

Monotherapy

Table 58 Probabilistic sensitivity analysis results for primary prevention - monotherapy

Technologies	Incremental costs	Incremental LYG	Incremental QALYs	ICER
No Treatment	-	-	-	-
Ezetimibe 10mg	£5,169	0.4731	0.1762	£29,332

Figure 28 Scatterplot of PSA results for patients with 20% CV risk

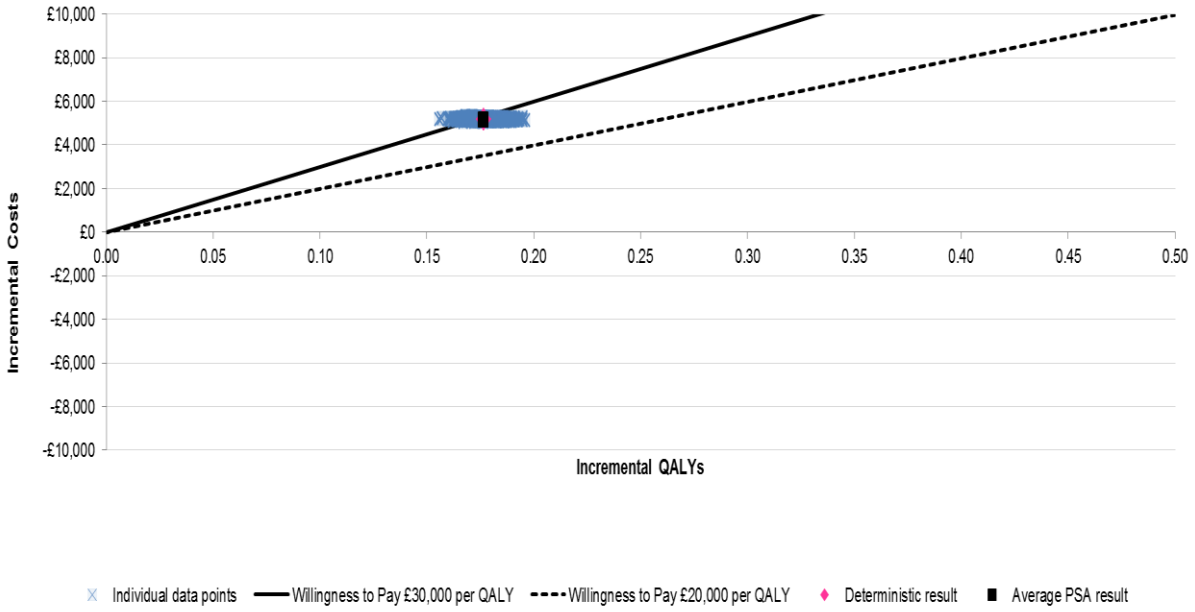
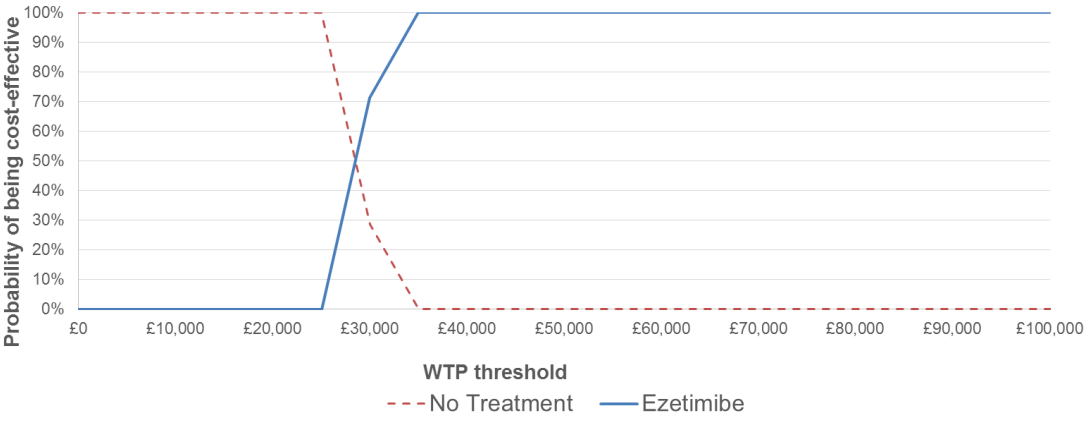


Figure 29 Cost-effectiveness acceptability curves for patients with 20% CV risk



Add-on to statin

Table 59 Probabilistic sensitivity analysis results for primary prevention – Add-on

Technologies	Incremental costs	Incremental LYG	Incremental QALYs	ICER
Atorvastatin 20mg	-	-	-	-
Ezetimibe 10mg + Atorvastatin 20mg	£5,427	0.2696	0.0968	£56,088

Figure 30 Scatterplot of PSA results for patients with 20% CV risk

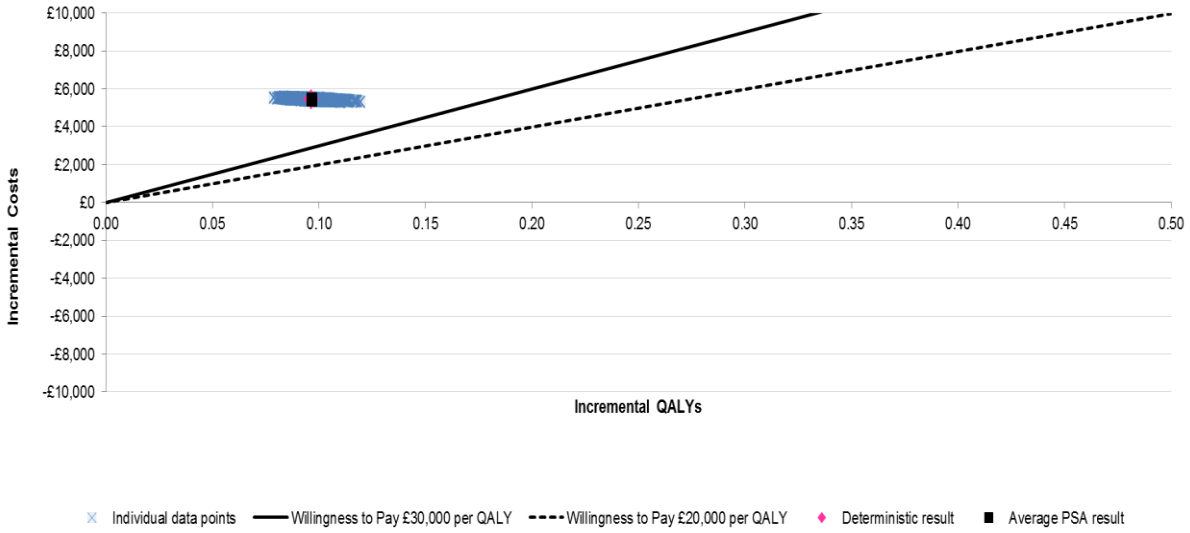
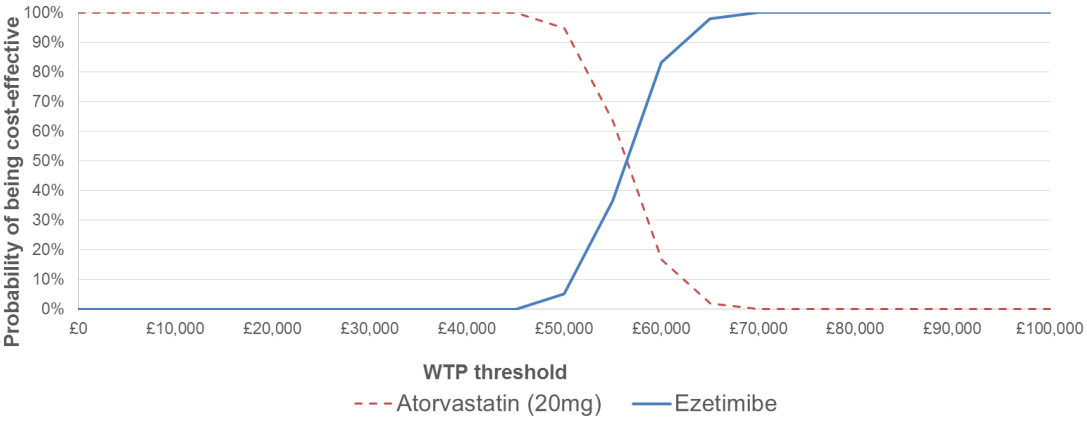


Figure 31 Cost-effectiveness acceptability curves for patients with 20% CV risk



Secondary prevention

Monotherapy

Table 60 Probabilistic sensitivity analysis results for secondary prevention - monotherapy

Technologies	Incremental costs	Incremental LYG	Incremental QALYs	ICER
No Treatment	-	-	-	-
Ezetimibe 10mg	£3,885	0.6827	0.2202	£17,644

Figure 32 Scatterplot of PSA results for patients with in secondary prevention

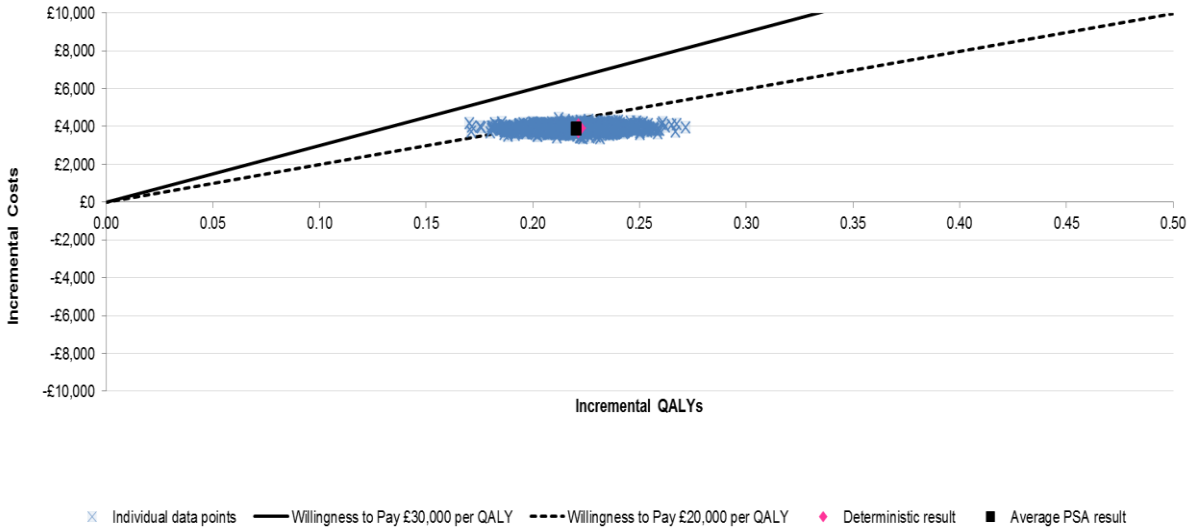
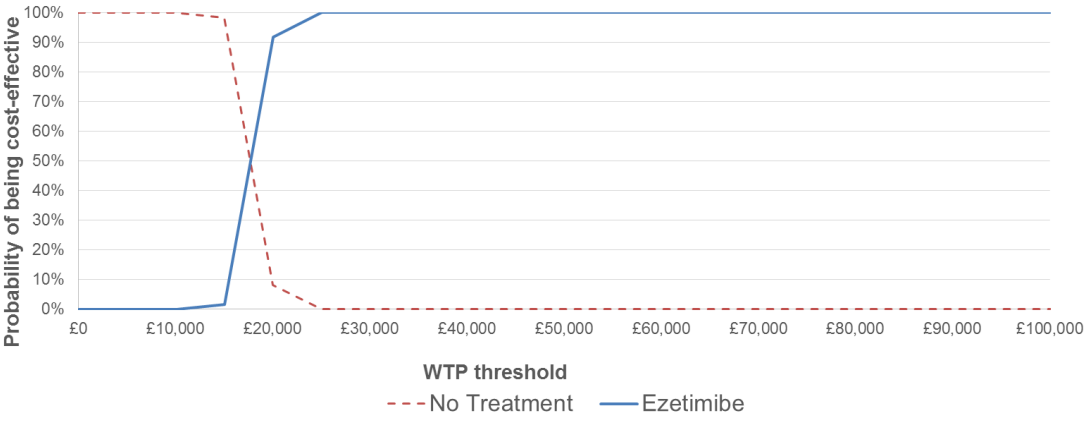


Figure 33 Cost-effectiveness acceptability curves for patients in secondary prevention



Add-on to statin

Table 61 Probabilistic sensitivity analysis results for primary prevention – Add-on

Technologies	Incremental costs	Incremental LYG	Incremental QALYs	ICER
Atorvastatin 40mg	-	-	-	-
Ezetimibe 10mg + Atorvastatin 40mg	£4,104	0.4213	0.1330	£30,861

Figure 34 Scatterplot of PSA results for patients with in secondary prevention

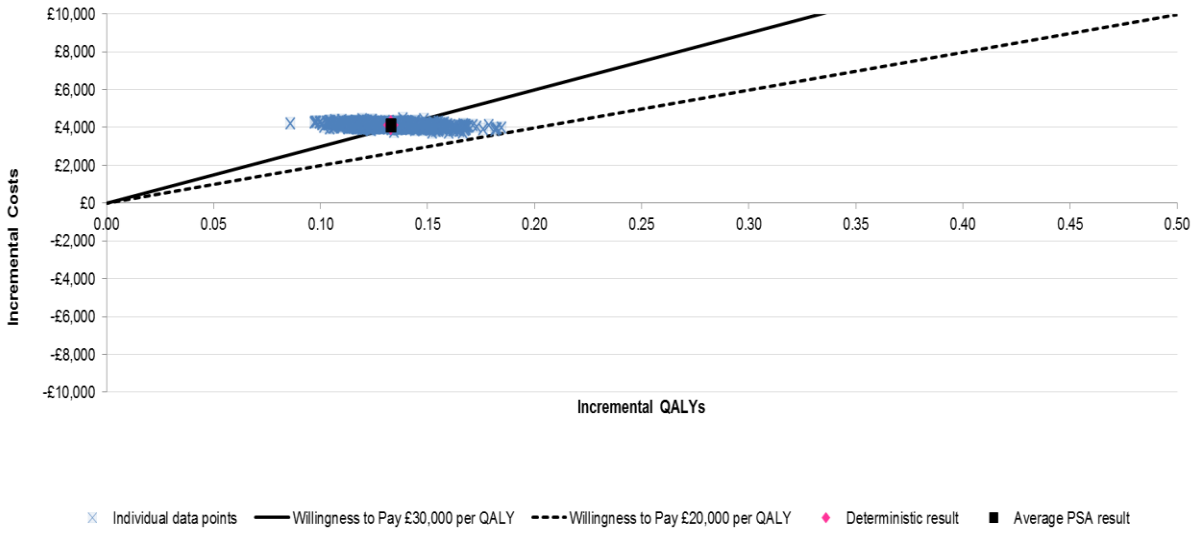
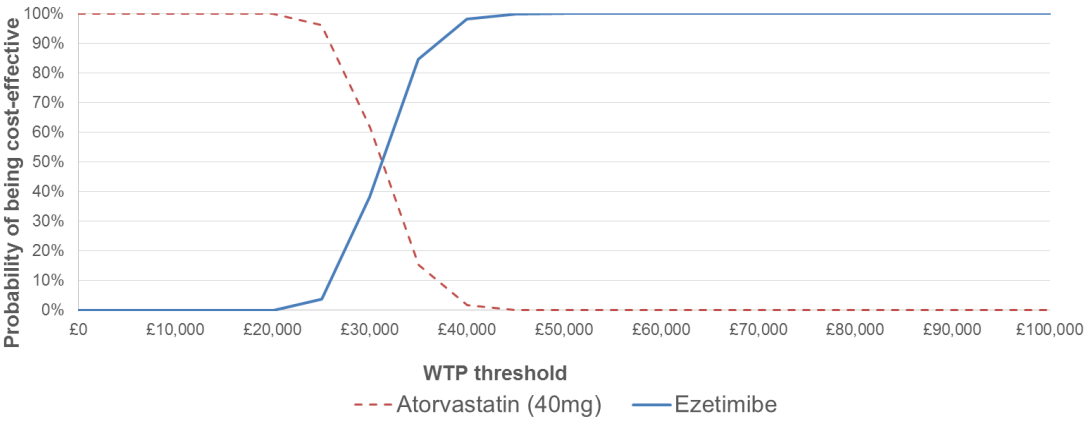


Figure 35 Cost-effectiveness acceptability curves for patients with 20% CV risk



Deterministic sensitivity analysis

One-way sensitivity analyses were performed around all relevant model parameters to evaluate the impact upon the ICER. Key parameters were varied by the upper and lower bound value and those with the greatest impact on the ICER were plotted on tornado diagrams and are:

- Risk Ratios: LDLC Other non CVD Death (non - Vascular death)
- Discount rates for costs and QALYs varied between 0% and 6%
- Risk Ratios: LDL-c Non-fatal stroke
- Risk Ratios: LDL-c Unstable angina
- Risk Ratios: LDL-c All Vascular (causes of death)

- % reduction in LDLC-Ezetimibe add on to statin: Meta-analysis
- Post Stroke utility value
- Post stroke health state costs
- MI health state costs

Primary prevention

Figure 36 Tornado diagram presenting the results of the deterministic sensitivity analysis for monotherapy

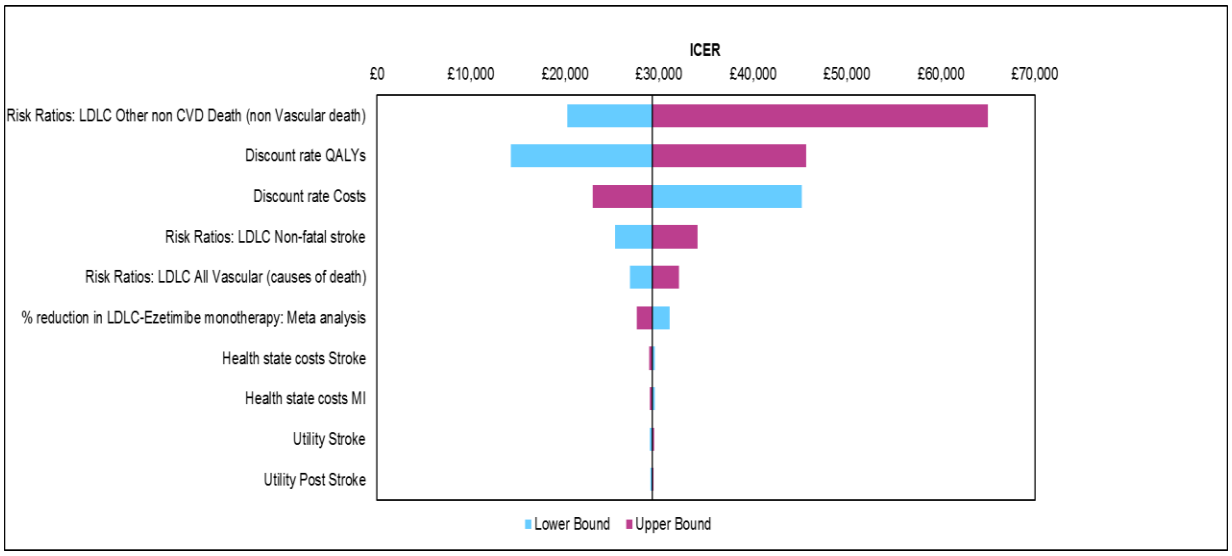
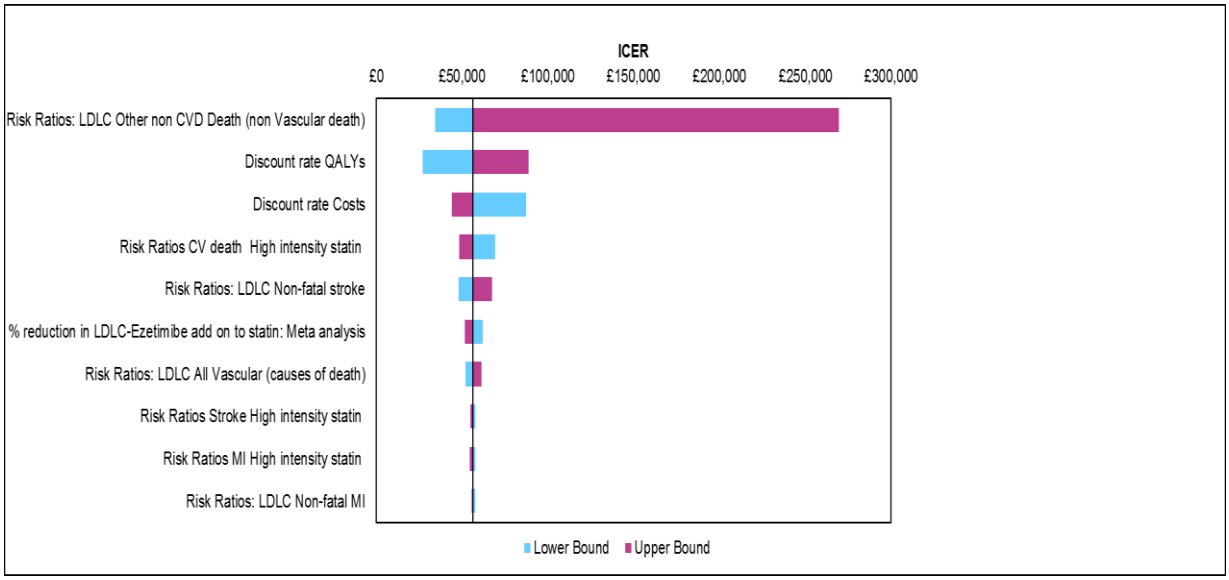


Figure 37 Tornado diagram presenting the results of the deterministic sensitivity analysis for add-on



Secondary prevention

Figure 38 Tornado diagram presenting the results of the deterministic sensitivity analysis for monotherapy

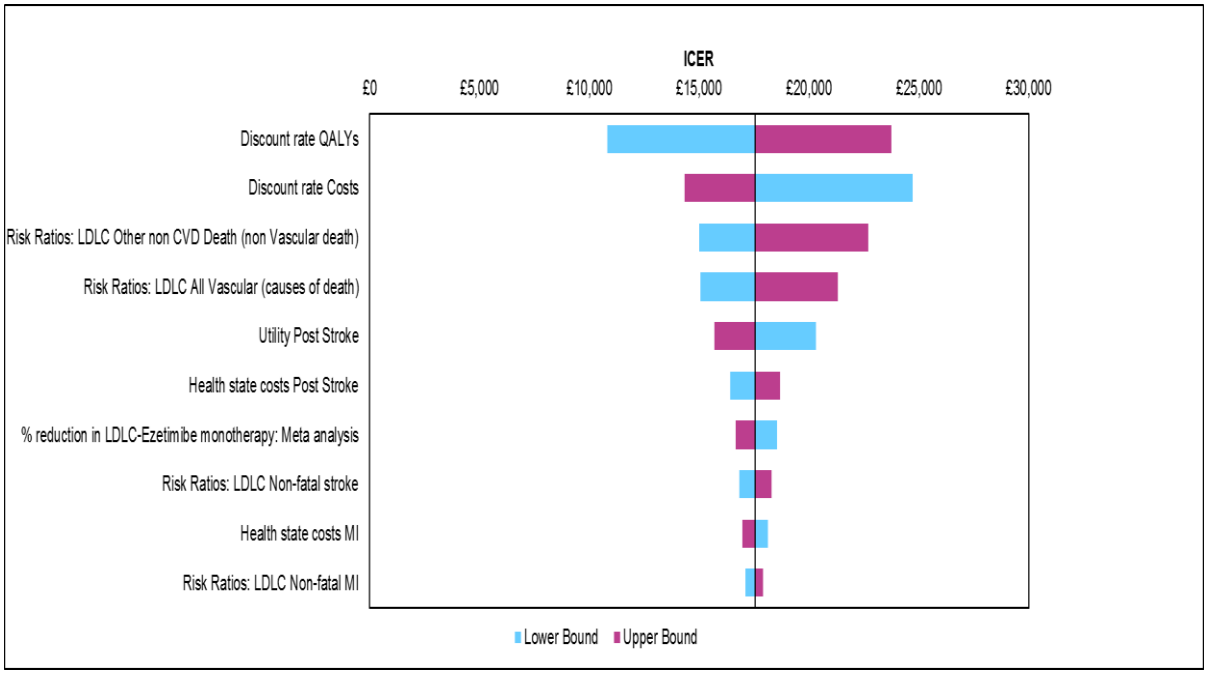
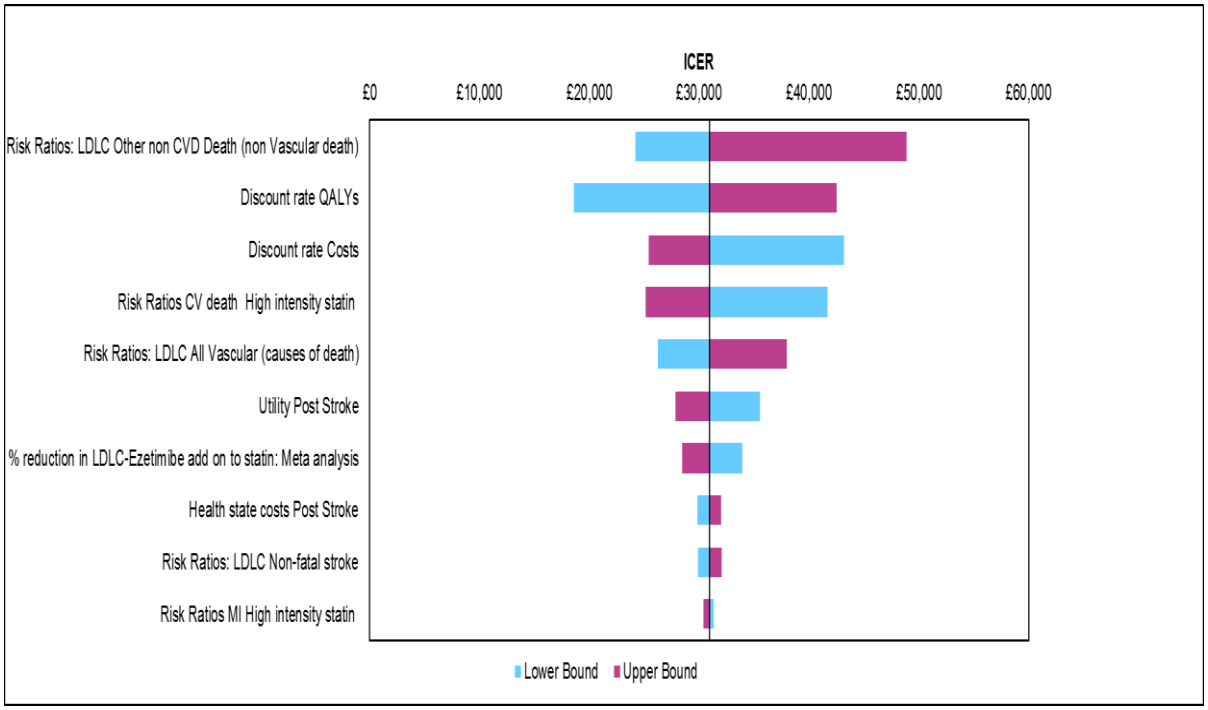


Figure 39 Tornado diagram presenting the results of the deterministic sensitivity analysis for add-on



Scenario analysis

5.8.8 Scenario analyses conducted for the cost-effectiveness analyses

Table 62 below summarises the details of each scenario analysis performed.

Table 62 Description of scenario analyses

Scenario	Description	Rationale
A	Alternative pre-statin LDL-c levels	To evaluate the impact of alternative pre-statin LDL-c levels
B1	Primary prevention – 10-year CV risk of 10%	To evaluate the impact of alternative 10-year CV risk levels
B2	Primary prevention – 10-year CV risk of 30%	
C	Ezetimibe patent expiry in April 2018 – Ezetimibe generic price (75% price reduction) applied from year 3 in the model	To explore impact of ezetimibe's patent expiry in April 2018
D1	Model TIA and stable angina health states: RR between treatment arms, TIA and stable angina = 1 (i.e. no difference)	To evaluate the impact of re-distributing incidence rates to CV events of modelled
D2	Addition of TIA and stable angina health states to model structure: RR between treatment arms, TIA = same as RR for non-fatal stroke RR between treatment arms, stable angina = same as RR for non-fatal MI	To evaluate the impact if ezetimibe has an impact on reducing a wider range of CV events than modelled in the base case
E	RR between treatment arms for unstable angina = 1 (i.e. no difference)	RR data in base case is an assumption. This is to test the impact of the assumption on the ICER
F	Add-on to statin analysis, post-ACS population for simvastatin 40mg vs. simvastatin 40mg + ezetimibe. Relative risks from IMPROVE-IT applied	To explore the cost-effectiveness of using ezetimibe added-on to simvastatin 40mg in IMPROVE-IT population (post-ACS population)
G	Adding on ezetimibe to alternative doses of atorvastatin: Primary prevention (atorvastatin 10mg & 40mg) Secondary prevention (atorvastatin 10mg & 20mg)	In the base case, the main atorvastatin dose recommended in CG181 and relevant to clinical practice have presented for each relevant population In clinical practice, alternative atorvastatin doses may be used with patients based on the maximum tolerated doses.
H	Alternative time horizons: 10-years; 20-years & 30-years	To explore the impact of alternative time horizons
I	Base case results, by starting age and gender	To reflect age and gender as risk factors for CVD disease

Scenario A – Alternative pre-statin, LDL-c levels

A mean value for baseline LDL-c has been applied for the base case analyses. Analyses using alternative LDL-c values have been inputted to evaluate the cost-effectiveness of each population.

Scenario B1 & B2 – Alternative 10-year CV risk levels, primary prevention

In clinical practice, there is variation in the CV risk thresholds used to identify patients eligible for lipid modification management. For the base case, a 20% 10-year risk level, as measured by QRISK2, has been used. Scenario analyses applying alternative 10-year CV risk levels of 30% and 10% for the primary prevention population are evaluated in section 5.8.

Scenario C – Generic ezetimibe from April 2018

In the base case analyses, the annual cost of ezetimibe applied is £343.20 per patient (MIMS, Mar 2015[15]). In April 2018, ezetimibe patent in the UK will expiry and in the cost-effectiveness approach, the generic price of ezetimibe is applied from year 3 onwards. The estimated cost of the generic has been based on the current price of generic versions of ezetimibe in Canada, where generic have been available since September 2014. In Canada, generic ezetimibe has fallen by 75% compared to the price of branded ezetimibe, which equates to £85.80.[157]

Scenario D1 & D2 – TIA and stable angina

In the base case, major CV events are modelled, which includes unstable angina, MI, Stroke and death (CV and non-CV-related). The original TA132 analysis of ezetimibe also modelled treatment benefit associated with reducing TIA and stable angina events.[7] As such, two scenario analyses are conducted as follows:

- Firstly, TIA and stable angina were included in the underlying distribution data used to calculate the baseline event rates for first and subsequent events rates. Scenario B adds four health states to the model, TIA. Post-TIA, stable angina and post-stable angina to evaluate the impact of excluding these. The relative risks applied in the model are that of no difference;
- Secondly, the TIA, post-TIA, stable angina and post-stable angina health states are included in the scenario C cost-effectiveness analysis, and a treatment benefit is modelled. TIA and stable angina were not endpoints evaluated in the CTTC analysis[9], and therefore, the same approach as TA132 has been adopted, where the same RR as stroke are applied to TIA and the same RR as MI are applied to

unstable angina. This is biologically plausible, due to close relationship of these conditions.[7]

Cost and utility data is applied for these four health states, and this is summarised in the following sections.

Table 63 Summary of utility values for cost-effectiveness analysis (scenario analysis)

State	Utility value: mean	Standard error	N	Reference in submission	Justification
Stable angina	0.808	Not reported	58	Meslop et al, 2003 [158]	Limited utility data consistent with reference case; US study previously used in Ward *et al.*[103], TA132[7] and CG181[88]
Post-stable angina	0.808	Not reported	458	Assumption based on Meslop *et al.* 2003[158]	Meslop found TTO score were stable across 2 successive annual interviews
TIA	0.76	0.017*	244	6 month data point, Luengo-Fernandez, 2013[143]	Only publication consistent with NICE reference case[89]
Post TIA	0.76	0.020*	173	24-month data point, Luengo-Fernandez, 2013[143]	Only publication consistent with NICE reference case;[89] Data up to 5-years shows HRQoL stabilises post-6 months

*calculated from standard deviation

TIA and post-TIA utilities

Only one study that was consistent with the NICE reference case was identified from previous economic evaluations and the updated systematic review and this has been used to source utility values for the TIA and post-TIA health states. This was the OXVASC study, which captured and reported utility data for patients with TIA up to 5 years. For the scenario analysis, the utilities applied to TIA and post-TIA were taken from the EQ-5D data at 6-months (0.76) and 24-months (0.76), respectively, which showed that the HRQoL of patients remains stable over time.

The Haacke 2006[159] study used in the Ara *et al.* publication{Ara, 2008 43 /idwas exclude as it is based on a non-UK setting.

Stable angina and post-stable angina utilities

There is limited data consistent with the reference data available. Two studies potential sources of utility values were identified from economic evaluations. A study conducted by Lenzen *et al.{Lenzen, 2006 4429 /id}* in 31 European countries evaluated HRQoL using EQ-5D in patients with coronary artery disease. The study reported a median EQ-5D of 0.85 and 0.76 for individuals eligible and not eligible for revascularisation, respectively, at discharge. A US study conducted by Meslop *et al.*[158], found patients with angina had a mean TTO of 7.03 compared to 8.7 to those with angina. The later has been utilised in the model as the patients had angina and this value has been used in previous NICE technology appraisal.

Although Lacey and Walters[134] has been used to source utility values for stable angina in previous economic evaluations, it has been excluded from consideration in this instance, as the study does not include relevant patients.

Table 64 summarises the costs for the four additional health states used for scenario analyses D1 and D2.

Table 64 TIA, post TIA, stable angina and post-stable angina health state costs

Health state	Annual cost in health state	Original Prices	Reference
Stable angina	£242.38	£201	TA132[7] (costs in 2006 prices inflated to 2014)
Post stable angina	£242.38	£201	TA132[7] (costs in 2006 prices inflated to 2014)
TIA	£3,982.31	£3,660	Luengo-Fernandez et al 2012[150] (costs in 2009 prices inflated to 2014)
Post TIA	£1,386.22	£1,274	Luengo-Fernandez et al 2012[150] (costs in 2009 prices inflated to 2014)

TIA and post TIA costs

With regards to TIA and post TIA health states costs, in previous HTA activities (TA94[12] and Ara et al. [86])the costs were based on clinical expert opinion. Two recent studies by Luengo-Fernandez *et al.*[150;152] were identified estimating the hospital care costs of TIA and stroke based on the population-based cohort study OXVASC study. The study by Luengo-Fernandez *et al.* 2012[150] calculated the hospital costs before and following one year of the event, whereas the study by Luengo-Fernandez *et al.* 2013[152] estimated the hospital

resource costs over a period of 5 years providing a deeper understanding of the incurred costs. The values from the latest study were selected for inclusion in the cost-effectiveness model.

Stable and post stable angina costs

The costs for post stable angina health state were assumed to be equal to the costs assigned to the stable angina health state which were inflated from TA132[7] based on three GP appointments and medication costs (£201). The literature search did not yield any updated cost studies for these health states and specific breakdown in medication doses was not described in TA132 to allow re-calculation using latest drug prices and GP appointment costs.

Scenario E – relative risks for unstable angina

Unstable angina was not an endpoint evaluated in the CTTC meta-analysis[9], and therefore, in the base case the same approach was TA132 adopted, where the same RR as MI are applied to unstable angina. This is biologically plausible, due to close relationship of these conditions as captured under the medical term acute coronary syndrome. As such, a scenario analysis has been performed to evaluate the impact of modelling no difference (i.e. a RR = 1).

Scenario F – Cost-effectiveness of IMPROVE-IT population

As discussed previously, the IMPROVE-IT study, which evaluated the reduction of CV events when ezetimibe is added on to simvastatin 40mg, represents a subset of ezetimibe licensed population and has limited relevance to UK clinical practice as the patients' LDL- c were well controlled on entry to the study. A scenario analysis has been conducted evaluating the cost-effectiveness of adding ezetimibe to simvastatin 40mg based on the population in IMPROVE-IT (i.e. post-ACS). The baseline characteristics have been taken from the IMPROVE-IT study and are summarised in Table 65 below. To reflect the post-ACS population, the patients in this scenario analysis have been distributed to the MI or unstable angina (1st year) health state, using the distribution of patients to these events in IMPROVE-IT.

Table 65 Baseline characteristics, IMPROVE-IT population (Scenario F)

Patient characteristic	Mean	Source
Starting age	64	IMPROVE-IT study[11];CSR
% female	24.3%	
Type of index event		
Myocardial infarction	75.8%	
Unstable angina	24.2%	

To adjust the baseline events for the first events and subsequent events, these have been adjusted as per the base case to reflect the background therapy of simvastatin 40mg, applying the percentage LDL-c expected to simvastatin and linking this to the CTTC meta-analysis. The percentage in LDL-c reduction versus placebo for simvastatin 40mg has been taken from the same source as atorvastatin in the base case[8], which reported a 37% reduction.

The relative risk reductions from IMPROVE-IT have been applied to generate the transition probabilities when ezetimibe is added-on to simvastatin. Based on the IMPROVE-IT data, non-fatal MI (RR 0.871, 95% CI: 0.798–0.950), non-fatal stroke (RR 0.802, 95% CI: 0.678–0.949) and CV death (RR 1.000, 95% CI: 0.887–1.127) were applied that align with the definitions of the health states used in the model. For non-CV death, a RR of 1 has been applied due to the lack of biological plausibility for a reduction in such events, supported by the evidence in the IMPROVE-IT trial (HR 1.035, 95% CI: 0.914–1.171).

Table 66 Relative risks applied in the cost-effectiveness model for simvastatin 40mg + ezetimibe in comparison with simvastatin 40 mg (Scenario F)

Health state	Relative Risk	Source
Unstable angina	0.87	Equals RR for MI
MI	0.87	IMPROVE-IT study[11]
Stroke	0.80	IMPROVE-IT study[11]
CV death	1.00	IMPROVE-IT study[11]
Non-CV Death	1.00	No difference assumed

The drug acquisition costs for simvastatin 40mg not included in the base case are shown in Table 67.

Table 67 Annual drug acquisition costs, simvastatin 40 mg

Drug	Cost per 28 day pack	Annual cost of treatment	Source
Atorvastatin 40 mg	£0.36	£4.70	eMit (12 months to Dec 2014)[146]
Key: eMit, electronic market information tool; mg, milligram			

Scenario G – alternative dose of atorvastatin as background therapy

In the base case analyses, the main dose of atorvastatin that is recommended in the NICE Lipid Modification guideline and used in clinical practice has been used as the background statin dose for the add-on to statin analyses. In clinical practice, there is variation in the background atorvastatin dose that patients received. In particular, it is common for patients that are prescribed high dose of statin post-ACS events, such as atorvastatin 80mg, to be down-titrated to a lower dose when they released into primary care for their ongoing management due to tolerability issues. To reflect the variation in clinical practice, the following additional scenario analyses have been performed to explore the impact of adding ezetimibe to alternative doses of statin in the primary and secondary prevention population:

- primary prevention (atorvastatin 10 mg and 40 mg)
- secondary prevention (atorvastatin 10 mg, 20 mg & 80 mg).

The drug acquisition costs for these alternative doses not included in the base case are shown in Table 68.

Table 68 Annual drug acquisition costs, atorvastatin 10mg

Drug	Cost per 28 day pack	Annual cost of treatment	Source
Atorvastatin 10 mg	£0.74	£9.65	eMit (12 months to Dec 2014)[146]
Key: eMit, electronic market information tool; mg, milligram			

Scenario H – Alternative time horizons

In the base case a lifetime time horizon is adopted up to a maximum of 100 years. The number years evaluated varies dependent on the starting age of the cohort at baseline. A scenario analysis is conducted to evaluate the impact of alternative time horizons of 10, 20 and 30 years.

Scenario I – stratified by gender and starting age

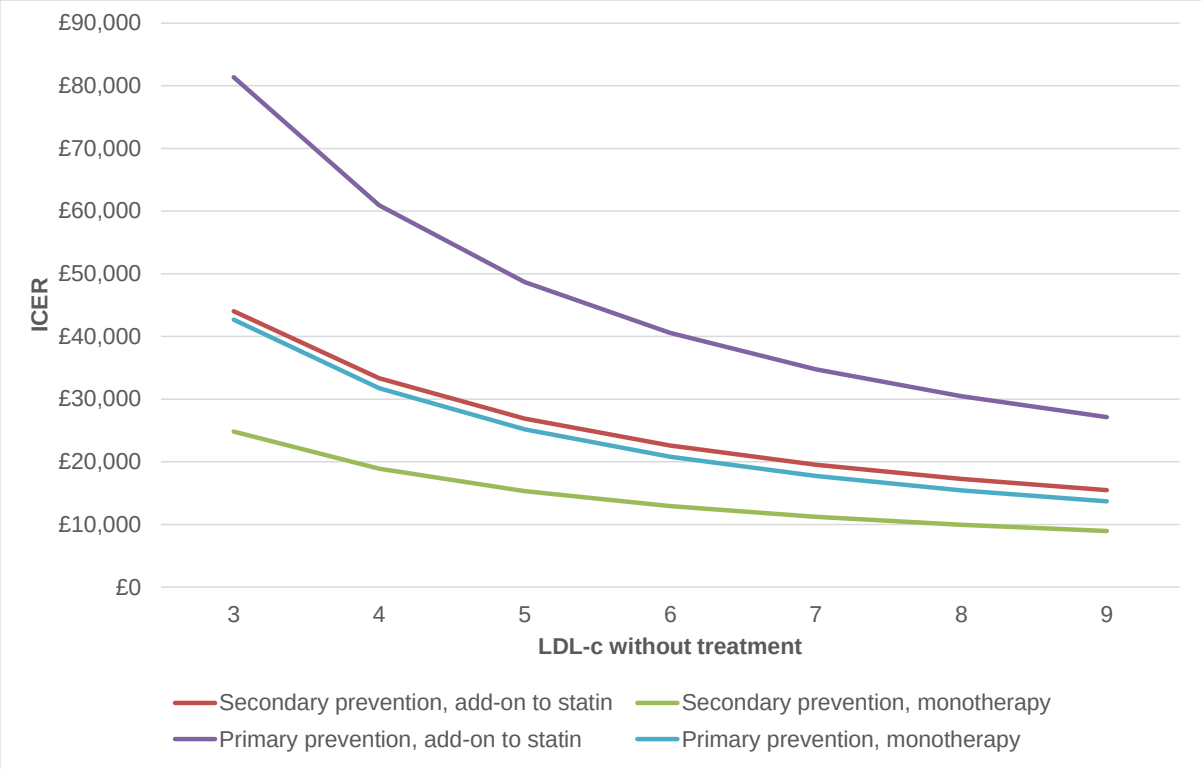
Gender and age are risk factors of cardiovascular disease. As such, to reflect the impact of these factors on the underlying risk of patients, the base case results for the primary and secondary prevention populations are shown by gender and starting age.

5.8.9 Results of scenario analyses

Scenario A – Alternative pre-statin, LDL-c levels

Figure 40 below summarises the impact of varying the baseline LDL-c value applied from 3 to 9 mmol/L on the ICER in each of the four populations evaluated in the base case.

Figure 40 Scenario A: Incremental cost-effectiveness ratios (ICERs), by varying baseline LDL-c levels



Primary prevention, monotherapy scenario analyses

Table 69 and Table 70 provide a summary of the cost-effectiveness results from the scenario analyses for the primary prevention population with ezetimibe monotherapy. Scenarios F & G are not relevant to the primary prevention, monotherapy analyses.

Table 69 Scenario B-E & H cost-effectiveness results, primary prevention – monotherapy

Primary prevention, monotherapy			
Scenario	**Parameter**	**CV Risk**	**ICER (cost per QALY), ezetimibe vs. no treatment**
Base case		**20%**	**£29,286**
B1 – 10-year CV risk of 10%		10%	£47,067
B2 – 10-year CV risk of 30%		30%	£21,187
C – generic ezetimibe from April 2018		20%	£10,146
D1 – Addition TIA and stable angina health states (with no treatment benefit)		20%	£26,224
D2 – Addition of TIA and stable angina health states (with treatment benefit)		20%	£22,426
E – relative risks for unstable angina (RR = 1)		20%	£29,307
H – Alternative Time Horizons	30 years	20%	£32,982
	20 years	20%	£47,206
	10 years	20%	£101,898
TIA = transient ischaemic attack; CV = cardiovascular; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year			

Table 70 Scenario I cost-effectiveness results by age and gender, primary prevention – monotherapy

Population	**CVD Risk**	**ICER (Cost per QALY), by starting age Ezetimibe vs. no treatment**			
		40 years	**50 years**	**60 years**	**70 years**
Male	20%	£35,232	£25,208	£28,726	£26,483
Female	20%	£36,927	£30,531	£29,491	£25,937

Primary prevention, add-on to statin scenario analyses

Table 71 and

Table 72 provide a summary of the cost-effectiveness results from the scenario analyses for the primary prevention population with ezetimibe co-administered with a statin. Scenario F is not relevant to the primary prevention, add-on to statin analyses.

Table 71 Scenario A-B2, C2-E & H cost-effectiveness results, primary prevention – add-on to statin

Primary prevention, add-on to statin			
Scenario	**Parameter**	**CV Risk**	**ICER (cost per QALY)**
Base case (A20 + E10 vs. A20)		**20%**	**£56,394**
B1 – 10-year CV risk of 10% (A20 + E10 vs. A20)		10%	£84,752
B2 – 10-year CV risk of 30% (A20 + E10 vs. A20)		30%	£41,783
C – generic ezetimibe from April 2018 (A20 + E10 vs. A20)		20%	£20,540
D1 – Addition TIA and stable angina health states (with no treatment benefit) (A20 + E10 vs. A20)		20%	£48,090
D2 – Addition of TIA and stable angina health states (with treatment benefit) (A20 + E10 vs. A20)		20%	£45,608
E – relative risks for unstable angina (RR = 1) (A20 + E10 vs. A20)		20%	£55,409
G – Alternative dose of atorvastatin as background therapy	A10 + E10 vs. A10	20%	£51,558
	A40 + E10 vs. A40	20%	£56,395
H – Alternative Time Horizons (A20 + E10 vs. A20)	30 years	20%	£64,909
	20 years	20%	£94,184
	10 years	20%	£199,460

A20 = atorvastatin 20 mg; E10 = ezetimibe 10 mg; A10 = atorvastatin 10 mg; A40 = atorvastatin 40 mg;

Table 72 Scenario I cost-effectiveness results by age and gender, primary prevention – add-on to statin

Population	CVD Risk	ICER (Cost per QALY), by starting age A20 + E10 vs. A20			
		40 years	50 years	60 years	70 years
Male	20%	£87,358	£58,592	£56,202	£47,997
Female	20%	£78,247	£62,836	£55,491	£45,956

Secondary prevention, monotherapy scenario analyses

Table 73 and Table 74 provide a summary of the cost-effectiveness results from the scenario analyses for the secondary prevention population with ezetimibe monotherapy. Scenarios F & G are not relevant to the secondary prevention, monotherapy analyses.

Table 73 Scenario C–E & H cost-effectiveness results, secondary prevention – monotherapy

Scenario	Parameter	ICER (cost per QALY), ezetimibe vs. no treatment
Base case		**£17,553**
C – generic ezetimibe from April 2018		£8,140
D1 – Addition TIA and stable angina health states (with no treatment benefit)		£18,951
D2 – Addition of TIA and stable angina health states (with treatment benefit)		£18,951
E – relative risks for unstable angina		£17,402
H – Alternative Time Horizons	30 years	£17,625
	20 years	£19,763
	10 years	£30,858

Table 74 Scenario I cost-effectiveness results by age and gender, secondary prevention – monotherapy

Population	ICER (Cost per QALY), by starting age Ezetimibe vs. no treatment			
	40 years	50 years	60 years	70 years
Male	£30,428	£25,049	£19,783	£17,019
Female	£34,355	£27,722	£22,141	£18,364

Secondary prevention, add-on to statin scenario analyses

Table 75 and Table 76 provide a summary of cost-effectiveness results from the scenario analyses of the secondary prevention population with ezetimibe co-administered with a statin. Scenarios B1 and B2 are not relevant to the secondary prevention, add-on to statin analyses.

Table 75 Scenario C–E & H cost-effectiveness results, secondary prevention – add-on to statin

Secondary prevention, add-on to statin		
Scenario	**Parameter**	**ICER (cost per QALY)**
Base case		**£30,940**
C – generic ezetimibe from April 2018 (A40 + E10 vs. A40)		£13,874
D1 – Addition TIA and stable angina health states (with no treatment benefit) (A40 + E10 vs. A40)		£34,730
D2 – Addition of TIA and stable angina health states (with treatment benefit) (A40 + E10 vs. A40)		£34,730
E – relative risks for unstable angina (A40 + E10 vs. A40)		£30,821
F – IMPROVE-IT population		£137,642
G – Alternative dose of atorvastatin as background therapy	A10 + E10 vs. A10	£28,256
	A20 + E10 vs. A20	£30,939
H – Alternative Time Horizons (A40 + E10 vs. A40)	30 years	£31,153
	20 years	£36,564
	10 years	£61,766
A20, atorvastatin 20 mg; E10, ezetimibe 10 mg; A10, atorvastatin 10 mg; A40, atorvastatin 40 mg; A80, atorvastatin 80 mg		

Table 76 Scenario I cost-effectiveness results by age and gender, secondary prevention – add-on to statin

Population	**ICER (Cost per QALY), by starting age A40 + E10 vs. A40**			
	40 years	**50 years**	**60 years**	**70 years**
Male	£58,036	£46,163	£35,739	£30,229
Female	£63,237	£49,500	£38,401	£31,957
E10, ezetimibe 10 mg; A10, A40, atorvastatin 40 mg				

Summary of sensitivity analyses results

The probabilistic sensitivity analysis results confirm the robustness of the results of the deterministic analyses. At a WTP threshold of £20,000 per QALY, ezetimibe has 93% of being cost-effective in secondary prevention as monotherapy. At an increased WTP threshold of £30,000, ezetimibe has 73% probability in primary prevention when ezetimibe is the only appropriate treatment option for patients with 20% 10-year CV risk. At the same WTP value, ezetimibe co-administered with atorvastatin 40mg has approximately 40% probability of being cost-effective for patients with history of CV events.

Deterministic sensitivity analysis results demonstrated that the RR of any non-vascular death per mmol/L LDL-c reduction sourced from the CTT meta-analysis has the greatest impact on the ICERs presented across primary prevention and in the add-on population of secondary prevention. Varying the discount rates of costs and QALYs has also demonstrated to have an impact on the ICERs.

The scenario analyses show that higher baseline LDL-c levels for all populations and increasing 10-year CV risk for the primary prevention populations decreases the ICERs. Ezetimibe is more cost-effective as the baseline CV risk increases.

The exclusion of TIA and stable angina health states compared to the previous Ara et al. and Ward et al. analyses has minimal impact on the ICER. There is no change in the ICER observed for scenarios D1 and D2 in secondary prevention, when alternative treatment benefits are applied because the underlying subsequent event transition probabilities do not allow transitions from CV health states to stable angina or TIA (Table X). Furthermore, removing the treatment benefit modelled in the base case for unstable angina has shown to have a limited impact on the ICER.

The scenario analysis reflecting the generalisation of ezetimibe in April 2018 shows significant falls in the ICERs well below the cost-effectiveness threshold of £20,000 per QALY for monotherapy in both primary and secondary prevention populations and when where ezetimibe is co-administered with a statin in the secondary prevention population.

5.9 Subgroup analysis

5.9.1 Subgroups considered in the cost-effectiveness analyses

Ezetimibe is used for the treatment of primary hypercholesterolaemia. There are three relevant sub-groups due to the differences in the baseline CV risk and the lipid-modification management strategies appropriate for these sub-groups:

- Primary prevention for people with diabetes
- People with chronic kidney disease (CKD)
- Heterozygous familial hypercholesterolaemia (HeFH)

The lipid modification management of patients for these sub-groups has been evaluated as part of the NICE guideline CG181[8], 2014 and CG71, 2008.

Patients with diabetes are at two to three time higher risk of cardiovascular events compared to those without diabetes.[22] Further data has also demonstrated that patients with diabetes have the equivalent CHD risk to those patients without diabetes and with established CHD.[160;161] The recent NICE Lipid Modification Guideline recommended offering atorvastatin 20mg for primary prevention for people with diabetes. At least one third of people with type 2 diabetes are expected to develop CKD.

People with CKD are a distinct sub-group (see Section 3.1.4). The recent NICE Lipid Modification Guideline[8], recommends that patients with CKD are offered a lower dose of atorvastatin due to risk of adverse events associated with high dose atorvastatin. The maximum dose of statin that can be used is limited by the level renal impairment and some patients may require additional cholesterol reduction. At least one third of patients with diabetes are expected to develop CKD (see Section 3.1.4).

Patients with HeFH are at elevated risk of CVD disease and are a high risk group, and intensive lipid modification management is required to manage their high CVD risk levels. The risk of coronary events has been reported to be greater than 50% risk of coronary events by the age of 50 in males, and greater than 30% risk of coronary events by the age of 60 in females. [162]

5.9.2 Analysis of subgroups

Primary prevention for people with diabetes

Sub-group cost-effectiveness analysis for the primary prevention of type 2 diabetes has been undertaken, as the baseline risks have been taken from the type 2 diabetes specific risk assessment tool (UKPDS) and using a sub-group meta-analysis in patients with diabetes. However, it was not possible to undertake specific cost-effectiveness analysis for people with type 1 diabetes because no specific risk tool has been identified ; this is consistent with the approach adopted in CG181. [88]

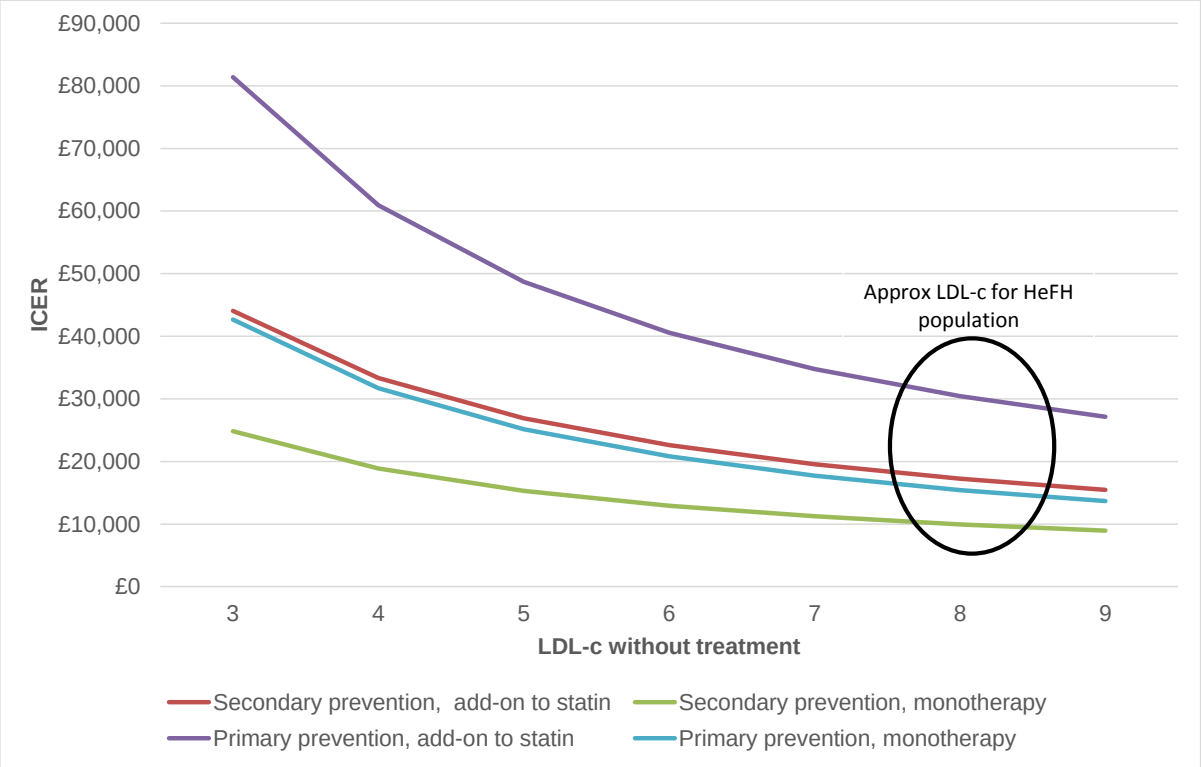
People with CKD

The option to uptitrate statin dose for those patients not appropriately controlled on their initial statin is limited in people with CKD and therefore, the additional option of ezetimibe is required to address the significant unmet need in this group. An analysis reflecting a maximum atorvastatin dose of atorvastatin 20mg has been evaluated. This has been run for the secondary prevention population, as the base case results for primary prevention evaluated this dose. This group have elevated baseline risks, however, there is no distinct risk assessment tool available for people with CKD. As such, the same baseline risks as the base population have been applied. Furthermore, the RRs derived from the clinical review in CG181 assumes that different high-intensity doses of atorvastatin (20 mg, 40 mg and 80 mg) have the same reduction of risk, this simplifying assumption has the consequence that the baseline risks for this analysis may be an overestimate of true risk levels.

People with HeFH

Patients with HeFH are at significantly elevated CV risk. It has not been possible to conduct specific cost-effectiveness analyses due to the extremely limited data available on the baseline risks of this group. Patients with HeFH have extremely high LDL-c of at least 8 mmol/L.[69;162] The scenario analysis for the base case, demonstrates that at such high levels of LDL-c, ezetimibe is a highly cost-effective option (Figure 41).

Figure 41 Incremental cost-effectiveness ratios (ICERs) for base populations, by varying baseline LDL-c levels



5.9.3 Definition of the characteristics of patients in the subgroup

Primary Prevention for people with type 2 diabetes

The cost-effectiveness for the primary prevention population with type 2 diabetes has been evaluated at 20% 10-year risk level, as well as looking at 10% and 30%, using the type 2 diabetes-specific risk assessment tool, UKPDS. The baseline characteristics representative of the primary prevention population with type 2 diabetes are presented in Table 77, which have been informed which have been informed by a retrospective, UK observational study that evaluated patients with type 2 diabetes.[30]

Table 77 Baseline characteristics, primary prevention population

Patient characteristic	Mean	Source
Starting age	67	Jameson et l., 2014[30]
% female	44.3%	

Consistent with the base case, a baseline LDL-c level pre-treatment of 4.32 mmol/L has been applied, which was sourced from Van Staa *et al.* CPRD study.[27]

5.9.4 Description of cost-utility methodology

The same Markov model developed for the base case has been used for the sub-group analyses, with key alterations in the baseline characteristics, the baseline risks and and the clinical effectiveness inputs applied.

Primary Prevention with type 2 diabetes

The comparator and interventions used for the monotherapy and add-on to statin analyses for this sub-group are the same as the base case. The comparator used in the monotherapy cost-effectiveness analyses is 'no treatment', while atorvastatin 20mg is used for the add-on to statin to be consistent with the NICE Lipid Modification guideline.[8]

The baseline event rates for the first CV event are derived in a similar way to the base, although the 10-year CVD risk has been defined using UKPDS risk assessment tool, which is specific to type 2 diabetes and to those patients with no history of CVD. UKPDS is based on the landmark diabetes study conducted in the UK. The use of the tool is consistent with the modelling approach used in CG181[88], and reflects the higher baseline risk of these patients. The UKPDS tool estimates an individual's risk of experiencing non-fatal or fatal MI or stroke events. This represents three of the types of CV events included in the distribution

of CV events data (sourced from Ward *et al.*[12]) (Table 78) used to calculate the transition probabilities from the 'Well' states to the first CV event.

Table 78 Distribution of patients to primary CVD event health states, sourced from Ward *et al.*, 2007.[12]

Age (years)	Stable angina	Unstable angina	MI	TIA	Stroke	CVD Death	Total CV event rate per 1000 / annum
Male							
40-54*	30.7%	10.7%	29.5%	6.0%	12.9%	10.1%	4.2
55-64	32.8%	7.1%	17.2%	8.9%	20.6%	13.4%	13.7
65-74	21.4%	8.3%	17.3%	10.0%	27.0%	16.0%	24.3
75-84	19.1%	8.1%	16.1%	8.0%	34.3%	14.3%	37.5
85-100	21.4%	9.6%	18.6%	1.6%	35.1%	13.7%	42.6
Female							
40-54*	32.5%	11.7%	8.0%	16.0%	22.9%	9.1%	1.6
55-64	34.6%	7.3%	9.2%	9.5%	28.8%	10.6%	6.6
65-74	20.2%	5.2%	12.1%	7.3%	38.2%	17.1%	12.4
75-84	14.9%	3.4%	10.2%	9.8%	46.4%	15.2%	23.4
85-100	13.6%	2.9%	10.0%	8.7%	50.1%	14.7%	32.9

* It has been assumed that the annual incidence rates and distributions for the 45-54 age group are the same for the 40-44 age group

These incidence rates were re-weighted based on the 3 CV events included in UKPDS in order to match the total number of events for these event types to the total number of events presented within the distribution dataset. The rates for TIA and stable angina in the original dataset were set to zero and the resultant relative rates of first events are summarised in Table 79. This allows the higher baseline risk of patients with type 2 diabetes to be reflected whilst keeping the distribution of the types of events constant. Incidence rates did not require reweighting for QRISK2 in the base case as QRISK2 contains the same events used within the model.

Table 79 Adjusted relative rates of first events in primary prevention

Age (years)	Unstable angina	MI	Stroke	CV death	TIA	Stable angina	Sum
Male							
40-54	0.2038	0.5619	0.2457	0.1924	0.1143	0.5848	1.2038
55-64	0.1387	0.3359	0.4023	0.2617	0.1738	0.6406	1.1387
65-74	0.1376	0.2869	0.4478	0.2653	0.1658	0.3549	1.1376
75-84	0.1252	0.2488	0.5301	0.2210	0.1236	0.2952	1.1252
85+	0.1424	0.2760	0.5208	0.2033	0.0237	0.3175	1.1424
Female							
40-54	0.2925	0.2000	0.5725	0.2275	0.4000	0.8125	1.2925
55-64	0.1502	0.1893	0.5926	0.2181	0.1955	0.7119	1.1502
65-74	0.0772	0.1795	0.5668	0.2537	0.1083	0.2997	1.0772
75-84	0.0474	0.1421	0.6462	0.2117	0.1365	0.2075	1.0474
85+	0.0388	0.1337	0.6698	0.1965	0.1163	0.1818	1.0388

In terms of subsequent event rates, it has been assumed that the risk of the same for patients with or without type 2 diabetes.

A meta-analysis of all RCTS available was conducted to determine the change in LDL-c from baseline when ezetimibe is added to a statin for people with diabetes and without diabetes (section 4.9). Among patients with diabetes, the mean difference for ezetimibe plus statin vs statin monotherapy was -18.8% (95% CI -20.7 to -17.0). Among patients without diabetes, the mean difference was -15.0% (95% CI -15.8 to -14.1). The estimated difference in treatment effect between patients with diabetes and those without was -3.87% (95% CI -5.85 to -1.90). Given the statistically significant difference observed in the diabetes group, the diabetes-specific meta-analysis data (Table 80) has been incorporated into the cost-effectiveness model for this sub-group analysis.

Table 80 Meta-analysis results used to inform reduction in LDL-C with ezetimibe

% reduction in LDL-c	Mean	N	SD	SE	95% Confidence interval
Ezetimibe add on to statin (diabetes sub-group)	18.83%	155	11.61	0.93	[20.66; 17.00]

Key: LDL-c, low-density lipoprotein cholesterol; N, number of patients; SD, standard deviation; SE, standard error.
*Ezetimibe monotherapy analysis in diabetes sub-group was not feasible due to insufficient data. As such, in the model, when running the analysis for monotherapy, patients with type 2 diabetes, the ezetimibe monotherapy data for the base case population is applied

The same costs and utility data used in the base have been applied in the sub-group analysis for primary prevention in patients with type 2 diabetes. Although a relevant study by Alva *et al.* reporting utility data for patients with type 2 diabetes were found in the systematic reviews (**Error! Reference source not found.**), the study did not report utility data per ealth state to incorporate in the cost-effectiveness model.

People with CKD

An analysis reflecting a maximum atorvastatin dose of atorvastatin 20mg has been evaluated for the secondary prevention population. The same baseline risks as the base population have been applied. The baseline risks are adjusted to reflect atorvastatin 20 mg using the RRs derived from the clinical review in CG181 (

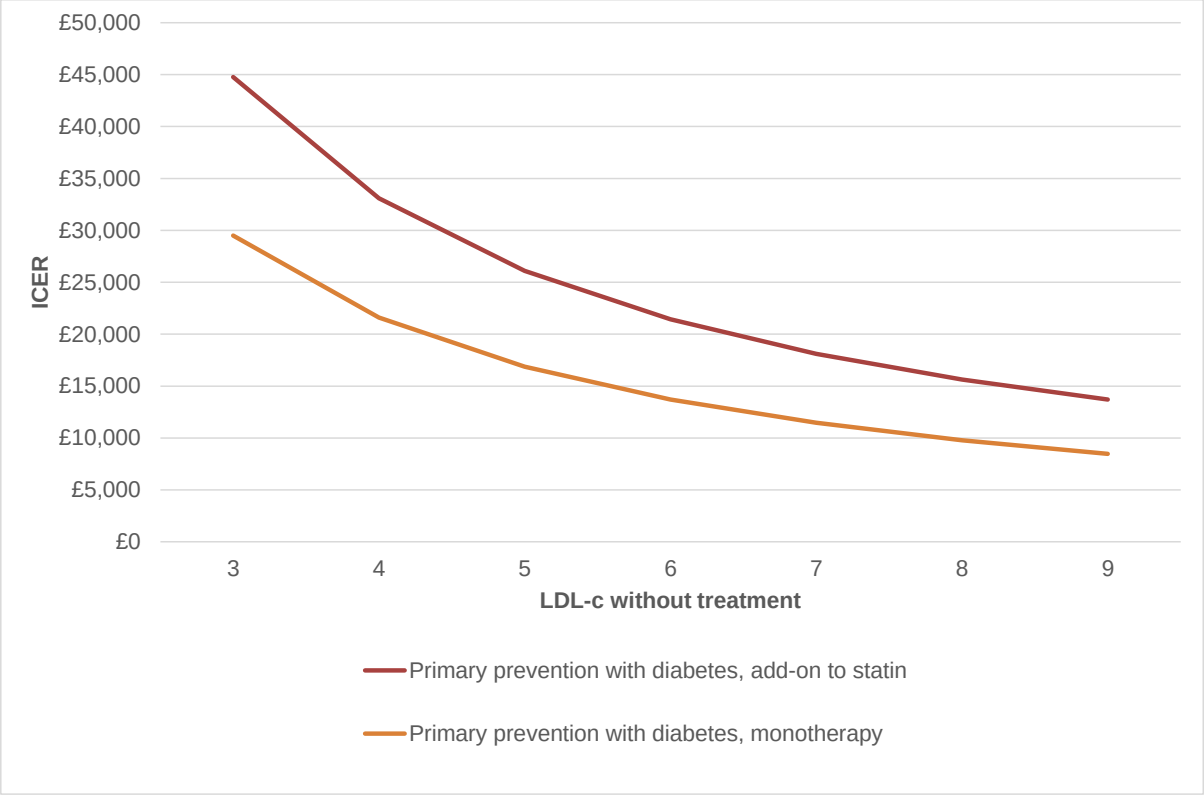
Table 30), which assumes that different high-intensity doses of atorvastatin (20 mg, 40 mg and 80 mg) have the same reduction of risk. This simplifying assumption has the consequence that the baseline risks for this analysis may be an overestimate of true risk levels.

5.9.5 Results of subgroup analyses

Primary Prevention with type 2 diabetes

Figure 42 below summarises the impact of varying the baseline LDL-c value applied from 3 to 9 mmol/L on the ICER in the primary prevention for people with diabetes population for ezetimibe as a monotherapy or co-administered with a statin.

Figure 42 Incremental cost-effectiveness ratios (ICERs) for base populations, by varying baseline LDL-c levels



Primary Prevention with type 2 diabetes, monotherapy

Table 81 below summarises the cost-effectiveness results for patients who are not eligible for statin treatment based on a 10-year CV level of 20%, and further analyses are presented to evaluated the impact of alternative 10-year risk levels of 30% and 10%. In this population, ezetimibe consistently incurs higher incremental costs and QALYs compared to no treatment deriving ICERs of £19,852 at 20% 10-year risk level. At alternative risk levels of 10% and 30%, the ICERs are £32,986 and £14,527, respectively.

Table 81 Sub-group results for primary prevention with diabetes – monotherapy

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
20% CV Risk							
No Treatment	£8,494	18.07	9.39	-	-	-	-
Ezetimibe 10mg	£12,582	18.55	9.60	£4,089	0.478	0.206	£19,852
10% CV Risk							
No Treatment	£5,662	19.01	9.93	-	-	-	-
Ezetimibe 10mg	£10,162	19.35	10.06	£4,501	0.343	0.136	£32,986
30% CV Risk							
No Treatment	£11,105	17.22	8.89	-	-	-	-
Ezetimibe 10mg	£14,878	17.80	9.15	£3,773	0.579	0.260	£14,527

The probabilistic sensitivity analyses results presented in the tables below confirm the robustness of the results for the primary prevention with diabetes population. Additionally, the CEACs highlight that at a WTP threshold of £20,000 and £30,000, ezetimibe monotherapy has approximately 55% and 100% probability of being cost effective in primary prevention population with diabetes.

Figure 43 Scatterplot of PSA results for patients with 20% CV risk (monotherapy)

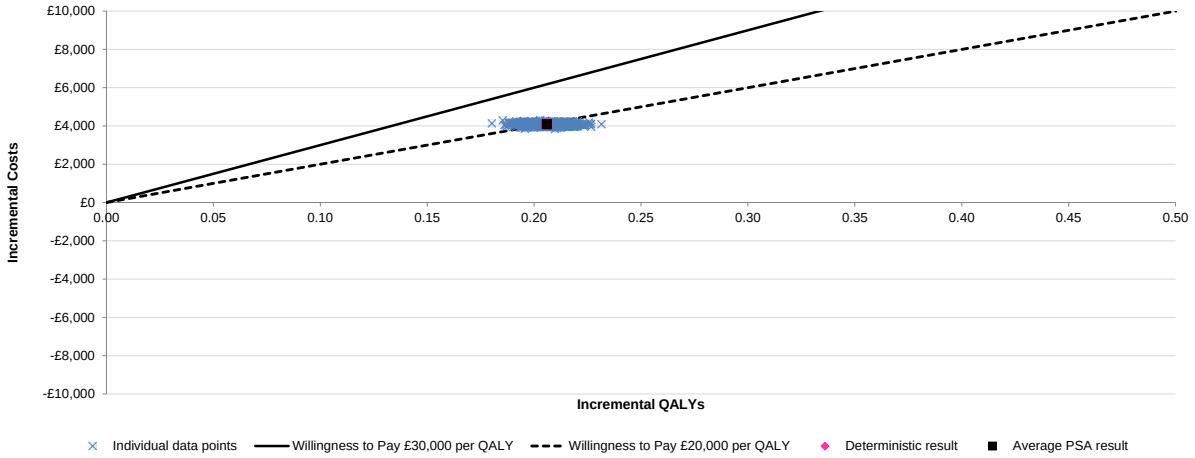
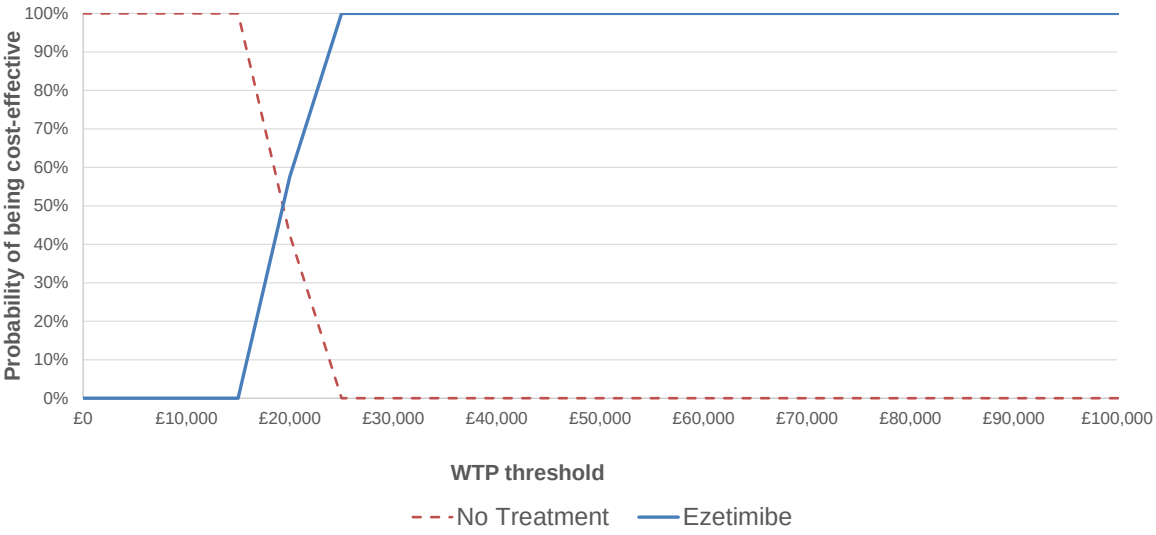


Figure 44 Cost-effectiveness acceptability curves for patients with 20% CV risk (monotherapy)



Primary Prevention with type 2 diabetes, add-on to statin

Table 82 below summarises the cost-effectiveness results for patients who are not eligible for statin treatment based on a 10-year CV level of 20%, and further analyses are presented to evaluated the impact of alternative 10-year risk levels of 30% and 10%. In this population, ezetimibe consistently incurs higher incremental costs and QALYs compared to no treatment deriving ICERs of £30,503 at 20% 10-year risk level. At alternative risk levels of 10% and 30%, the ICERs are £47,929 and £22,335, respectively.

Table 82 Sub-group results for primary prevention with diabetes – add-on to statin

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
20% CV Risk							
Atorvastatin 20mg	£8,512	18.96	9.77	-	-	-	-
Ezetimibe 10mg + Atorvastatin 20mg	£12,496	19.30	9.91	£4,345	0.334	0.142	£30,503
10% CV Risk							
Atorvastatin 20mg	£5,785	19.59	10.15	-	-	-	-
Ezetimibe 10mg + Atorvastatin 20mg	£10,459	19.84	10.25	£4,674	0.253	0.098	£47,929
30% CV Risk							
Atorvastatin 20mg	£10,474	18.35	9.39	-	-	-	-
Ezetimibe 10mg + Atorvastatin 20mg	£14,531	18.75	9.57	£4,057	0.403	0.182	£22,335

The probabilistic sensitivity analyses results presented in the tables below confirm the robustness of the results for the primary prevention with diabetes population. Additionally, the CEACs highlight that at a WTP threshold of £20,000 and £30,000, ezetimibe as add-on to statin has approximately 1% and 46% probability of being cost effective in the population for primary prevention with diabetes, respectively.

Figure 45 Scatterplot of PSA results for patients with 20% CV risk (add-on to statin)

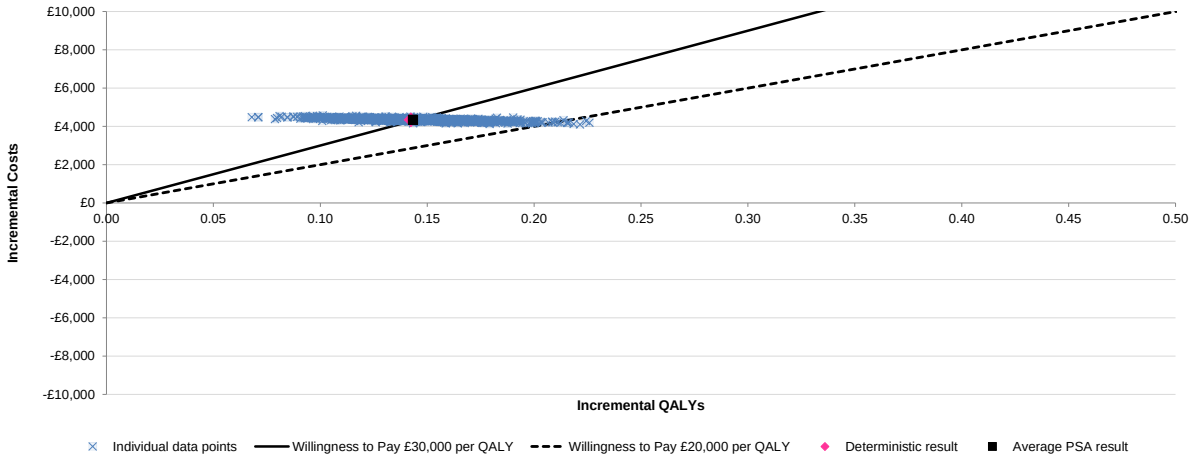
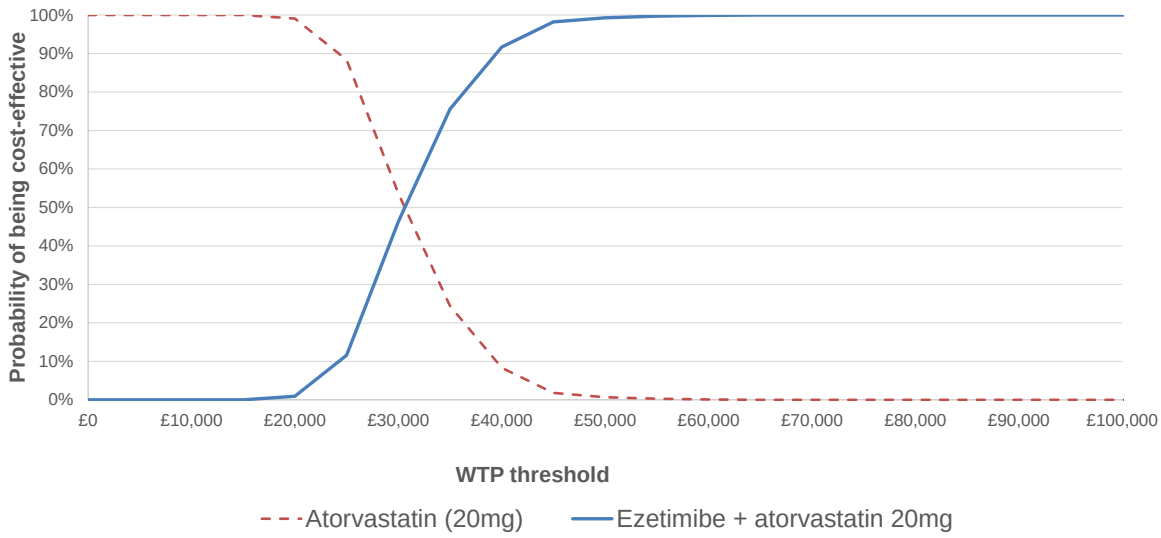


Figure 46 Cost-effectiveness acceptability curves for patients with 20% CV risk (add-on to statin)



People with CKD

Table 83 below summarises the cost-effectiveness results for the secondary prevention of CVD for people with CKD, who are limited to atorvastatin 20 mg. In this population, ezetimibe consistently incurs higher incremental costs and QALYs compared to atorvastatin 20 mg alone, deriving an ICER of £30,939.

Table 83 Sub-group results for people with CKD, secondary prevention – add-on to statin

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
Atorvastatin 20mg	£31,694	15.30	6.24	-	-	-	-
Ezetimibe 10mg + Atorvastatin 20mg	£35,807	15.73	6.37	£4,112	0.422	0.133	£30,939

The probabilistic sensitivity analyses results presented in the tables below confirm the robustness of the results for the secondary prevention of CVD in people with CKD. Additionally, the CEACs highlight that at a WTP threshold of £20,000 and £30,000, ezetimibe as add-on to statin has approximately 0% and 40% probability of being cost effective in this population, respectively.

Figure 47 Scatterplot of PSA results for people with CKD (secondary prevention, add-on to statin)

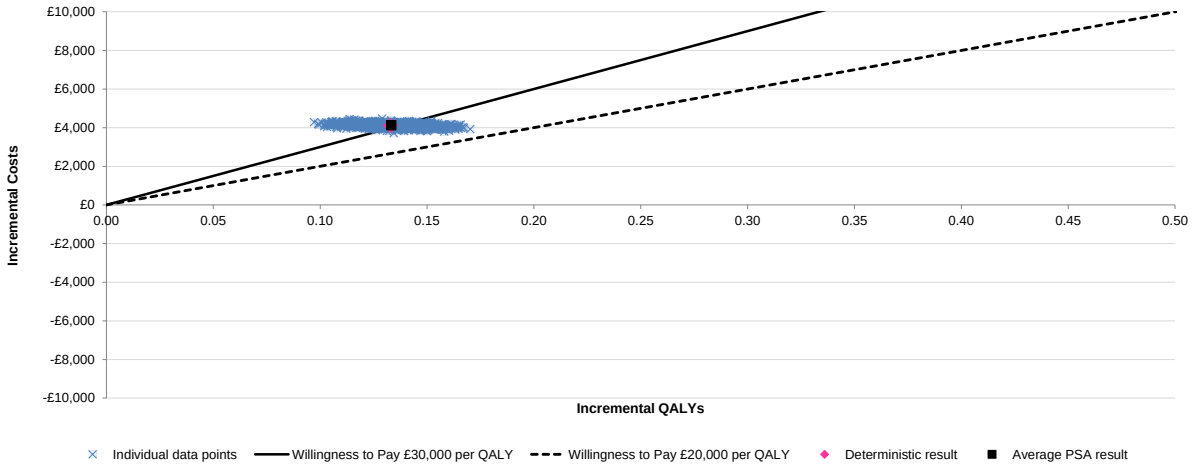
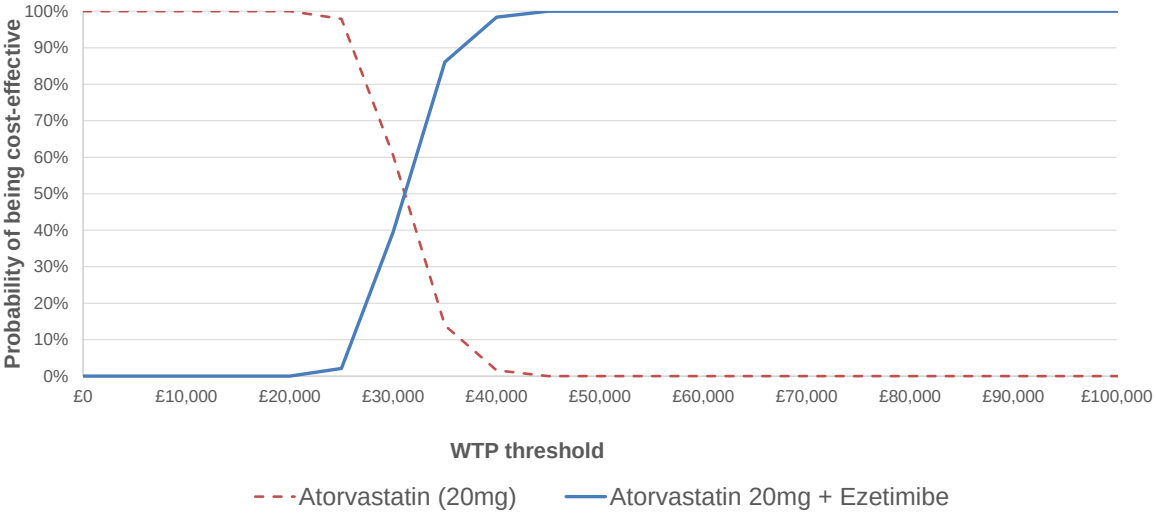


Figure 48 Cost-effectiveness acceptability curves for people with CKD (secondary prevention, add-on to statin)



5.9.6 Identification of any obvious subgroups that were not considered

No further relevant sub-groups have been identified.

5.10 Validation

Validation of de novo cost-effectiveness analysis

The model was quality-assured by the internal processes of the external economists who produced the economic model. In these processes, an economist not involved in the model adaptation reviewed the model for coding errors, inconsistencies and the plausibility of inputs. The model was also put through an internal and external checklist of known modelling errors, and the assumptions were questioned.[163]

The cost-utility analysis approach adopted for this submission is consistent with the previous de novo economic modelling analysis used by Ward *et al* and Ara *et al.* for TA94 and TA132, respectively.[12] [86]

Efforts were made to validate the model using data from the IMPROVE-IT trial. As concerns the results of the cost-effectiveness model compared to the results observed in the IMPROVE it trial, there is a reasonable level of fit. In order to validate the model in the secondary preventative population the model time horizon was set to five years as the mean follow up for the IMPROVE-IT trial was 64.7 months.[11] The average number of per patient events was calculated in both the cost-effectiveness model and for the IMPROVE-IT trial. LDL-C reductions for both simvastatin 40mg monotherapy and for ezetimibe + simvastatin 40mg were inputted into the cost-effectiveness model in order to predict the number of events which would be expected to occur.

Table 84 Comparison of events in IMPROVE-IT and the cost-effectiveness model

Events	Cost-effectiveness model (6 year time horizon)		IMPROVE IT Study (mean number of events per patient)	
	ezetimibe + simvastatin 40mg	simvastatin 40mg monotherapy	ezetimibe + simvastatin 40mg	simvastatin 40mg monotherapy
MI	0.098	0.113	0.104	0.119
Stroke	0.012	0.015	0.027	0.034
CV death	0.071	0.072	0.059	0.059
Non CV death	0.046	0.046	0.056	0.055

While the cost-effectiveness model fails to precisely predict the number of events per patient year observed in the IMPROVE-IT study there appears to be no directional bias and results are similar in scale. The cost-effectiveness model slightly under predicts the incidence of events such as MI, stroke and non CV death and over predicts the number deaths caused by CV events on both arms.

5.11 Interpretation and conclusions of economic evidence

The cost-effectiveness of ezetimibe as a monotherapy or co-administered with a statin has been demonstrated previously in the original NICE MTA in 2007 and previous economic evaluations (see section 5.1).[7] The updated cost-effectiveness analyses confirm the original findings that ezetimibe is cost-effective in high-risk groups where dose titration of the statin is inappropriate and/or limited by intolerance (such as people with CKD), or in monotherapy for those that are intolerant or contraindicated to statins.

Whilst the IMPROVE-IT and SHARP trials provide evidence demonstrating the clinical benefit of ezetimibe, these studies were conducted in sub-populations of the wider ezetimibe license. Extrapolation of the CV event reduction from these trials to the wider ezetimibe co-administered with a statin population is challenging as baseline characteristics, CV risk and the patient pathway would be significantly different to the other populations, e.g. primary prevention and treatment of high risk primary hypercholesterolaemia patients with diabetes, as well as monotherapy. As the clinical evidence has demonstrated that the benefit associated with ezetimibe is consistent with the CTTC meta-analysis, the association between absolute LDL-c reduction and CV risk reductions established by CTTC has been used in the model, employing the percentage LDL-c reductions from the meta-analyses performed. The recent CTTC analysis from 2010 that included 26 RCTs showed that a reduction in LDL-c of 1.0 mmol/L reduced the risk of major vascular events by up to 22%.

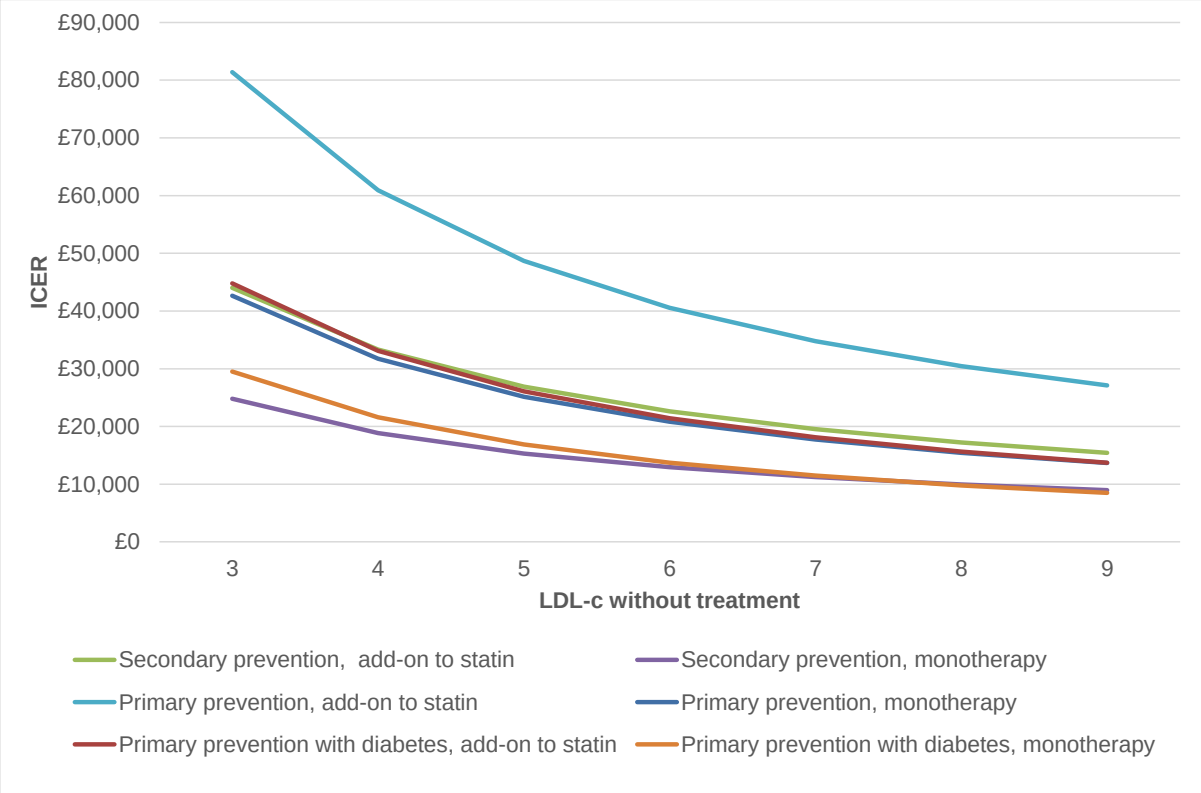
Table 45 to Table 48 above present the results for the four populations in the base case. In the base case analysis for the primary prevention population at a 10-year CV risk of 20%, the ICER is £29,286 for monotherapy and £56,394 for add-on to statin. In the secondary prevention population, the ICER is £17,553 for monotherapy and £30,940 for ezetimibe co-administered with statin treatment. Overall, in a cohort of 1000 patients, treatment with ezetimibe can result in avoiding from 22 CV events (primary prevention – co-administered with statin) to 96.5 CV events when it is used as monotherapy. treatment. For the add-on to statin analysis where a lower dose of atorvastatin is applied (i.e atorvastatin 20 mg) the results are expected to be an underestimate. This is because the statin relative risk estimates applied reflect a pooled analysis of all high intensity doses of atorvastatin (20 – 80 mg).

There are three relevant sub-groups due to the differences in the baseline CV risk and the lipid-modification management strategies appropriate for these sub-groups: primary prevention for people with diabetes, people with chronic kidney disease (CKD) and heterozygous familial hypercholesterolaemia (HeFH). In the base case analysis for the primary prevention population with diabetes, at a 10-year CV risk of 20%, the ICER is £19,852 for monotherapy and £30,503 for add-on to statin (Table 4). No specific analyses were possible for people with type 1 diabetes, however, the elevated risk associated with these patients is reflected by the type 2 diabetes analyses. An analysis reflecting a maximum atorvastatin dose of atorvastatin 20mg has been evaluated for the secondary prevention population with CKD, with an estimated ICER of £30,953. This is a conservatative estimate as the baseline risk is expected to be an underestimate for this population because no specific data for this group was identified. Patients with HeFH have extremely high LDL-c levels, and while no specific analyses for this subgroup was possible due to lack of baseline

risk data, increased LDL-c levels to such high levels, has shown that ezetimibe is a cost-effective option in the analyses.

At higher baseline LDL-levels for all poulations examined and higher 10-year risk levels for the primary prevention population, the cost-effectiveness of ezetimibe increases (as shown in Figure 1).

Figure 49 Incremental cost-effectiveness ratios (ICERs), by varying baseline LDL-c levels



Finally, the patent expiry for ezetimibe is anticipated in April 2018 and significant price falls are expected in-line with other lipid-lowering therapies. The ICERs for ezetimibe fall substantially under the £20,000 per QALY threshold when this is applied in year 3 of the analysis.

Overall, the evidence presented in this submission demonstrates that ezetimibe is a clinically and cost-effective option in high-risk groups where dose titration of the statin is inappropriate and/or limited by intolerance (such as people with CKD), or in monotherapy for those that are intolerant or contraindicated to statins.

6 Assessment of factors relevant to the NHS and other parties

6.1 Analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical and cost effectiveness

Not applicable.

6.2 Number of people eligible for treatment in England

It is estimated that there are 4.17 million people with primary hypercholesterolaemia in England, and 1.28 million of these patients have been prescribed a statin. The definition and prevalence of hypercholesterolaemia has changed over time and the criteria used to define cut-off values for TC and LDL-c have evolved with emerging evidence which have demonstrated the benefits of lower levels and reducing CV risk. Using the Quality and Outcomes Framework's (QOF) target of TC ≤ 5.0 mmol/L has been employed to define hypercholesterolaemia (see section 3.1.1).[19] Based on a recent CPRD study, the prevalence of hypercholesterolemia (defined as TC > 5mmol/L) was found to be 7.8% in England.[164] To estimate the population of people with hypercholesterolaemia, this figure has been applied to the latest population estimates in England from the Office of National Statistics, removing those patients with specific types of familial hypercholesterolemia's not relevant to the scope of this appraisal. The types of familial hypercholesterolaemia excluded include familial defective apo-B, homozygous familial hypercholesterolemia, abnormalities of PCKS9, familial combined hyperlipdemia and type III hyperlipoproteinaemia, which have a combined prevalence of 0.81%.[20;165]

Table 85 Key parameters used to estimate number of patients eligible

Parameters	Estimate	Source
Total population – England	53,865,800	ONS Mid-2013 UK population estimates[117]
Prevalence of types of familial hypercholesterolemia not relevant to the scope of the appraisal (excluded)	0.81%	Bhatnagar *et al.*, 2008; Thompson 2006[20;165]
Prevalence primary hypercholesterolemia – England	7.8%	Amber *et al.*, 2014[164]
Proportion of patients with hypercholesterolaemia receiving statins	30.7%	Amber *et al.*, 2014[164]
Proportion not appropriately controlled on statin	17.5%	Quality and Outcomes Framework, England, 2013-14[23]
Proportion where a statin is considered inappropriate or is contraindicated or not tolerated	14.8%	Expert Opinion, 16 UK health care professionals*

*16 UK health care professionals participating in advisory boards conducted by the manufacturer in Q2 2015, completed a short questionnaire

The relevant place in therapy for ezetimibe in clinical practice is either as a monotherapy where a statin is considered inappropriate or is contraindicated or not tolerated, or alternatively, co-administered with a statin in people who condition is not appropriately controlled with a statin alone and have been titrated to the maximum tolerated dose. In clinical practice, statin intolerance is commonly reported by health care professionals. In a survey undertaken with 16 UK clinical experts in Q2 2015 by the manufacturer, they reported that, on average, 14.8% of patients with hypercholesterolemia do not tolerate or are contraindicated to statins. Read codes in GP systems do not fully capture statin intolerance. A retrospective analysis of a sample of GP practice data in IMS Disease Analyzer for the 12 month period between February 2014 and January 2015, which has been projected to UK level, estimated that there are approximately 65,700 patients that are intolerant or contraindicated to statins (IMS Health, Disease Analyzer, Patient numbers, MAT JANUARY 2015). This underestimates the true burden of statin intolerance, and thus the clinical expert sourced data has been utilised in the model.

The percentage of patients not appropriately controlled in statins is based on the latest Quality and Outcomes Framework that included indicators for the percentage of patients with CHD and patients with stroke that had total cholesterol of less than 5 mmol/L in the preceding 12 months. Based on data for 1.8 million patients in the UK, 17.5% were not to target. This has been used as a proxy to estimate this population.

6.3 Assumptions that were made about current treatment options and uptake of technologies

Ezetimibe has an established role in lipid management in the UK when co-administered with a statin and where statin therapy is inappropriate or is contraindicated or not tolerated. As such, the anticipated recommendations from this re-review, will have limited impact on further uptake of the medicines. It has been assumed that the underlying eligible population will grow at 3% per year.

6.4 Assumptions that were made about market share in England

Ezetimibe has an established role in lipid management in the UK when co-administered with a statin and where statin therapy is inappropriate or is contraindicated or not tolerated. The current level of usage based on the latest ezetimibe prescribing cost of ezetimibe in England in 2014 (£53.5 million) has been used to estimate the market share and level of anticipated usage in Year 1. Further data has estimated that in the 12 month period to January 2015, 38% of the prescriptions of ezetimibe were in monotherapy and 62% co-prescribed with a statin. As such, it has been calculated that there is currently a 31.5% and 43.0% market share for ezetimibe of the eligible population in the monotherapy and add-on to statin settings respectively, equating to a total of £53.5 million prescribing cost for ezetimibe in year 1.

6.5 Other significant costs associated with treatment that may be of interest to commissioners

There are no further significant costs expected for ezetimibe. Ezetimibe is an oral tablet, and it is expected that patients will be receiving repeat prescriptions. Furthermore, there are no treatment specific monitoring costs or expected costs for managing adverse events.

6.6 Unit costs assumed and how they were calculated

The annual cost of ezetimibe is £343.20 per patient, based on once-daily dosing and the 28-tablet pack costs of £26.31(MIMS, Mar 2015).[15] In April 2018, ezetimibe patent in the UK will expiry. The estimated cost of the generic has been based on the current price of generic versions of ezetimibe in Canada, where generic have been available since September 2014. In Canada, the genericisation of ezetimibe has resulted in an initial 75% reduction in the price of branded ezetimibe, and this has been applied in the budget impact analysis after year 3, which equates to £85.80.[157]

6.7 Estimates of resource savings

Further to considerations of net ingredient acquisition costs, there is a reduction in the overall budget impact as a consequence of reducing CV events. The cost-effectiveness model was used to estimate the average, annual cost savings associated with CV event reduction per patient over the first five years for patients receiving ezetimibe monotherapy or co-administered with a statin. The estimated, average annual cost reduction in CV events per 1,000 patients is £25,296 and £10,988 for for patients receiving ezetimibe monotherapy or co-administered with a statin.

6.8 Estimated annual budget impact on the NHS in England.

Table 86 below summarises the eligible number of patients for ezetimibe, and the net budget impact relecting net acquisition costs and cost savings related to CV event reduction. In year 1, the net budget impact is estimated to be £51.0 million, dropping significant in year 3 due to the patent expiry of exetimibe to £11.3 million.

Table 86 Net annual budget impact from Year 1 to 5

Description	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients with hypercholesterolaemia	4,167,496	4,250,846	4,335,863	4,422,580	4,511,031
Number of patients treated with a statin	1,279,421	1,305,010	1,331,110	1,357,732	1,384,887
Number of eligible patients (monotherapy)	189,114	192,897	196,755	200,690	204,704
Number of eligible patients (add-on to statin)	224,152	228,635	233,208	237,872	242,629
Total number of eligible patients	413,266	421,532	429,962	438,562	447,333
Ezetimibe market share, monotherapy	31.5%	31.5%	31.5%	31.5%	31.5%
Ezetimibe market share, add-on	43.0%	43.0%	43.0%	43.0%	43.0%
Number of patients, ezetimibe (monotherapy)	59,571	60,762	61,978	63,217	64,482
Number of patients, ezetimibe (add-on to statin)	96,385	98,313	100,279	102,285	104,331
Total number of patients, ezetimibe	155,956	159,075	162,257	165,502	168,812
Current and predicted net acquisition costs, ezetimibe	£53,524,936	£54,595,435	£13,921,836	£14,200,273	£14,484,278
Estimated cost savings, CV event reduction	£2,565,958	£2,617,277	£2,669,623	£2,723,015	£2,777,476
Net budget impact	£50,958,978	£51,978,158	£11,252,213	£11,477,257	£11,706,803

6.9 Identify any other opportunities for resource savings or redirection of resources that it has not been possible to quantify.

No other quantifiable resource savings or redirection of resources is expected.

6.10 Highlight the main limitations within the budget impact analysis.

Given that ezetimibe has an established position in clinical practice in the UK, the anticipated level of usage estimated are robust. The limitations that should be considered include:

- the estimated population of patients that are contraindicated and intolerant to statins is based on clinical experts. Intolerance is poorly recorded in GP databases, but there is a wide variation in the reports of the percentage of patients that are contraindicated or intolerant to statins, varying from 2% to 25%.[5]

- the impact on uptake of ezetimibe has been assumed to be stable post patent expiry.

- anticipated price of ezetimibe post-patent expiry in April 2018. The anticipated price adopted in the model has been based on the current generic ezetimibe price in Canada, where generic versions of ezetimibe have been available since September 2014. There are some notable differences between the generic market in Canada and the UK, and the previous patent expiry of atorvastatin in May 2012, saw prices of atorvastatin fall rapidly within 3 months to less than 10% of the branded version.

[5] 16 UK health care professionals participating in advisory boards conducted by the manufacturer in Q2 2015, completed a short questionnaire

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Appendices

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Single Technology Appraisal (STA) Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia (review of TA132) [ID627]

Dear [redacted]

The Evidence Review Group, Aberdeen HTA Group, and the technical team at NICE have now had an opportunity to take a look at the submission by Merck Sharp and Dohme UK Ltd received on 22 June. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm, Wednesday 29 July**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

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If you have any further queries on the technical issues raised in this letter then please contact Linda Landells, Technical Lead (linda.landells@nice.org.uk). Any procedural questions should be addressed to Lori Farrar, Project Manager (lori.farrar@nice.org.uk) in the first instance.

Yours sincerely

Dr Frances Sutcliffe
Associate Director – Appraisals
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Encl. checklist for in confidence information

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Section A: Clarification on effectiveness data

A1 **PRIORITY**: **Page 66, List of relevant RCTs:** The included RCTs vary in terms of patient populations and some of them do not seem to fit the clinical definition of primary hypercholesterolaemia for this appraisal. In particular, there is considerable variation with regard to the LDL-c cut offs used and some trials report very low LDL-c levels at baseline. Please clarify the definition of **primary hypercholesterolaemia** considered for the purpose of the review of clinical effectiveness evidence (including limits of cholesterol level) and whether this includes other terms such as dyslipidemia.
In particular, would you please clarify why the following clinical trials were included?

Included trials	Population	Clarification
IMPROVE-IT 2015	Acute coronary syndrome	
Farnier 2005	Mixed hyperlipidemia	
Zinellu 2012	CKD stage 3	
Stojakovic 2010	Coronary heart disease	

A2 Please clarify whether all the clinical trials in the systematic review of clinical effectiveness evidence included an eligible population as described in the NICE final scope (that is, people whose condition is not appropriately controlled with a statin alone or in whom a statin is considered inappropriate or is not tolerated). The inclusion of patient populations considered for primary prevention (10–30% 10-year risk of developing cardiovascular disease) and secondary prevention (established cardiovascular disease) (page 12, Table 1 Decision problem) does not appear to be in line with the NICE final scope, please clarify.

A3 Apolipoprotein B and Lipoprotein (a) are listed among the outcomes considered by the company. Is Lipoprotein (a) correct or should this read Apolipoprotein A? Please clarify.

A4 The submission implies (Table 6, page 27) that ezetimibe co-administered with rosuvastatin versus rosuvastatin monotherapy will not be considered. However rosuvastatin is included in Table 14 (page 64) and in the search strategy. Would you please clarify whether rosuvastatin was included or

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excluded from the review of clinical effectiveness evidence? If rosuvastatin was not considered suitable for inclusion, please clarify why.

A5 Would you please clarify if the reporting of cardiovascular outcomes, survival/mortality, and health-related quality of life (Table 13, page 62) were considered eligibility criteria for study inclusion, as specified in the NICE final scope?

A6 **PRIORITY:** The submission states that studies with 100% Japanese and Indian patients were removed from the analysis because *these populations metabolise a number of drugs differently* (page 73). Among the 27 included trials, two were conducted in India (Shankar 2008, Clement 2014) and two in Japan (Harbara 2014, Kinouchi 2013). Three of these trials were removed from the meta-analyses but one (Clement 2014) was retained (see Figure 6). It is worth noting that among the included RCTs there were also multinational trials that enrolled participants from South/East Asia (Ballantyne 2003 from Singapore; Goldberg 2004; from Malaysia, Singapore, and Taiwan; IMPROVE-IT 2015 from Hong Kong, India, Malaysia, Singapore, South Korea, and Taiwan). Please clarify why only some South Asian/East Asian patients were excluded from some of the meta-analyses.

A7 **PRIORITY - Page 73–74 Outcome and evidence synthesis:** Data could have been double counted in the meta-analyses in two instances. Sager 2003 is a secondary report to Davidson 2002, and Knopp 2001 is an abstract of a fully-reported study (Knopp 2003). Please clarify why each publication has been treated as a separate trial in the meta-analyses.

A8 Please further explain why studies of less than 12 weeks of duration were excluded from the review of clinical effectiveness evidence? Section 4.7 (page 67) suggests that all studies in the review of less than 12 weeks reported a multiplicative analysis of percentage change (Figure A) and that all longer studies used an additive analysis (Figure B). The statement in the first paragraph of page 68 does not appear to be consistent with this. Please clarify also why studies of less than 12 weeks were excluded from the review of ezetimibe monotherapy when an additive analysis of change scores was not possible for these studies.

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A9 The submission states (page 70) that a correlation coefficient of 0.5 was used to estimate the standard error of the mean percentage change. Would you please clarify whether this refers to the method reported in section 16.1.3.2 of the Cochrane Handbook for Systematic Reviews of Intervention (www.handbook.cochrane.org)? Please provide a reference for the use of a coefficient of 0.5 in this context.

A10 Please clarify which dose was selected for inclusion in the primary meta-analyses for trials that included more than one statin arm.

A11 Please clarify which time point was selected for inclusion in the primary meta-analyses for studies that collected data at more than one time point.

A12 Please clarify the formulae used to obtain the data in Appendix 12. The calculations do not seem to match the example provided in Figure B on page 68. How were weights calculated for the weighted average? Please explain whether the language used when referring to this 23.5% result on pages 19, 51, 74, and 78 is correct.

Section B: Clarification on cost-effectiveness data

B1 Please provide further explanation for the approach of applying a set baseline CV risk of 20% for the cohort, rather than using the average characteristics of a UK primary/secondary prevention cohort (on and off statin therapy) to estimate the actual baseline risk of the patient cohort that might be considered for ezetimibe therapy.

B2 **PRIORITY**: Please supply more details about the approach used to inflate baseline risks of CV events annually in the economic model? Given that the base probabilities are based on a linearly transformed 10 year probability of 20%, will the approach of inflating these each year not result in a modelled 10 year risk over 20%? Please clarify why this approach was taken rather than just updating the CV risk every 10 years in the model.

B3 **PRIORITY**: Worksheet “Background mortality” column M: the age 60 row seems to be referencing the age 40 row in the worksheet “Age adjusted PP risks”. Please clarify.

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B4 **PRIORITY**: It seems the annual age risk increase is being proportionally inflated twice in the model to account for the assumed increase in non CHD CV events (e.g. see sheet "Background mortality" column M, and "Age adjusted PP risks", from column J, row 81 down). Please clarify.

B5 **PRIORITY:** The approach to estimating risk reductions for statin versus no treatment applies direct relative risks for CV events, whilst the ezetimibe benefit is modelled indirectly through its effect on LDL-C via the published CTT meta-analysis. However, the baseline LDL-C level does not appear to be updated to account for partial response to statin therapy, and remains at the pre-treatment level when estimating the absolute additional LDL-C reduction associated with ezetimibe therapy. This may overestimate the CV relative risk reduction for ezetimibe as an add-on to statin therapy. Similarly, applying direct relative risks to model the effect of statin therapy on baseline pre-treatment CV risks may underestimate the baseline CV risk in those who have inadequate control on a statin; i.e. the population being modelled in the ezetimibe add-on scenario. Please provide an additional analysis of longer-term outcomes on statin therapy (with inadequate control) when the LDL-C level is below the pre-treatment value but above the target level, which would lead to consideration of ezetimibe as an add-on.

B7 Please provide an analysis in which directly estimated relative risks for CV events (with ezetimibe) are applied in the model for the primary prevention population.

B8 The approach being used also results in a slightly lower relative risk of death from other causes for ezetimibe compared with statin alone (0.94 vs 0.96). Is there enough evidence to justify this additional modelled benefit? Please provide further details to support your approach.

B9 It is noted that the stroke and post stroke utility values applied in the model does not necessarily reflect a UK population, and that more recent UK-based EQ-5D estimates (*Luengo-Fernadez et al., 2013*) appear to have been rejected in favour of this value. Would you please clarify this further?

B10 In the model, the proportional distribution across different types of CV event appear to have been applied deterministically as point estimates. Please clarify the associated uncertainty by applying a Dirichlet distribution in the PSA.

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B11 A structural anomaly in the model allows patients to transit from the post stroke state (which has high costs and low utility) to the MI or unstable angina (UA) state and then on to the respective post event states for MI and UA. Whilst these transitions are realistic, the post UA/MI event pay-offs do not account for the prior history of stroke, and so effectively it seems that having an MI or unstable angina can improve health status (from 0.628 to 0.8) and reduce ongoing follow-up costs by 90% for a small proportion of the population that make this transition. By setting the transition from post-stoke to the MI and UA states to zero, please clarify the uncertainty arising from this structural assumption, and the effect on the ICERs.

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Section A: Clarification on effectiveness data

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In particular, would you please clarify why the following clinical trials were included?

Primary hypercholesterolaemia is defined as abnormalities of lipoprotein transport associated with high levels of cholesterol and is usually related to the interaction between genetic predisposition and environmental factors. Whilst this can include dyslipidaemia, in general the evidence base suggests that lowering LDL-c prevents CVD, so clinicians concentrate on CV risk management, of which LDL-c is one of the major modifiable risk factors for the prevention of CVD (section 3.1 of the submission). A patient's LDL-c value can vary, the critical aspect is to prevent progression to CHD and prevent CV events. This practice is evident with the publication of the new NICE guideline CG181 in July 2014. Patients are identified using risk calculators and in clinical practice clinicians treat CV risk and statins will be initiated for people at risk and not at a fixed cholesterol level. For example someone could have an LDL-c of 2.0 mmol/L, but still be very high-risk of an (further) event and warrant having their cholesterol lowered and therefore by definition be hypercholesterolaemic. The IMPROVE-IT study has supported this shift in practice, demonstrating that lower LDL-c really is better in terms of prevention of CV events. The most important point is that controlling LDL-c controls an individual's CV risk and high-risk patients can be treated to lower levels of LDL-c to reduce CV events as discussed in section 3.2.1 to 3.2.6 of the submission. As for specific targets for LDL-c, high-risk patients can be treated to LDL-c <2.0 mmol/L (NICE guidance CG67 and CG87) or <1.8 mmol/L (JBS III and ESC/EAS guidance), therefore a patient with baseline LDL-c above these values could be eligible for LMT.

Included trials	Population	Clarification
IMPROVE-IT 2015	Acute coronary syndrome	This is a high-risk patient group as they were hospitalised for a CV event. The focus is on the prevention of further events. The mean LDL-c at time of qualifying event was 2.4

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		mmol/L. These patients could to treated to a lower LDL-c level, i.e. <1.8 or 2.0 mmol/L.
Farnier 2005	Mixed hyperlipidaemia	Mixed hyperlipidaemia (elevated LDL-c and TG) with/without diabetes and CV risk <20% with a mean baseline LDL-c of 4.2 and 4.1 mmol/L in the placebo and ezetimibe arms respectively.
Zinellu 2012	CKD stage 3	High risk patient group with a mean baseline LDL-c of 4.14 mmol/L
Stojakovic 2010	Coronary heart disease	Patients with diabetes and/or CHD which are considered high risk and could be treated to <2.0 or <1.8 mmol/L. Mean LDL-c at baseline of 2.64 mmol/L in the fluvastatin arm and 2.90 mmol/L in the fluvastatin+ezetimibe arm.

A2 Please clarify whether all the clinical trials in the systematic review of clinical effectiveness evidence included an eligible population as described in the NICE final scope (that is, people whose condition is not appropriately controlled with a statin alone or in whom a statin is considered inappropriate or is not tolerated). The inclusion of patient populations considered for primary prevention (10–30% 10-year risk of developing cardiovascular disease) and secondary prevention (established cardiovascular disease) (page 12, Table 1 Decision problem) does not appear to be in line with the NICE final scope, please clarify.

The wording 'people whose condition is not appropriately controlled with a statin alone or in whom a statin is considered inappropriate or is not tolerated' comes from the licensed indication for ezetimibe, and is also reflected in the original recommendation from TA132. The clinical data that was used to support the regulatory filing was from trials that did not enrol people whose condition was not appropriately controlled with a statin alone or in whom a statin was considered inappropriate or was not tolerated. Additionally, people enrolled within these trials might have been able to tolerate the next dose of statin. The definition of 'statin is considered inappropriate or is not tolerated' varies widely and to our knowledge no

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trials of non-statin LMT had the inclusion criteria of patients in whom a statin is considered inappropriate or is not tolerated.
During discussions with NICE and at the decision problem meeting, one of the critical reasons discussed for undertaking this review was to reflect updated NICE guidance in CG181, which assessed primary prevention (>10% 10-year risk of developing CVD) and secondary prevention (established CVD). Whilst the license for ezetimibe does not consider risk of developing CVD, or primary/ secondary prevention, MSD, in consultation with NICE are attempting to reflect the evolution of clinical practice and guidance in this review of TA132.

A3 Apolipoprotein B and Lipoprotein (a) are listed among the outcomes considered by the company. Is Lipoprotein (a) correct or should this read Apolipoprotein A? Please clarify.

MSD extracted data from the relevant RCTs to reflect the final scope from NICE, which listed Lipoprotein (a) as an outcome. Lipoprotein (a) is an atherogenic particle; it is made up of an LDL connected to an ApoA protein. LDL is a particle which is marked by ApoB, a protein that surrounds the lipid bilayer, which contains cholesterol + triglycerides. ApoA is an apolipoprotein that surrounds HDL molecules. Lipoprotein (a) has received more attention in recent years because it varies in the population and is thought to be atherogenic.

A4 The submission implies (Table 6, page 27) that ezetimibe co-administered with rosuvastatin versus rosuvastatin monotherapy will not be considered. However rosuvastatin is included in Table 14 (page 64) and in the search strategy. Would you please clarify whether rosuvastatin was included or excluded from the review of clinical effectiveness evidence? If rosuvastatin was not considered suitable for inclusion, please clarify why.

Whilst NICE does not recommend rosuvastatin in CG181, in clinical practice ezetimibe is and can be used in combination with rosuvastatin. In order to include the widest available evidence for ezetimibe, rosuvastatin was included in the systematic review to estimate the treatment effect for ezetimibe. An assumption used for the clinical approach is that the % reduction in LDL-c for ezetimibe is independent of the co-administered statin. No RCTs were identified for ezetimibe add-on to rosuvastatin versus same dose of rosuvastatin. For the purposes of the submission the cost effectiveness section focuses on ezetimibe co-administered with first line therapy atorvastatin.

A5 Would you please clarify if the reporting of cardiovascular outcomes, survival/mortality, and health-related quality of life (Table 13, page 62) were considered eligibility criteria for study inclusion, as specified in the NICE final scope?

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Yes CV outcomes and survival/mortality were considered eligibility criteria for inclusion. There are only three outcomes trials for ezetimibe, and only one (IMPROVE-IT) fits the populations in this review. Health-related quality of life was not considered eligibility criteria for inclusion.

A6 **PRIORITY:** The submission states that studies with 100% Japanese and Indian patients were removed from the analysis because *these populations metabolise a number of drugs differently* (page 73). Among the 27 included trials, two were conducted in India (Shankar 2008, Clement 2014) and two in Japan (Harbara 2014, Kinouchi 2013). Three of these trials were removed from the meta-analyses but one (Clement 2014) was retained (see Figure 6). It is worth noting that among the included RCTs there were also multinational trials that enrolled participants from South/East Asia (Ballantyne 2003 from Singapore; Goldberg 2004; from Malaysia, Singapore, and Taiwan; IMPROVE-IT 2015 from Hong Kong, India, Malaysia, Singapore, South Korea, and Taiwan). Please clarify why only some South Asian/East Asian patients were excluded from some of the meta-analyses.

MSD agree the Clement 2014 study was performed in India. The meta-analysis has been re-run removing Clement 2014 and is presented in the response to A7 (Figure 1). The four trials Shankar 2008, Clement 2014, Habara 2014 and Kinouchi 2013 were performed in 100% Indian or Japanese patients. The other trials discussed in question A6 were multinational trials with predominantly EU and US patients. We believe it is acceptable to include these trials in the meta-analysis as the ethnicity of the majority of patients in these trials reflects UK demographics, whilst also exploring the diversity found in the UK:

Ballantyne 2003:	ethnicity: white 82-88% in the arms of the study
Goldberg 2004:	ethnicity: white 77-83% in the arms of the study
IMPROVE-IT:	ethnicity: white 84% in the arms of the study

A7 **PRIORITY - Page 73–74 Outcome and evidence synthesis:** Data could have been double counted in the meta-analyses in two instances. Sager 2003 is a secondary report to Davidson 2002, and Knopp 2001 is an abstract of a fully-reported study (Knopp 2003). Please clarify why each publication has been treated as a separate trial in the meta-analyses.

MSD agree that some of the data has been double counted. The meta-analyses have been re-run to reflect:

- Removal of Sager 2003, Knopp 2001 and Clement 2014 (question A6) from the ezetimibe versus placebo meta-analyses

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- Removal of Sager 2003 from the ezetimibe + statin versus statin meta-analyses.

The two key LDL-c values used in the cost effectiveness analysis presented in the submission are shown in Table 1, demonstrating that removal of these trials resulted in little change in the mean difference values.

Table 1. Differences in LDL-c MD values in the submission and after re-run of the meta-analyses.

Figure in original submission	Meta-analysis	MD value in submission [95% CI]	MD value after re-run [95% CI]
Figure 6	Ezetimibe vs. placebo – LDL-c	-20.44 [-21.60, -19.27]	-20.59 [-22.13, -19.05]
Figure 8	Ezetimibe + statin vs. matching statin dose – LDL-c	-15.52 [-16.92, -14.11]	-15.60 [-17.06, -14.13]

The re-run of the appropriate analyses from section 4.9 of the submission are presented here:

Ezetimibe vs placebo – LDL-c

Thirteen studies (N=3,137) assessing combinations of ezetimibe monotherapy versus placebo reported %CFB in LDL-c and TC, see Appendix 11 below for this analysis. One study that included 100% Indian patients was removed from the analysis for the purposes of this appraisal. These populations are known to metabolise a number of drugs differently.

Therefore, twelve studies (N=3,094) assessing ezetimibe monotherapy versus placebo reported %CFB in LDL-c and TC. Figure 1 summarises these studies with respect to LDL-c. The random-effects meta-analysis demonstrated that ezetimibe monotherapy resulted in a significantly greater reduction of LDL-c compared to placebo (MD -20.6%, 95% CI -22.1 to -19.1). The relative treatment effect in the individual studies ranged from -30.0% to -12.7%. There was a large degree of heterogeneity present (I^2=99.68 for all studies combined).

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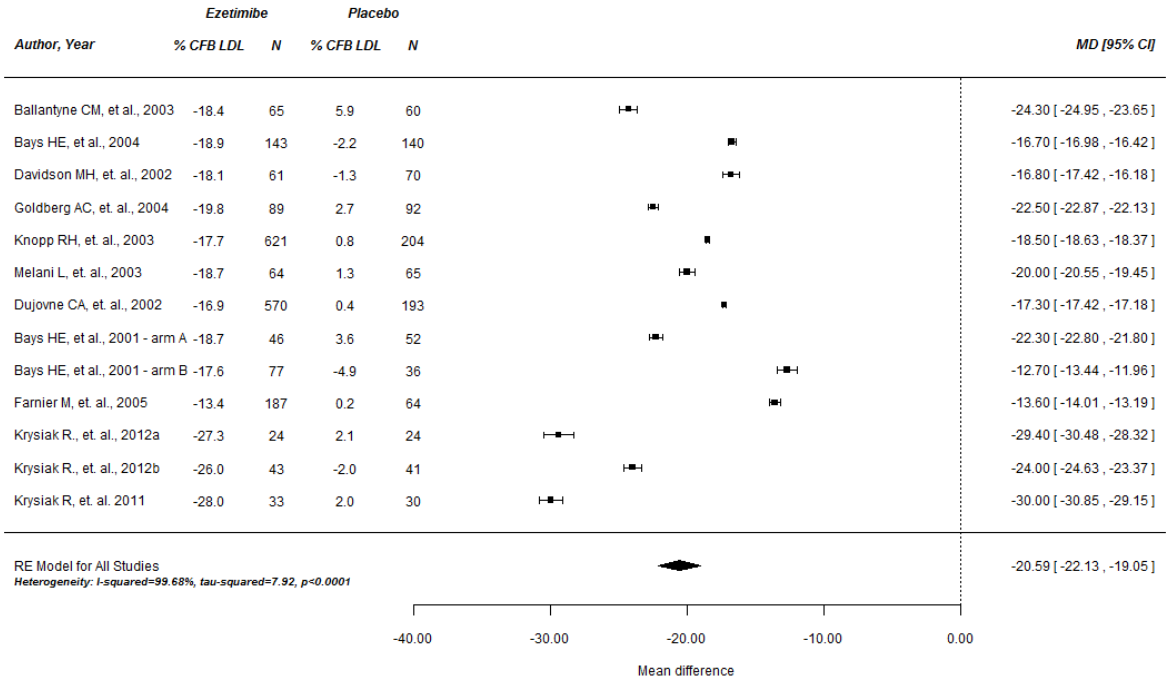
Figure 1 Percent change in LDL-c (mmol/L) among studies comparing ezetimibe monotherapy to placebo



Ezetimibe vs placebo - TC

Figure 2 summarises % CFB in TC among the studies (N=2,887) assessing ezetimibe monotherapy vs placebo. The mean difference between ezetimibe monotherapy and placebo was -16.1% (95% CI -17.0 to -15.1); individual study treatment effect ranged from -25.0% to -11.9%. The I^2 value was 99.48, which indicates a very large degree of heterogeneity.

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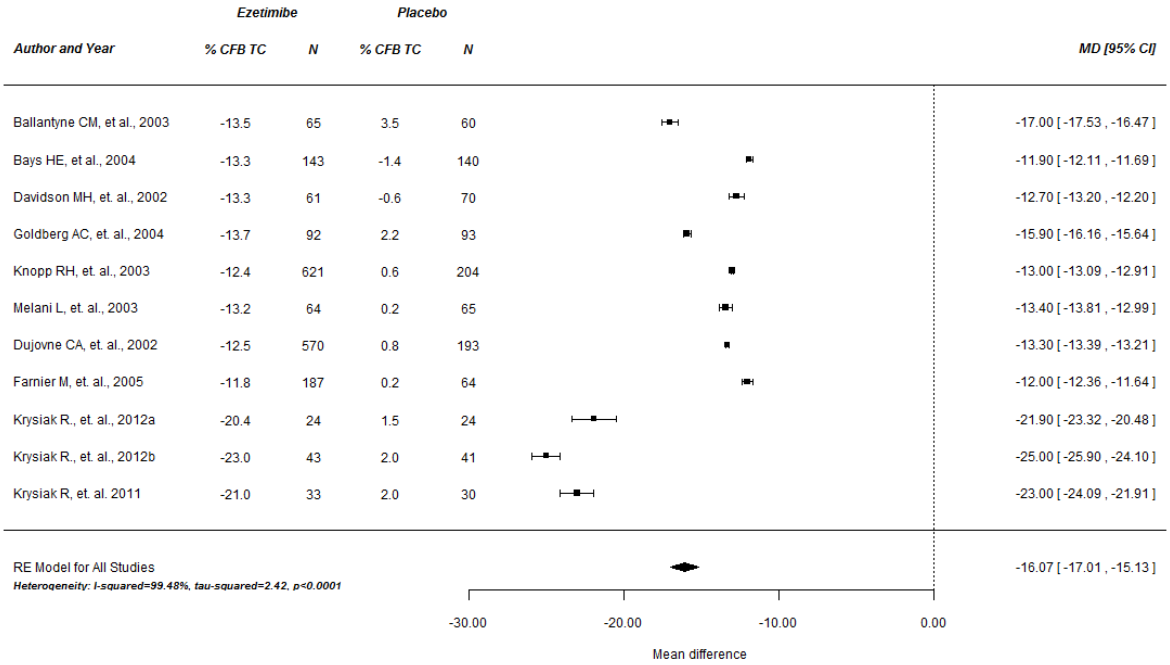
Figure 2 Percent mean difference in TC among studies comparing ezetimibe monotherapy to placebo



Ezetimibe vs matching statin dose – LDL-c

Twenty studies (N=19,313) assessing combinations of ezetimibe and statins versus matching statin dose reported %CFB in LDL-c and TC, see Appendix 11 below for this analysis. Three studies that included 100% Japanese or Indian patients were removed from the analysis for the purposes of this appraisal. These populations are known to metabolise a number of drugs differently.

Therefore, seventeen studies (N=18,966) assessing combinations of ezetimibe and statins versus matching statin dose reported %CFB in LDL-c and TC.

Figure 3 presents a summary of these studies with respect to LDL-c, overall and by statin. The MD of ezetimibe plus fluvastatin versus fluvastatin monotherapy was -15.7% (95% CI -18.9 to -12.4). The MD of ezetimibe plus simvastatin to simvastatin monotherapy was -16.1% (95% CI -17.8 to -14.4). Combinations of ezetimibe and atorvastatin and pravastatin were only reported by one study each; for these studies no meta-analysis was performed. For all statins combined, the MD of ezetimibe in combination versus matching statin dose was -15.6% (95% CI -17.1 to -14.1).

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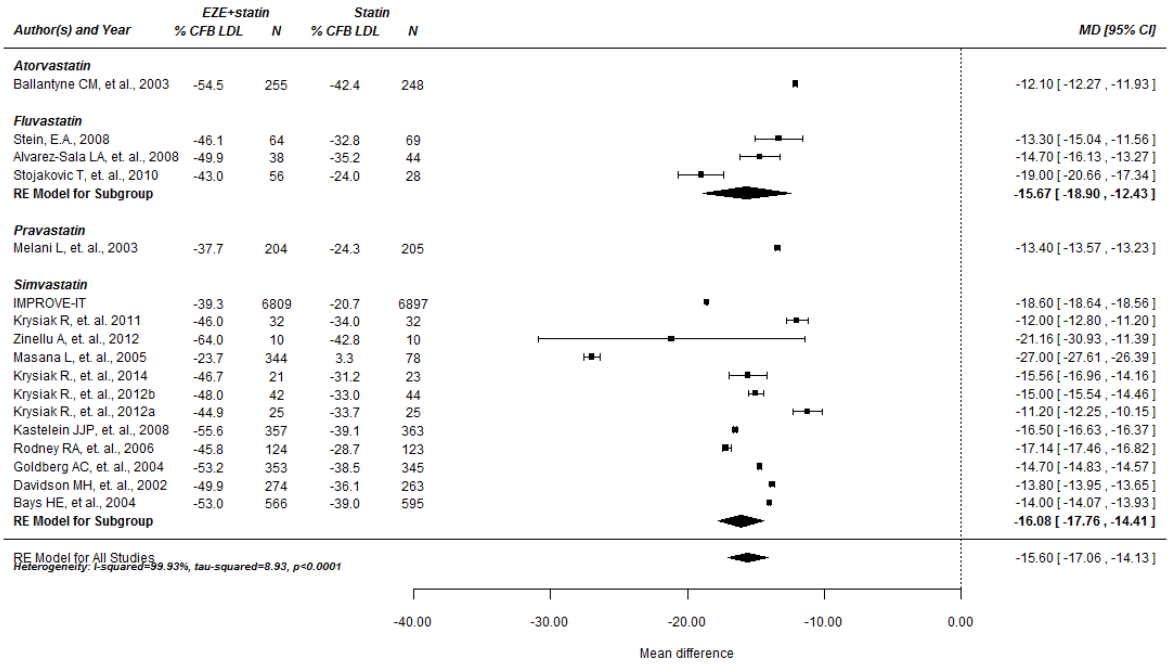
Overall, there was a large degree of heterogeneity present (I^2=99.93 for all studies combined).

Figure 3 Percent mean difference in LDL-c (mmol/L) among studies comparing ezetimibe + statin to matching statin dose



As described at the beginning of section 4, the trials included in this review required washout of LMT prior to randomisation, and so the LDL-c change is reported as mean % change from baseline using the additive approach. The more meaningful representation of the clinical efficacy of ezetimibe is to present LDL-c as a change from baseline on stable statin, the multiplicative approach. This has been calculated from the studies included in the meta-analysis, Appendix 11. By using a weighted average ezetimibe provides a further LDL-c lowering of 23.5%.

Ezetimibe vs matching statin dose - TC

Figure 4 summarises % CFB in TC among the studies assessing ezetimibe in combination with statins vs matching statin monotherapy (for the full meta-analysis including 100% Japanese and Indian studies please refer to Appendix 11 below). The MD in TC between ezetimibe in combination with a statin and matching statin

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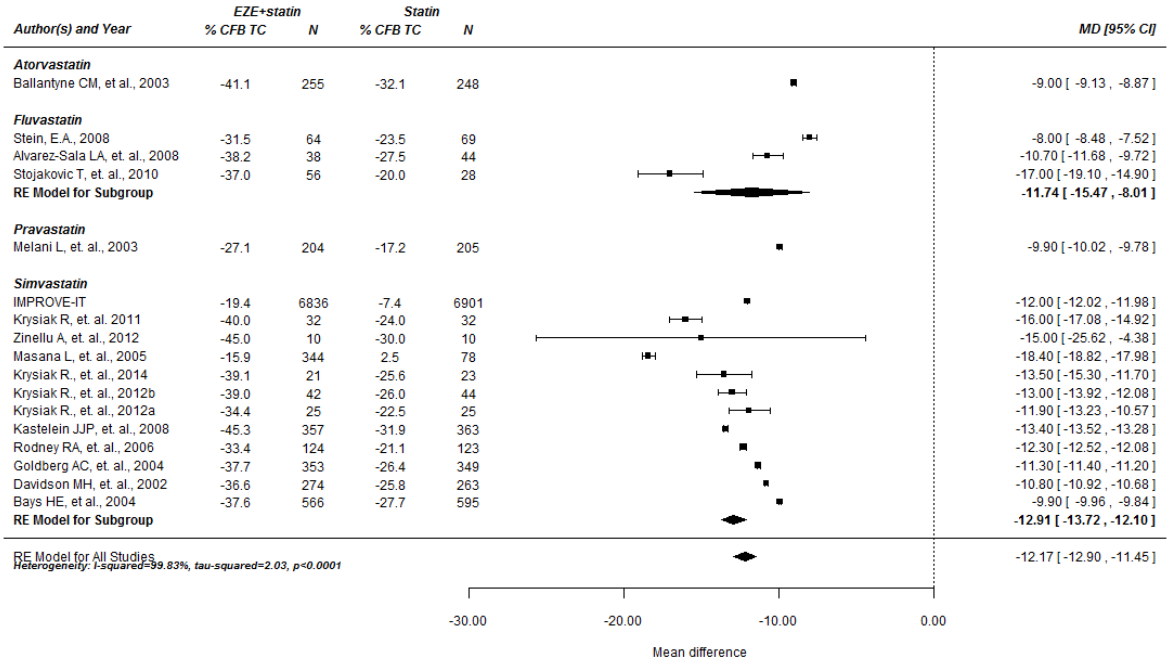
dose was -12.2% (95% CI -12.9 to -11.5); treatment effect in the individual studies ranged from -18.4% to -8.0%. The I^2 value was 99.83, which indicates a large degree of heterogeneity between the trials.

Figure 4 Percent mean difference in TC among studies comparing ezetimibe + statin to matching statin dose



Appendix 11

Ezetimibe vs placebo – LDL-c

Thirteen studies (N=3,137) studies assessing ezetimibe monotherapy vs placebo reported %CFB in LDL-C and TC. The figure below summarizes these studies with respect to LDL-C. The random-effects meta-analysis showed that ezetimibe monotherapy resulted in a significantly greater reduction of LDL compared to placebo (MD -20.8%, 95% CI -22.3 to -19.3). The relative treatment effect in the individual studies ranged from -30.0% to -12.7%. There was a large degree of heterogeneity present (I^2=99.66 for all studies combined).

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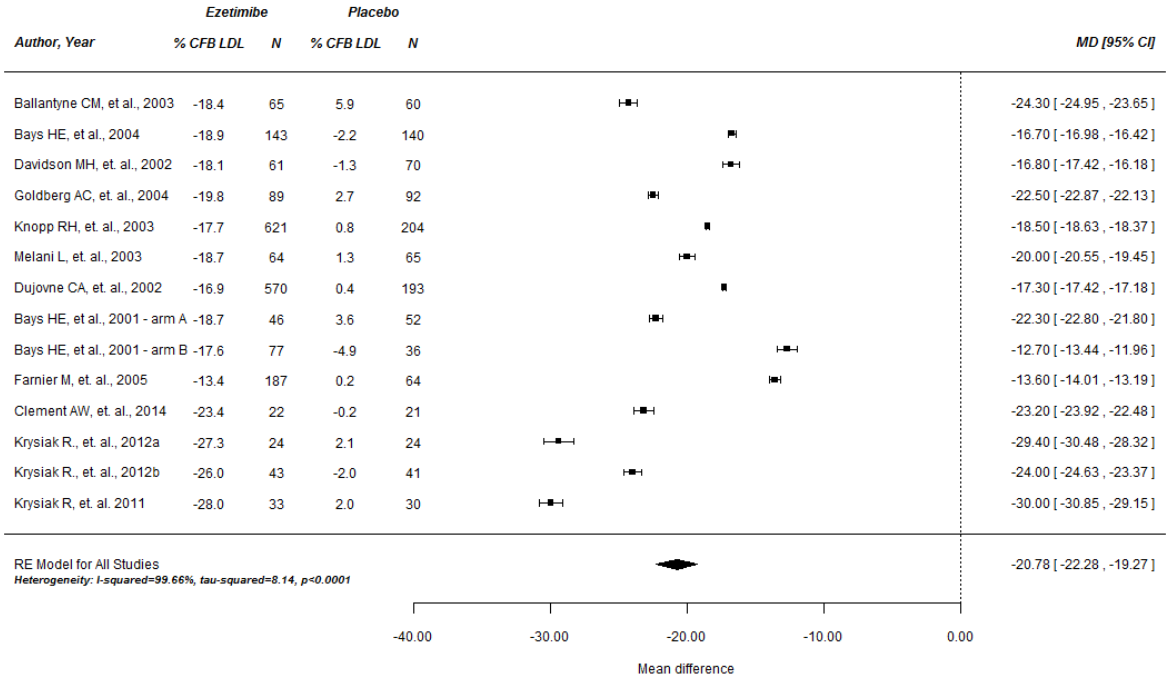
Percent mean difference in LDL-c (mmol/L) among studies comparing ezetimibe to placebo



Ezetimibe vs placebo – TC

The figure below summarizes % CFB in TC among the studies (N=2,930) assessing ezetimibe monotherapy vs placebo. The mean difference between ezetimibe monotherapy and placebo was -16.5% (95% CI -17.5 to -15.6); individual study treatment effect ranged from -25.0% to -11.9%. The I^2 value was 99.54, which indicates a very large degree of heterogeneity.

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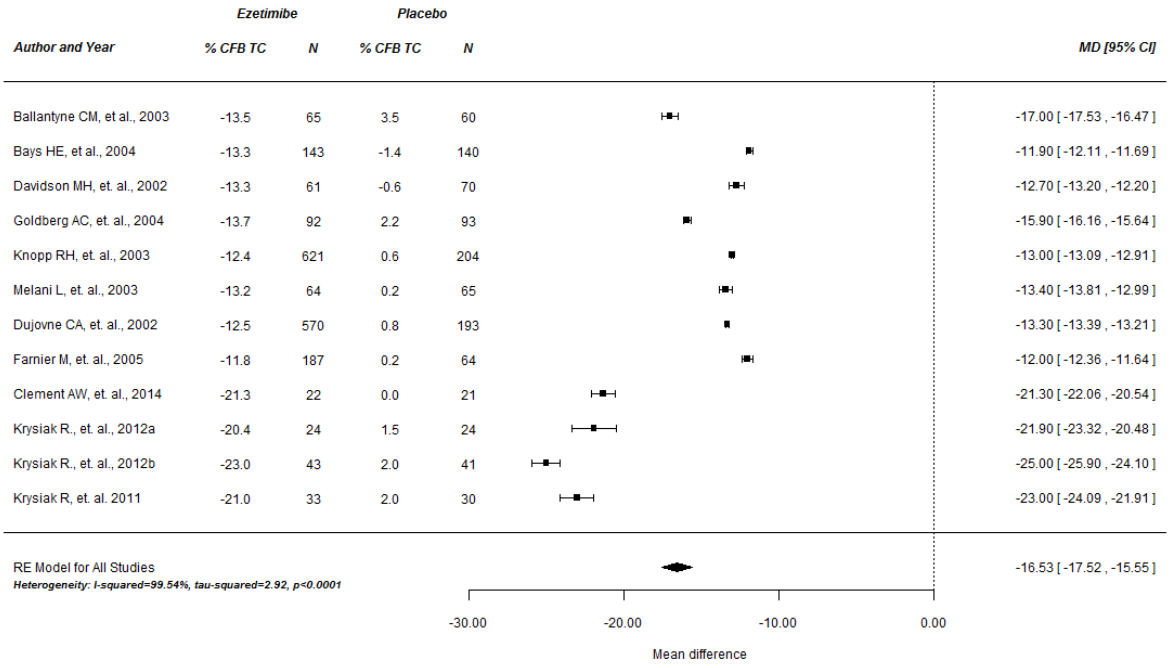
Percent change in TC among studies comparing ezetimibe to placebo



Ezetimibe vs matching statin dose – LDL-c

Twenty studies (N=19,313) assessing combinations of ezetimibe and statins versus matching statin dose reported %CFB in LDL-c and TC. The figure below presents a summary of these studies with respect to LDL-c, overall and by statin. Overall, the combination of ezetimibe and statins produced a larger %CFB in LDL-c than the matching dose of statin monotherapy MD -15.1% (95% CI -16.4 to -13.7). Among the subgroup of studies assessing simvastatin, ezetimibe in combination produced a MD of -15.4% (95% CI -17.0 to -13.8) compared to simvastatin monotherapy. Ezetimibe in combination with fluvastatin produced a MD of -15.3% (95% CI -19.1 to -11.4). Combinations of ezetimibe and atorvastatin and pravastatin were only reported by one study each; for these studies no meta-analysis was performed. Overall, there was a large degree of heterogeneity present (I^2=99.92 for all studies combined).

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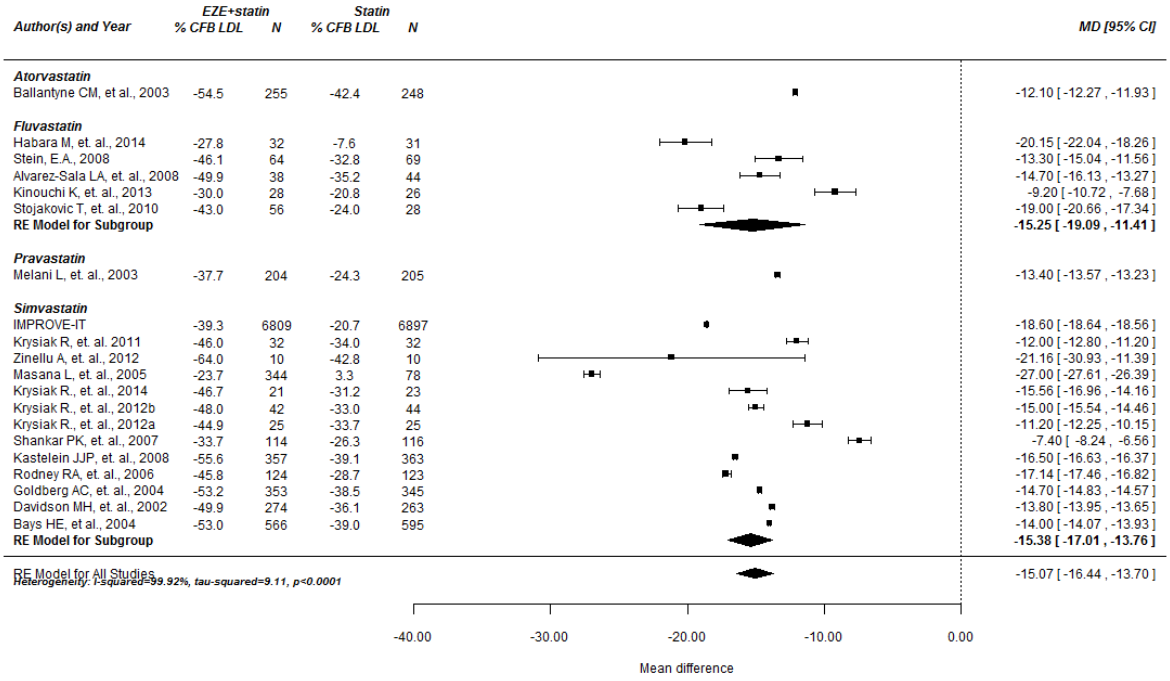
Percent mean difference in LDL-c (mmol/L) among studies comparing ezetimibe + statin to matching statin dose



Ezetimibe vs matching statin dose - TC

The figure below summarises % CFB in TC among the studies assessing ezetimibe in combination with statins vs matching statin monotherapy. The mean difference between ezetimibe in combination and matching statin dose was -11.4% (95% CI -12.1 to -10.7); treatment effect in the individual studies ranged from -18.4% to -2.8%. The I^2 value was 99.82, which indicates a very large degree of heterogeneity between the trials.

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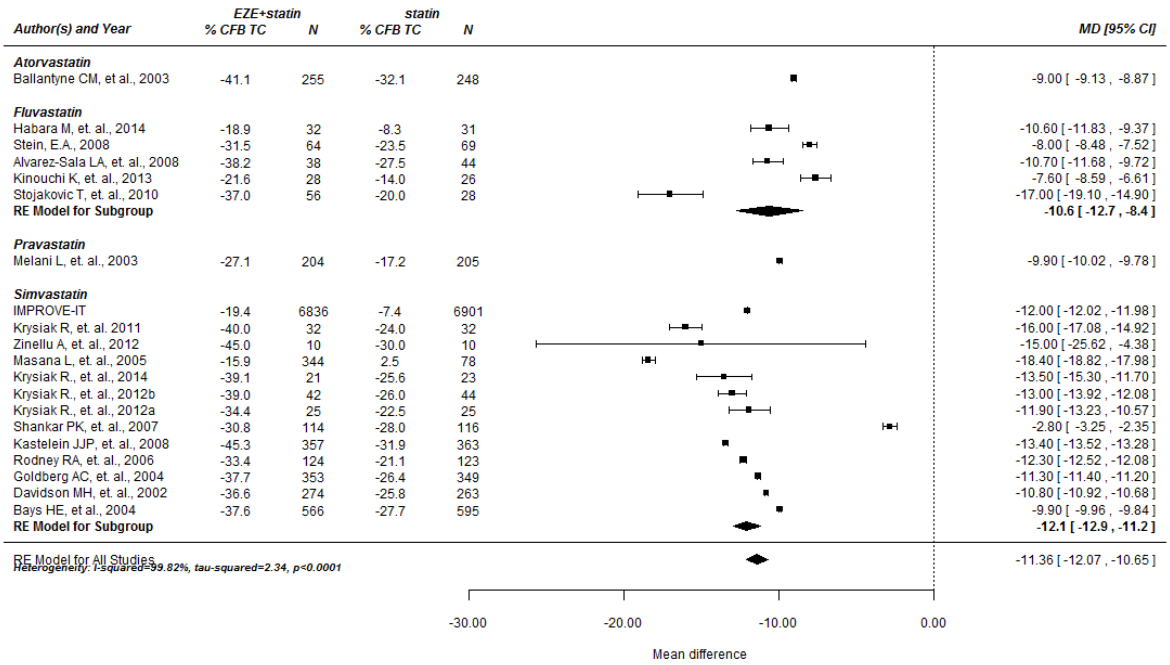
Percent change in TC among studies comparing ezetimibe + statin to matching statin dose



A8 Please further explain why studies of less than 12 weeks of duration were excluded from the review of clinical effectiveness evidence? Section 4.7 (page 67) suggests that all studies in the review of less than 12 weeks reported a multiplicative analysis of percentage change (Figure A) and that all longer studies used an additive analysis (Figure B). The statement in the first paragraph of page 68 does not appear to be consistent with this. Please clarify also why studies of less than 12 weeks were excluded from the review of ezetimibe monotherapy when an additive analysis of change scores was not possible for these studies.

Most systematic reviews that have informed previous guidelines (CG67, CG181) and technology appraisals (TA132) have used the eligibility criteria of including studies ≥12 weeks. One reason for this is to allow the LDL-c value that is achieved from a lipid modifying therapy to stabilise to enable to true effect of the LMTs efficacy. For this submission, the eligibility criteria of studies for both ezetimibe monotherapy and add-on to statin used ≥12 week.

Section 4.7 of the submission describes the two methods that have been used in ezetimibe add-on to statin RCTs to calculate the LDL-c lowering efficacy of ezetimibe. The calculation changes dependant on whether the study enrols patients on stable statin (Figure A) or on no LMT (Figure B). The paragraph at the top of

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page 68 is just trying to outline that for add-on to a statin, the efficacy of ezetimibe is discussed in clinical practice as a further % lowering of LDL-c (i.e. from the multiplicative analysis [Figure A]).

A9 The submission states (page 70) that a correlation coefficient of 0.5 was used to estimate the standard error of the mean percentage change. Would you please clarify whether this refers to the method reported in section 16.1.3.2 of the Cochrane Handbook for Systematic Reviews of Intervention (www.handbook.cochrane.org)? Please provide a reference for the use of a coefficient of 0.5 in this context.

We can confirm that we used the method as laid out in the Cochrane handbook to calculate standard error for change from baseline. We do feel that using a value of 0.5 is the most conservative approach, and allows the use of the largest number of studies possible.

A10 Please clarify which dose was selected for inclusion in the primary meta-analyses for trials that included more than one statin arm.

For the primary meta-analyses, for trials with more than one statin arm the pooled analysis was used.

A11 Please clarify which time point was selected for inclusion in the primary meta-analyses for studies that collected data at more than one time point.

Some of the trials that reported more than one time point were 12 week trials, which also reported cholesterol values at time points <12 weeks. In these instances the study endpoint 12 week value was used. In studies that were longer than 12 weeks we used the time point used in the primary analysis of the publication.

A12 Please clarify the formulae used to obtain the data in Appendix 12. The calculations do not seem to match the example provided in Figure B on page 68. How were weights calculated for the weighted average? Please explain whether the language used when referring to this 23.5% result on pages 19, 51, 74, and 78 is correct.

Please see Table 2 on next page. The %E incremental reduction was calculated for each trial by:

$$\frac{\text{LDL achieved on statin+ezetimibe arm} - \text{LDL-c achieved on statin arm}}{\text{LDL-c achieved on statin arm}}$$

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The weighted average was calculated by multiplying the %E incremental reduction for each trial by the N for each trial. All these individual weighted values were added and then divided by the total N for all trials. The table has been recalculated after removal of Sager 2003 (question A7). The 23.5% value is the one represented on pages 19, 51, 74 and 78

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Table 2: Calculation of the % incremental reduction for ezetimibe

Study	Statin arm			Statin + ezetimibe arm			Percentage reduction			
	n	Baseline LDL-c (mmol/L)	LDL-c achieved (mmol/L)	n	Baseline LDL-c (mmol/L)	LDL-c achieved (mmol/L)	%S	%E+S	%E further reduction	Weighted number
Alvarez-Sala 2008	44	5.60	3.63	38	5.10	2.56	35.2%	49.9%	29.5%	2419
Ballantyne 2003	248	4.65	2.68	255	4.65	2.12	42.4%	54.5%	20.9%	10512.7
Bays 2004	595	4.59	2.80	566	4.56	2.14	39.0%	53.0%	23.6%	27399.6
Davidson 2002	263	4.61	2.95	274	4.56	2.28	36.1%	49.9%	22.7%	12189.9
Goldberg 2004	345	4.55	2.80	353	4.55	2.13	38.5%	53.2%	23.9%	16682.2
IMPROVE-IT 2015	6897	2.43	1.93	6809	2.43	1.48	20.7%	39.3%	23.6%	323461.6
Kastelein 2008	363	8.22	5.01	357	8.25	3.66	39.1%	55.6%	26.9%	19368
Krysiak 2011	32	4.71	3.11	32	4.73	2.55	34.0%	46.0%	18.0%	1152
Krysiak 2012a	25	4.71	3.12	25	4.70	2.59	33.7%	44.9%	17.0%	850
Krysiak 2012b	44	4.73	3.17	42	4.71	2.45	33.0%	48.0%	22.7%	1952.2
Krysiak 2014	23	4.81	3.31	21	4.76	2.54	31.2%	46.7%	23.3%	1025.2
Masana 2005	78	N/A	N/A	344	3.53	2.69	3.3%	23.7%	23.8%	10043.6
Melani 2003	205	4.60	3.48	204	4.60	2.87	24.3%	37.7%	17.5%	7157.5
Rodney 2006	123	4.52	3.22	124	4.56	2.47	28.7%	45.8%	23.3%	5755.1
Stein 2008	69	4.50	3.02	64	4.47	2.41	32.8%	46.1%	20.2%	2686.6
Stojakovic 2010	28	2.64	2.01	56	2.90	1.65	24.0%	43.0%	17.9%	1503.6
Zinellu 2012	10	4.24	2.43	10	4.27	1.54	42.8%	64.0%	36.6%	732
Total N in each arm	9392			9574						444890.8
Total N	18966									

Weighted average = 444890.8 / 18966 = 23.5%

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Section B: Clarification on cost-effectiveness data

B1 Please provide further explanation for the approach of applying a set baseline CV risk of 20% for the cohort, rather than using the average characteristics of a UK primary/secondary prevention cohort (on and off statin therapy) to estimate the actual baseline risk of the patient cohort that might be considered for ezetimibe therapy.

The NICE Clinical Guideline for Lipid Modification (CG181, 2014) recommends that for the primary prevention of cardiovascular disease (CVD), people who have a 10% or greater 10-year risk of developing CVD should be offered lipid modification therapy, where diet and lifestyle advice is inadequate. The use of this threshold is only applicable to the primary prevention of CVD. The use of a 10-year CVD risk level has been used to reflect clinical practice and clinical guidelines, as well as previous modelling approaches for lipid-lowering therapies (TA94, TA132, CG181).

For the base case, a 10-year CVD risk of 20% was applied because this represents the risk level for the majority of patients currently managed with lipid-lowering therapy (Van Staa, 2013), which is consistent with the previous threshold recommended in the NICE Clinical Guideline for Lipid Modification (CG67, 2008).

A number of different populations and sub-groups are relevant to lipid modification management and relevant to this appraisal, including primary and secondary prevention cohorts, as well as people with diabetes, chronic kidney disease (CKD) or heterozygous familial hypercholesterolaemia (HeFH). To ensure that the modelling approach is reflective of all the relevant populations and sub-groups, and to be consistent with previous technology appraisals and clinical guidelines in this area, the same baseline risk data as previously used in TA94, TA132 and CG181 have been used. There are cardiovascular risk calculators for primary prevention and QRISK2 and UKPDS are the most relevant to UK clinical practice. However, utilising these to calculate baseline risks for the cost-effectiveness analyses are limited by the fact that these calculators are not suitable for use in a number of the key populations relevant to this appraisal such as secondary prevention, people with CKD and people with HeFH.

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B2 **PRIORITY**: Please supply more details about the approach used to inflate baseline risks of CV events annually in the economic model? Given that the base probabilities are based on a linearly transformed 10 year probability of 20%, will the approach of inflating these each year not result in a modelled 10 year risk over 20%? Please clarify why this approach was taken rather than just updating the CV risk every 10 years in the model.

Baseline risks of CV events apply only to the primary prevention population and are used to calculate the distribution and risk of an initial CV event. The baseline risks of CV events were calculated using a similar approach used in TA94, TA132 and CG181, based upon an initial baseline risk with an additional age-related risk applied annually (section 5.3 in manufacturer's submission). The baseline risks of CV events has been based on the data originally analysed by Ward *et al.* for TA94 and was included in TA132 and CG181 cost-effectiveness analyses. The data is provided within five different age bands.

The incidence rates of first CV events (see page 104 of manufacturer's submission and 'Baseline risks_PP' sheet in the CUA model) are multiplied by the 1-year CV probabilities, which was calculated by converting the 20% 10-year CVD risk using the following formula below (which was used in CG181):

$$Selected\ rate\ (r) = \frac{-\ln(1-P)}{t}$$

$$Transition\ probability(P) = 1 - e^{-rt}$$

$$Where\ P = probability\ of\ event\ over\ time\ t$$
$$and\ t = time\ over\ which\ probability\ occurs\ (10\ years)$$
$$r = selected\ rate\ \ and\ t = cycle\ length\ (1\ year)$$

The midpoint was taken within the age band and it was assumed that this was equal to the categories baseline risk (see row 19 on sheet "Age adjusted PP risks" as an example). From this point an annual age adjusted risk is added to the sum of all the CV events for any age within the group that is above the midpoint, and subtracted if it is below the midpoint.

The initial age selected for the cohort represents the age at which the patient is eligible for treatment with ezetimibe or the relevant comparator.

A patient's risk of a CV event increases over time (Ward *et al.* 2007); this age related increase in risk was applied as a gender specific yearly increase fixed at 0.03% for males and 0.008% for females. This yearly age-related risk increase is applied for each year beyond the initial baseline age at the start of eligibility for treatment.

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To incorporate the age-related risk, the initial starting age was selected within the background mortality sheet, and the age-adjusted increase was calculated within column M sheet “Background Mortality”. This risk was weighted according to background mortality using the anticipated ratio of males to females alive, which varies throughout the time horizon within the model.

The starting age, the baseline risk and the age adjusted risk are then collated in sheet “Age adjusted PP risks” row 81 where there are two tables, one for Ezetimibe and one for the selected comparator. Within this table the initial baseline risk is found relating to the baseline age selected within the model, the corresponding age related risk found in the “Background Mortality” sheet is then added to the sum of the prior year’s CV events (columns J and S in the “Age adjusted PP risks”). This increase is distributed equally amongst all CV events within that current year. Relative risks for ezetimibe and the chosen comparator are multiplied by these primary CV event risks. It is these values that are used within the patient flow sheets for ezetimibe and the chosen respective comparator.

The QRISK2 calculator estimates the risk of experiencing a CV event, defined as fatal or non-fatal angina, MI stroke or TIA (section 5.3, manufacturer submission). In the base case, stable angina and TIA have not been included in the model. As all the CV events included in the QRISK2 calculator are not considered in the current analysis, the compounded risk over 10 years for both baseline risk and age-related risk is slightly below the selected 10-year risk. For example in the primary prevention setting when considering monotherapy (where relative risks = 1), with the respective age and proportion of female patients being 60 and 44.3% respectively, the 10 year risk sums to 15.23% which is less than the 20% baseline risk. This was calculated by summing cells D81:I90 which are the health states included within the 10 year risk, in the monotherapy setting (such that all relative risks were one).

This approach was taken rather than just updating the CV risk every 10 years in the model as otherwise patients’ risk would in fact decrease over time in some cases as a result of the original data from Ward *et al.* 2007; this is not in line with either clinical expectation or the statement within the guidelines that risk increases with age. The annual age risk increase is not inflated twice within the current calculations; inflation happens once within the background mortality sheet with the inflated values carried through to the ‘Age adjusted PP risks’ sheet and distributed proportionately among the various types of CV events.

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B3 **PRIORITY**: Worksheet "Background mortality" column M: the age 60 row seems to be referencing the age 40 row in the worksheet "Age adjusted PP risks". Please clarify.

This error identified by the ERG has been fixed accordingly.

Column M in the 'background mortality' sheet should begin looking up age adjusted PP risks at age 40 (the starting age within the model), as such the wrong age was being referenced. This has been fixed within the updated model supplied with this response within cells M53 to M113. This formula calculates the anticipated increase in the age adjusted risk of incurring an event (within the primary prevention setting) and weights that increase according to the distribution of male and female patients alive. This is weighted as the age adjusted risk is different for men and women (0.03% and 0.008% annual increase respectively). The initial distribution of males and females is outlined at the start of the model in the controls sheet and varies slightly throughout time within the model based upon background mortality from ONS data, which in general shows that women have lower mortality rates per annum than men. Over time the age adjusted risk increase varies accordingly.

In incorporating the fix, the ICER varies within the primary prevention setting. Table 1 show the results when ezetimibe is prescribed as a monotherapy. Within this analysis the ICER has increased from £29,286 presented in the original submission to £30,129 per QALY.

Table 1: Results with age adjusted risk fix: Primary prevention, ezetimibe monotherapy

	Total Costs	Total QALYs	Total LYs	Incremental Costs	Incremental QALYs	ICER
No treatment	£8,143	11.82	23.76	-	-	-
Ezetimibe 10mg	£13,332	11.99	24.23	£5,188	0.172	£30,129

When ezetimibe is considered as added on to statin therapy, the applied fix has increased the ICER from £56,394 presented in the original submission to £58,473 per QALY.

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Table 2: Results with age adjusted risk fix: Primary prevention, add on to statin

	Total Costs	Total QALYs	Total LYs	Incremental Costs	Incremental QALYs	ICER
Atorvastatin 20mg	£8,359	12.10	24.57	-	-	-
Ezetimibe 10mg + Atorvastatin 20mg	£13,796	12.20	24.84	£5,437	0.093	£58,473

Table 3 shows the corrected results for the primary prevention population with diabetes at a 10-year CV risk of 20%, when ezetimibe is prescribed as a monotherapy Within this analysis the ICER has slightly increase from £19,852 presented in the original submission to £20,294 per QALY.

Table 3: Results with age adjusted risk fix: Primary prevention with diabetes, monotherapy

	Total Costs	Total QALYs	Total LYs	Incremental Costs	Incremental QALYs	ICER
No treatment	£8,709	9.36	18.00	-	-	-
Ezetimibe 10mg + Atorvastatin 20mg	£12,815	9.56	18.47	£4,106	0.202	£20,294

Table 4 shows the results with the fixes applied to the primary prevention population, for diabetic patients receiving add-on therapy. Within this scenario the ICER has increased slightly from £30,503 to £31,352 per QALY.

Table 4: Results with age adjusted risk fix: Primary Prevention with diabetes, add-on to statin

	Total Costs	Total QALYs	Total LYs	Incremental Costs	Incremental QALYs	ICER
Atorvastatin 20mg	£8,483	9.72	18.87	-	-	-
Ezetimibe 10mg + Atorvastatin 20mg	£12,843	9.86	19.20	£4,360	0.139	£31,352

The results for secondary prevention do not change as these calculations apply only to the primary prevention population.

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B4 **PRIORITY**: It seems the annual age risk increase is being proportionally inflated twice in the model to account for the assumed increase in non CHD CV events (e.g. see sheet "Background mortality" column M, and "Age adjusted PP risks", from column J, row 81 down). Please clarify.

Please see response to question B2.

B5 **PRIORITY:** The approach to estimating risk reductions for statin versus no treatment applies direct relative risks for CV events, whilst the ezetimibe benefit is modelled indirectly through its effect on LDL-C via the published CTT meta-analysis. However, the baseline LDL-C level does not appear to be updated to account for partial response to statin therapy, and remains at the pre-treatment level when estimating the absolute additional LDL-C reduction associated with ezetimibe therapy. This may overestimate the CV relative risk reduction for ezetimibe as an add-on to statin therapy. Similarly, applying direct relative risks to model the effect of statin therapy on baseline pre-treatment CV risks may underestimate the baseline CV risk in those who have inadequate control on a statin; i.e. the population being modelled in the ezetimibe add-on scenario. Please provide an additional analysis of longer-term outcomes on statin therapy (with inadequate control) when the LDL-C level is below the pre-treatment value but above the target level, which would lead to consideration of ezetimibe as an add-on.

The approach taken with the economic model was determined by the relevant input values that could be obtained for baseline risk and event rates, which are based on no treatment. Similarly the model replicates the clinical data observed in the meta-analysis, i.e. that from an additive approach to calculating the LDL-c efficacy of ezetimibe. There are significant methodological challenges of converting the additive value used in the primary RCT data to a multiplicative value. The major drawback is that as the multiplicative value cannot be derived directly from the meta-analysis, we don't have the associated standard errors that would be required to run PSA for the cost-effectiveness analysis. There are also challenges in calculating the percentage incremental reduction for ezetimibe from these studies in that there are differences between studies in terms of the end LDL-c value in the statin arms. Therefore a 'true' baseline value on stable statin prior to the addition of ezetimibe is not possible to be determined for each study.

Furthermore, the ERG has requested the analysis for where "*the LDL-c level is below the pre-treatment value but above the target level*". As described in the submission (including section 3.2.2), there are a number of different recommendations with

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regard to the cholesterol targets and there is variation in the targets used in clinical practice. As such, a range of cholesterol targets are applicable.

Based on the methodological limitations outlined regarding the clinical data, it is not appropriate to conduct this analysis. Should the ERG attempt to implement this alternative approach as outlined in the question, MSD would expect the opportunity to review the methodological approach due to the aforementioned methodological challenges, and any such analysis should be interpreted with extreme caution.

B7 Please provide an analysis in which directly estimated relative risks for CV events (with ezetimibe) are applied in the model for the primary prevention population.

There have been three clinical outcome trials that have examined the effectiveness of ezetimibe in reducing CV events in three distinct populations, and these did not include the primary prevention population (see beginning of section 4 of the submission for more details on these RCTs). As such, the requested analysis employing direct relative risk estimates for CV events is not possible. As the clinical evidence in two trials (SHARP and IMPROVE-IT) has demonstrated that the benefit associated with ezetimibe is consistent with the CTTC meta-analysis, the association between absolute LDL-c reduction and CV risk reductions established by CTTC has been applied in the submission to the wider licensed populations for ezetimibe. This has included the primary prevention cohort analysis, which employed the percentage LDL-c reductions from the meta-analyses.

B8 The approach being used also results in a slightly lower relative risk of death from other causes for ezetimibe compared with statin alone (0.94 vs 0.96). Is there enough evidence to justify this additional modelled benefit? Please provide further details to support your approach.

The treatment effect related to statin versus placebo for the add-on to statin analyses was derived from RCT data with CV endpoints that was identified and meta-analysed in the recent CG181 review. The risk ratios derived in CG181 have been applied and they also applied these in their cost-effectiveness analyses. The relative risk estimates used in the model regarding ezetimibe are derived from the CTTC meta-analysis, which included 26 RCTs with CV endpoints (see rationale in beginning of section 4 and section 5.3). Given the breadth of data included in these analyses, the mean values have been used as the most plausible estimates for non-CV death for ezetimibe and statins in the base case. The uncertainty associated with this has been assessed in the one-way sensitivity analysis and PSA.

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One of the tertiary endpoints in the IMPROVE-IT trial evaluated the relative risk of death for ezetimibe. The IMPROVE-IT results are consistent with the body of evidence relating to lipid lowering trials and mortality. Within the CTTC meta-analysis, several of the placebo controlled statin monotherapy trials showed a benefit on coronary, CV, and overall mortality (Baigent 2005). However, the so-called "more vs. less" statin trials (e.g., PROVE-IT [Ray 2005], TNT [LaRosa 2005], IDEAL [Pedersen 2005]), as with IMPROVE-IT, generally show similar risk for mortality between treatment groups (Baigent 2010). Neither these studies nor IMPROVE-IT were powered or designed to appropriately assess the potential benefit of incremental LDL-c reductions on mortality endpoints alone.

For the above reasons MSD feel it is appropriate to model relative risk of death from other causes using the approach taken in the submission.

B9 It is noted that the stroke and post stroke utility values applied in the model does not necessarily reflect a UK population, and that more recent UK-based EQ-5D estimates (*Luengo-Fernadez et al., 2013*) appear to have been rejected in favour of this value. Would you please clarify this further?

We selected the Teng *et al.* utility value for the stroke and the post-stroke health states because of its consistent use in previous NICE technology appraisals and clinical guidelines, including the original TA132 review and CG181. Comparing the utility values for minor, moderate and severe stroke reported by Tengs *et al.* and Luengo-Fernandez *et al.* show that Tengs *et al.* is a conservative approach.

The alternative values of 0.70 from Luengo-Fernandez *et al.* from 6-month and 1-year time points have been applied to the stroke and post-stroke health states. The 24-month utility value reported in the study (0.66) was rejected due to the uncertainty on the clinical plausibility of a further deterioration of HRQoL in the longer-term management of the disease that would not be captured by the age-related utility decrease applied in the model. Overall, the use of these alternative values has a minimal impact on the ICER compared to the base case (

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Table 5), which is consistent with the findings of the one-way sensitivity analyses presented in the original submission.

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Table 5 Incremental cost-effectiveness results (applying alternative stroke utilities)

Technologies (and comparators	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
Primary Prevention population, ezetimibe monotherapy							
No Treatment	£8,143	23.76	11.88	-	-	-	-
Ezetimibe 10mg	£13,332	24.23	12.05	£5.188	0.467	0.171	£30,358
Primary Prevention population, add-on to statin							
Atorvastatin 20mg	£8,359	24.57	12.17	-	-	-	-
Ezetimibe 10mg + Atorvastatin 20mg	£13,796	24.84	12.26	£5,437	0.263	0.092	£58,903
Secondary Prevention, ezetimibe monotherapy							
No Treatment	£31,072	13.80	5.99	-	-	-	-
Ezetimibe 10mg	£34,957	14.49	6.22	£3,885	0.683	0.228	£17,043
Secondary Prevention, add-on to statin							
Atorvastatin 40mg	£31,699	15.30	6.49	-	-	-	-
Ezetimibe 10mg + Atorvastatin 40mg	£35,811	15.73	6.63	£4,113	0.422	0.136	£30,145

B10 In the model, the proportional distribution across different types of CV event appear to have been applied deterministically as point estimates. Please clarify the associated uncertainty by applying a Dirichlet distribution in the PSA.

To implement a Dirichlet distribution to vary this information (Table 27, manufacturer's submission) within PSA, the total number of patients within the analysis and the total number of patients within each event state is required.

The original distribution of secondary events was sourced from an analysis conducted by Ward *et al.* (2007). Ward *et al.* did not provide a breakdown of the number of patients within each CV event state. It is stated within Ward *et al.* that distributions were based upon prevalence information from a study published by the British Heart Foundation for angina (not provided separately by stable/unstable in the original publication), MI and stroke. The original reference could not be found on the British Heart Foundation website, however, a British Heart Foundation publication from 2006 appeared to contain the data that may have been used by Ward *et al.* and has been used to implement the Dirichlet distribution. The uncertainty regarding the

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source of the data should be noted. Therefore to implement this request, the numbers were obtained by back calculating the numbers within each state individually using the proportional split from Ward *et al.*

Prevalence data providing the proportion of patients that have 'ever experienced' a CV event, alongside the sample size were used to estimate the number of patients within each state for the purposes of implementing the Dirichlet distribution (shown in Table 6).

Table 6: Information from BHF to inform a Dirichlet distribution

Male	**45-54**	**55-64**	**65-74**	**75+**	**85+***
Ever Experienced					
Angina	2.40%	7.50%	17.40%	19.60%	19.60%
MI	2.20%	6.70%	12.10%	15.70%	15.70%
Stroke	1.20%	2.20%	7.50%	13.30%	13.30%
Total N (for all events)	1,185	1,043	731	507	507
Female					
Angina	1.50%	5.00%	7.90%	14.80%	14.80%
MI	0.80%	2.10%	4.20%	8.10%	8.10%
Stroke	3.20%	3.50%	5.60%	5.50%	5.50%
Total N (for all events)	1,200	1,074	816	785	785

*assumed to be same as 75+

Information provided in Bots *et al.* 1997 was used by Ward *et al.* 2007 to source the relevant distribution for TIA. Bots *et al.* provided a similar level of information (the proportion of patients within the study who experienced TIA, reported by age group). This is shown below in Table 7. It was reported within Bots that 60.1% of patients within the study were female. From this the N for each gender within the respective age range could be calculated.

Table 7: Information from Bots *et al.* to inform a Dirichlet distribution

Male	**Patient with TIA**	**N within each category**
45-54*	1.00%	1,067
55-64	1.00%	1,067
65-74	2.70%	1,024
75-84	2.10%	624
85+	1.90%	219
Female		
45-54*	0.90%	1,607
55-64	0.90%	1,607
65-74	1.00%	1,542

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75-84	2.40%	940
85+	2.20%	331

*assumed to be the same as age 55-64

The total N within the Ward *et al.* analysis was approximated using these two data sources, and the totals are shown in Table 8.

Table 8: Total N approximated in each health state from BHF and Bots *et al.*

Total N for each event	Angina	MI	TIA	Stroke	Total
Male					
45-54*	28	26	11	14	79
55-64	78	70	11	23	182
65-74	127	88	28	55	298
75-84	99	80	13	67	259
85+	99	80	4	67	250
Female					
45-54*	18	10	14	38	80
55-64	54	23	14	38	129
65-74	64	34	15	46	159
75-84	116	64	23	43	246
85+	116	64	7	43	230

*assumed to be the same as age 55-64

As the distribution was already provided in Ward *et al.* 2007, we then applied this distribution to the total N within each age group to calculate the number of events for each age, gender and event type. From this, the N was varied using the Dirichlet method. Once the distributions were calculated, the results of males and females were weighted based upon the original male: female ratio. The total N within each event state once the Ward *et al*. 2007 distribution was applied are shown below in Table 9. It should be noted that within the base case of the model, health states stable angina and TIA are not considered.

Table 9: Approximate number of events within each state for the Dirichlet distribution

Total N for each event	N	Stable angina	Unstable angina	MI	TIA	Stroke
Male						
45-54	79	23	8	30	6	13
55-64	182	68	15	66	8	26
65-74	298	93	36	96	22	51

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75-84	259	75	32	79	12	60
85+	250	73	31	76	12	58
Female						
45-54	80	27	10	21	4	18
55-64	129	53	11	28	11	26
65-74	159	53	20	41	7	37
75-84	246	84	36	46	17	63
85+	230	79	34	43	16	58

*assumed to be the same as age 55-64

The results of the PSA performed for 1,000 iterations for secondary prevention, monotherapy and add-on to statin are shown in Figure 2 and Figure 3. The results of 1,000 iterations showed average incremental costs of £4,065 with incremental QALYs of 0.136. The corresponding probabilistic ICER was £17,130 and £29,554 for ezetimibe monotherapy and add-on to statin for secondary prevention, respectively, which is in line with their respective deterministic ICERs of £17,553 and £30,940.

Figure 2: PSA cost-effectiveness scatterplot incorporating a Dirichlet distribution (secondary prevention, monotherapy)

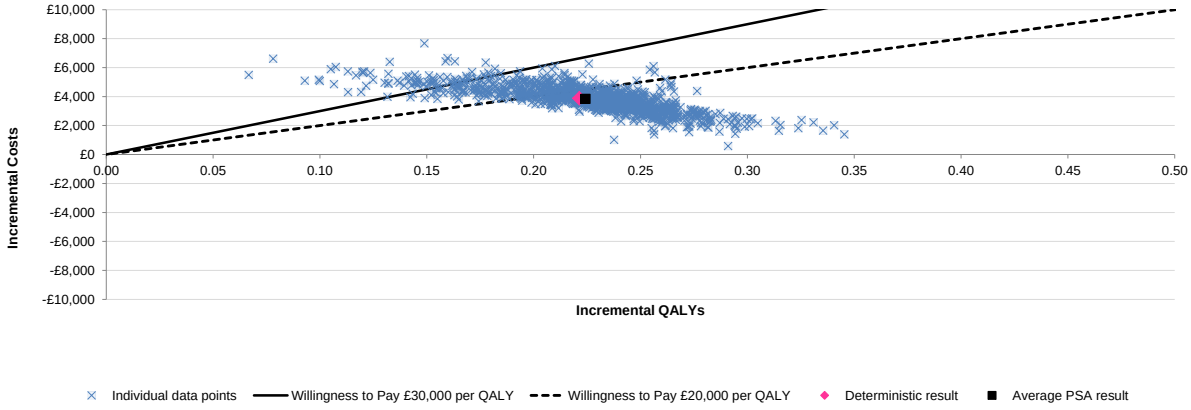

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Figure 3: PSA cost-effectiveness scatterplot incorporating a Dirichlet distribution (secondary prevention, add-on to statin)

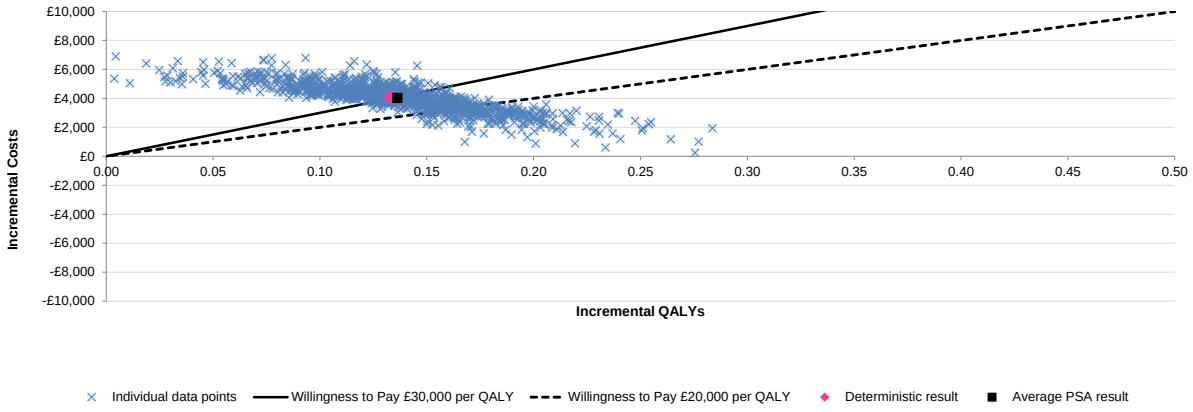

Figure 4 and Figure 5 shows the cost-effectiveness acceptability curve with 1,000 iterations. Within this analysis, there is a 51% probability that ezetimibe is cost-effective at a £30,000 willingness to pay threshold.

Figure 4: Cost-effectiveness acceptability curve incorporating a Dirichlet distribution (secondary prevention, monotherapy)

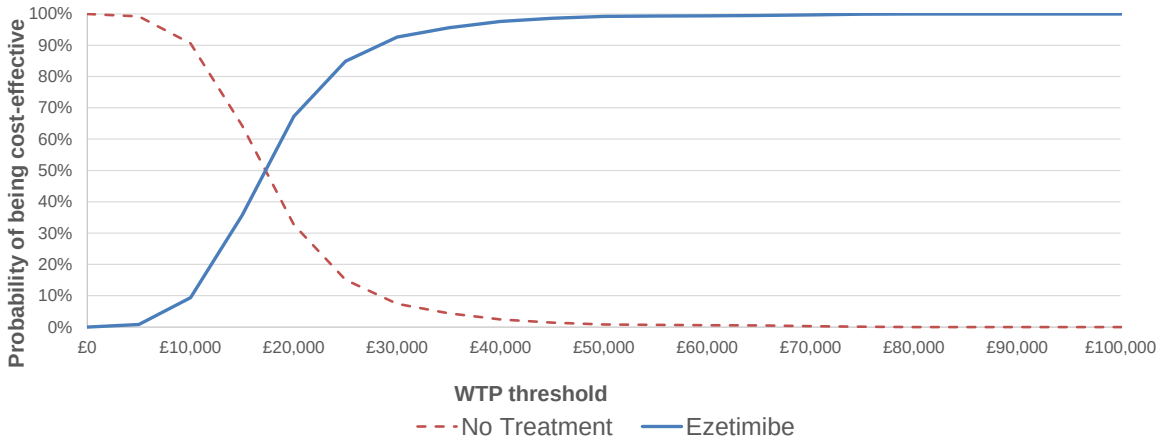

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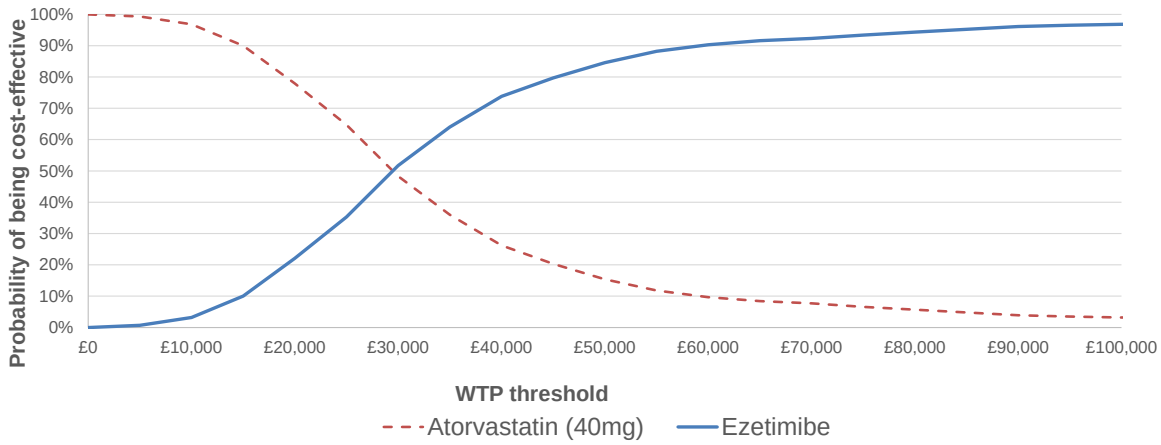
Figure 5: Cost-effectiveness acceptability curve incorporating a Dirichlet distribution (secondary prevention, add-on to statin)



It should be noted that there is considerable uncertainty regarding the validity of this analysis as the actual event numbers were not available to properly implement the requested Dirichlet distribution. Results from this analysis should be viewed in this context.

B11 A structural anomaly in the model allows patients to transit from the post stroke state (which has high costs and low utility) to the MI or unstable angina (UA) state and then on to the respective post event states for MI and UA. Whilst these transitions are realistic, the post UA/MI event pay-offs do not account for the prior history of stroke, and so effectively it seems that having an MI or unstable angina can improve health status (from 0.628 to 0.8) and reduce ongoing follow-up costs by 90% for a small proportion of the population that make this transition. By setting the transition from post-stoke to the MI and UA states to zero, please clarify the uncertainty arising from this structural assumption, and the effect on the ICERs.

As highlighted by this question, patients may experience more than one type of non-fatal CV event over a lifetime. Due to the memoryless feature of Markov models, the most recent CV event occurred is used to model the future cost and QALY impact of the patients (see Model Structure, Section 5.2 in manufacturer's submission).

The transitions outlined in this question account for a very small proportion of potential transitions; 2.08% of patients as a maximum within the oldest age group (1.04% from post-stroke to UA and 1.04% from post-stroke to MI shown in sheets 'Transitions_Ezetimibe' in cells AF93:AG93 and 'Transitions_Comparator' cells

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AF94:AG94) and therefore the simpler Markov model structure was felt to adequately reflect the key patient pathways. Whilst implementing the request above has some impact upon the ICER we would maintain that the test of the simplifying assumption proposed is biased against ezetimibe as removing transitions from post stroke to other health states removes the event costs and differences in utility from events post stroke which would be expected to be prevented with ezetimibe; this is clinically important as patients may well experience repeated cardiovascular events the prevention of which is a key benefit from treatment. This can be seen clearly in the differences in the incremental cost and QALY breakdowns (
Table **10**) with the proposed analysis versus the base case analysis using the original transitions.

Table 10 Incremental cost-effectiveness results (transitions from stroke to MI and unstable angina excluded)

Technologies (and comparators	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
Primary Prevention population, ezetimibe monotherapy							
No Treatment	£8,339	23.77	11.81	-	-	-	-
Ezetimibe 10mg	£13,491	24.24	11.99	£5,152	0.463	0.173	£29,775
Primary Prevention population, add-on to statin							
Atorvastatin 20mg	£8,475	24.58	12.10	-	-	-	
Ezetimibe 10mg + Atorvastatin 20mg	£13,895	24.84	12.19	£5,420	0.262	0.094	£57,958
Secondary Prevention, ezetimibe monotherapy							
No Treatment	£31,770	13.83	5.74	-	-	-	-
Ezetimibe 10mg	£35,562	14.50	5.96	£3,793	0.676	0.223	£16,986
Secondary Prevention, add-on to statin							
Atorvastatin 40mg	£32,114	15.31	6.22	-	-	-	-
Ezetimibe 10mg + Atorvastatin 40mg	£36,177	15.73	6.36	£4,062	0.420	0.135	£30,201

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia (review of TA132)

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: HEART UK

Your position in the organisation: [redacted]

Brief description of the organisation: HEART UK is the UK's cholesterol charity and provides support, guidance and education services to healthcare professionals and people and families with concerns about cholesterol. HEART UK is registered as a charity with the Charity Commission (charity number 1003904). We do not receive any government funding and are funded through donations from individuals and organisations.

(For example: who funds the organisation? How many members does the organisation have?)

We are asking for your collective view as an organisation and will be asking patient experts for their individual input separately. If you have the condition, or care for someone with the condition, you may wish to complete a patient expert questionnaire to give your individual views as well.

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Following a Familial hypercholesterolaemia (FH) diagnosis patients can often initially find it difficult to implement new lifestyle decisions, such as being more conscious about what they eat and how often they exercise. However, once these new habits are established and they have found a suitable medication, we find that patients can live care-free lives, unaffected by their disease.

In the long term though, patients can experience concern around passing the condition onto their children. Indeed, carers for children diagnosed with FH can find living this condition more difficult. Ensuring a young child is on a continual healthy diet and teaching them how to make the right choices themselves when they are offered various foods when they are out of the home, can prove extremely difficult.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

Patients want their cholesterol levels to be normal and their cardiac risk to be reduced to help increase life expectancy to the national average by avoiding any early onset heart problems, Preferably with few or no side effects so they can continue to live normal lives.What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

For most patients with familial and non-familial hypercholesterolaemia statins are the mainstay of treatment and they are generally well tolerated. Some patients cannot tolerate even a very low dose and in this circumstance Ezetimibe is likely to be required and is usually better tolerated.

In some patients, particularly those with more severe hypercholesterolaemia, maximum statin treatment does not reduce their cholesterol sufficiently and add on treatment is required. This is most effectively and easily given by Ezetimibe, but occasionally other treatments such as bile acid sequestrants or fibrates are used. Bile acids often produce gastrointestinal side effects and fibrates are not very efficacious. In extremely severe cases LDL apheresis may be considered, but this is very invasive, time consuming and not available in many parts of the country.

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)

- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

Ezetimibe, taken in conjunction with a statin, helps FH patients reduce their cholesterol. Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

Ezetimibe is a more preferential option than invasive and debilitating procedures such as apheresis.

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

5. Some patients find that they are more likely to stick with a singular treatment, involving only one pill a day, rather than having to take Ezetimibe along with a statin as two separate drugs.What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

Some patients report experiencing differing advice about statins and the use of secondary drugs, such as Ezetimibe to compliment them.Please

list any concerns patients or carers have about the treatment being appraised.

Whilst some patients did not consider there to be any disadvantages of Ezetimibe, Others would like greater clarity on whether or not Ezetimibe reduces cardiac risk and not just cholesterol.

There are also concerns around the expense of the treatment, with some patients concerned about the cost of paying for prescriptions for the rest of their lives. This is particularly a concern as there is disparity with other genetic or life-long conditions, such as diabetes, where patients are able to have free medication. If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

No

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

See section 3 above

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

There are a few patients who are poor responders to Ezetimibe ie their cholesterol will fall less than others. This is due to their individual metabolism/genetics wrt cholesterol absorption.

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

☐ Yes

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in

the clinical trials.

During trials patients generally have more intensive and frequent review

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

Yes, but not all trials have compared effect of adding Ezetimibe on top of statin treatment versus statin treatment alone.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

No

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

None

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

Those with difficulties swallowing tablets – no liquid form of Ezetimibe is available

9. Other issues

Do you consider the treatment to be innovative?

☐ Yes

If yes, please explain what makes it significantly different from other treatments for the condition.

It is a non-statin with reasonable efficacy

Are there any other issues that you would like the Appraisal Committee to consider?

The availability for Ezetimibe is vital for a number of FH patients and their families who feel that without it, they would be enable to stop the early onset of cardiac problems without the use of expensive, invasive, time consuming and debilitating procedures.

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- If FH is properly managed through lifestyle changes and medications, patients can live care-free lives, unaffected by their disease
- Patients want their cholesterol levels to be normal and their cardiac risk to be reduced to help increase life expectancy
- In some patients, particularly those with more severe hypercholesterolaemia, maximum statin treatment does not reduce their cholesterol sufficiently and add on treatment such as Ezetimibe is required
- Patients would like greater clarity on whether or not Ezetimibe reduces cardiac risk and not just cholesterol
- Ezetimibe is a non-statin with reasonable efficacy that is vital for a number of FH patients and their families

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia (review of TA132)

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted] and [redacted]

Name of your organisation: The Royal College of Pathologists
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **YES**
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)? **YES member**
- other? (please specify)

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia (review of TA132)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

REPLY: The mainstay of treatment for hyperlipidaemia is with statins where tolerated. Alternatives include ezetimibe, fibrates, bile acid sequestrants, fish oils (the latter are believed to be of poorer efficacy). As the only available drug in the cholesterol absorption inhibitor class, it is a unique drug but no longer considered innovative, nor a step change in management Ezetimibe is well tolerated and has an established role in lipid management but there are regional differences in prescribing of ezetimibe largely for historical reasons (differences in interpreting the previously available data – good evidence safety and efficacy in achieving modest LDL-cholesterol reduction, but lack of clinical endpoint outcome studies). Alternative lipid regulating drug previously considered are no longer recommended for non-FH in CG181. Bile acid sequestrants are therefore an appropriate comparator for FH only.
Patients with CKD and diabetes are at higher risk and may behave differently, so should be considered separately
Patients with familial hypercholesterolaemia (FH) are at greater risk, and may benefit from the greater efficacy of comination therapy (ezetimibe plus statin)
In the NICE FH pathway, ezetimibe fits in if optimal statin therapy is not effective (in reducing LDL-C by >50%) or is not tolerated; in the latter situation ezetimibe may be used with a reduced dose of statin, or exceptionally, as monotherapy. Ezetimibe is considered the current “standard of care” for statin intolerant patients, particularly those with myopathy. There is no good clinical outcome data for either of these indications, the expected benefits are extrapolated from other studies in different patient groups (such as IMPROVE-IT) based on changes in surrogate outcome measures (cholesterol reduction)
Use would mainly be in primary care and specialists lipid clinics within licensed indications. Ezetimibe is considered of value in sitosterolaemia, are rare condition

characterised by excessive absorption/retention of this phytosterol. Ezetimibe may be used for this indication in specialist clinics.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

REPLY: The technology is already in use throughout the UK, but with regional differences in practice.
The evidence base is not well reflected in clinical practice; evidence of favourable clinical outcome is now available for combination (with a statin) therapy, whereas ezetimibe has often been used instead of statin where the statin has been poorly tolerated; there is currently no outcome evidence to support this, although 'biochemical' efficacy has been demonstrated.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must

include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Ezetimibe blocks NCP1L1, inactivating genetic mutations of which have recently been shown to be associated with reduced cardiovascular disease risk

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

REPLY: not applicable – already in widespread use.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia (review of TA132)

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

REPLY: No such inequalities envisaged.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer expert statement (STA)

Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia (review of TA132) [ID627]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

the experience of having the condition or caring for someone with the condition

the experience of receiving NHS care for the condition

the experience of having specific treatments for the condition

the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)

preferences for different treatments and how they are given

expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

a patient

a carer (who may be voicing views for a patient who is unable to) or

somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

About you

Your name: Stephen Boley
Name of your nominating organisation: Heart UK
Do you know if your nominating organisation has submitted a statement?

☒ Yes ☐ No

Do you wish to agree with your nominating organisation's statement?

☐☒ Yes ☐ No

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

a patient with the condition?

☐☒ Yes ☐ No

I have FH treated with atorvastatin and ezetimibe

a carer of a patient with the condition?

☐ Yes ☐☒ No

a patient organisation employee or volunteer?

☐☒ Yes ☐ No

Do you have experience of the treatment being appraised?

☐☒ Yes ☐ No

If you wrote the organisation submission and do not have anything to add, tick here ☐ (If you tick this box, the rest of this form will be deleted after submission.)

Living with the condition

What is your experience of living with the condition as a patient or carer?

Fortunately no impact other than remembering to take one statin and one ezetimibe tablet every night. I like to think that I would do the good diet and exercise regime without having FH. Although I suspect it has been a factor in encouraging a 'healthy lifestyle'

Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

Key objective

A long and healthy life without any cardiovascular problems.

Secondary objectives

Having access to all the evidence to have confidence that the treatment meets the key objective

A good understanding of potential side effects.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

Taking Statin and ezetimibe is much easier than Questran.

I've always found the NHS care to be good and supportive in helping me manage my FH for over 30 yrs.

What do you consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

the course and/or outcome of the condition

physical symptoms

pain

level of disability

mental health

quality of life (such as lifestyle and work)

other people (for example, family, friends and employers)

ease of use (for example, tablets rather than injection)

where the treatment has to be used (for example, at home rather than in hospital)

any other issues not listed above

Please list the benefits that you expect to gain from using the treatment being appraised.

a long and healthy life with no cardiovascular disease

Please explain any advantages that you think this treatment has over other NHS treatments in England.

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.

Too many people seem over concerned about lowering cholesterol.

My focus is living longer and well.

I follow a lifestyle regime to increase my HDL C and take statins to reduce LDL C. I have been persuaded to supplement my statin with ezetimibe.

My concern is that ezetimibe studies have shown reduction in LDL C but limited benefit in reducing heart risk. My consultant assures me that the most recent study, Improve -IT, shows sufficient benefit. My reading is that this

benefit is "modest". There remain the previous studies which showed no benefit.

I'm concerned to establish whether there are increased risks from Ezetimibe which may outweigh its benefits in lowering LDL C. While it substantially reduces LDL C Ezetimibe does not appear to deliver the expected level of cardiovascular benefit so presumably it must have some negative impact / increased risk factors which do not appear to be fully understood.

There needs to be some straightforward patient guidance to help people decide whether they take just statins or statin + ezetimibe. Something similar to the statin guideline.

What do you consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

aspects of the condition that the treatment cannot help with or might make worse

difficulties in taking or using the treatment (for example, injection rather than tablets)

side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)

where the treatment has to be used (for example, in hospital rather than at home)

impact on others (for example, family, friends and employers)

financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)

any other issues not listed above

Please list any concerns you have about current NHS treatments in England.

Too much focus on cure and not enough on prevention. The NHS needs to do more to encourage a healthy lifestyle. I've found my own way to do this with limited encouragement.

Currently over 100,000 people with FH in UK not identified and being treated. Treatment is not expensive when compared with the costs to the economy of heart disease.

Little seems to be happening to identify and then treat FH sufferers

Please list any concerns you have about the treatment being appraised.

Is it improving my cardiovascular health as well as reducing my LDL C - see above

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

Patient population

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment?

☐Some of it Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.

cannot judge

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

i'd like to see clearer explanations about the pros and cons of this treatment. I need to judge whether I need to modify my treatment.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

not to my knowledge

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

☐ Yes ☐X No but would be interested in seeing them. I'd welcome more patient guidance - see above

If yes, please provide references to the relevant studies.

Equality

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

Other issues

Do you consider the treatment to be innovative?

☐ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

It may be better tolerated than statins in some people. However we need confidence that it reduces cardiovascular disease

Is there anything else that you would like the Appraisal Committee to consider?

Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

More support for a healthy lifestyle and disease prevention

Clear patient guidance on the benefits of statins + ezetimibe vs just statin or just ezetimibe

Better identification and treatment of people with FH

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia (review of TA132)

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the submission provided by Royal College of Pathologists and consequently I will not be submitting a personal statement.

Name: PROF A M KELLY.

Signed: [redacted]

Date: 7/9/15.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia (review of TA132)

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Dr Adie Viljoen

Name of your organisation
East and North Hertfordshire NHS Trust

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **Yes**
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? **No**
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? **No**
- other? (please specify)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Answers to questions

How is the condition currently treated in the NHS?
Ezetimibe is used as add-on to statin treatment in secondary prevention and in primary prevention (in particular for patients with familial hypercholesterolaemia e.g. CG 71). Ezetimibe is also prescribed a in monotherapy for lipid lowering in statin intolerant patients.

Are there differences of opinion between professionals as to what current practice should be?
Yes unsurprisingly professionals do have differences in opinion about this. Purists will follow the exact clinical trial data and only use this for the patients they see who mimic the population assessed in the clinical trial. More commonly, the potential benefits of Ezetimibe needs to be extrapolated to other populations.
Importantly this is easier to do when compared to other fields because LDL-cholesterol is a better surrogate than other surrogates such as HbA1c which is commonly used in diabetes medicine.
The other issue is whether a target LDL-cholesterol should be set or not. Guidelines and exerts in this filed disagree on this. The current lipid modification guidelines (CG181, July 2014) have fewer targets than the guidelines superseded by this one. Several current guidelines (e.g. type diabetes mellitus, familial hypercholesterolaemia, acute coronary syndrome) do however still have specific cholesterol targets.

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Single Technology Appraisal (STA)

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?
There are no alternative therapies that have demonstrated direct clinical benefit when combined with statin treatment. Nor are there other tolerable therapies available apart from statins which lower LDL-cholesterol. The only other therapy which is mildly efficacious but poorly tolerated is bile acid sequestrants and these are very rarely prescribed.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient?
Patients at higher risk of cardiovascular disease (CVD) have a poorer prognosis and these include patients for secondary prevention and the high risk populations for primary prevention are those with diabetes mellitus and familial hypercholesterolaemia.

Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?
No. There are the general pharmacogenomic differences between patients but generally this medication is very well tolerated and generally similarly efficacious in all populations. There are the hypothetical scenarios where it is expected that high cholesterol absorbers would benefit more and low cholesterol absorbers will benefit less form Ezetimibe, however this is not tested or known a priori in clinical practice.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics?
The medication can be prescribed in both primary and secondary care.

Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?
No. The medication is well tolerated.

If the technology is already available, is there variation in how it is being used in the NHS?
I believe so however I do not have excellent evidence to justify my statement. I work across three counties (Cambridgeshire, Hertfordshire and Bedfordshire) and I'm aware of local guideline differences. I was also directly involved with implementation of the TA132 when local guidelines were incongruent to the TA.

Is it always used within its licensed indications? If not, under what circumstances does this occur?
I believe Ezetimibe is generally prescribed within the licence. I can think of two scenarios where it is prescribed off licence: in children under 10 years who have familial hypercholesterolaemia and in chronic kidney disease (CKD) stages 3-5 (following the evidence from the SHARP study). Following the IMPROVE-IT study it may well be prescribed following ACS (acute coronary syndromes) for which it is not licensed per se.

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Single Technology Appraisal (STA)

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

Answer

No specific rules for stopping this treatment is recommended by other previous guidelines. LDL-cholesterol is expected to decrease by ~20% following treatment and including this as a pre-requisite for continuing therapy can be considered. There are however several other factors that can influence LDL-c results such as fasting status and biological and analytical variation. Furthermore it would be difficult to recommend a lower limit for an adequate response taken the paucity of data on this.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

Answer

The most notable studies are the long term CV outcomes studies namely SHARP and IMPROVE-IT. These studies together with the studies on statins cement the LDL hypothesis of atherosclerosis as well as LDL-cholesterol as an excellent surrogate marker. The surrogate marker is excellent in predicting long-term outcomes as was argued in the current TA for Ezetimibe.

The trial evidence for Ezetimibe is substantial but of course not in all populations where this is prescribed and recommended have direct cardiovascular benefits been demonstrated as these populations have not been studied (e.g. primary prevention, FH and diabetes mellitus). However sufficient trial evidence exists in all these populations using LDL-cholesterol as a surrogate. The most pivotal study of Ezetimibe, namely the IMPROVE-IT study did not employ the currently accepted standard statin medication namely Atorvastatin but in stead used Simvastatin. The results can be extrapolated by looking at the LDL-cholesterol at baseline and following treatments to extrapolate the potential benefits.

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Single Technology Appraisal (STA)

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Answer

The long-term placebo controlled trails in large populations have demonstrated the Ezetimibe is safe and very well tolerated. This certainly aids disease management as patients can be re-assured of the side-effect profile. I'm not aware of any concerning post marketing surveillance adverse effects and believe there are none of any significance.

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

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Single Technology Appraisal (STA)

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

I don't believe this will have any adverse impact on equality or diversity.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

I think the best current evidence is on all the currently available clinical trial data most notably the IMPROVE-IT study.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within

3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

I believe the guidance will improve patient care by reduction of cardiovascular events. The use of this medication is pretty well-established; the medication is well-known in CV prevention circles. Not all primary care professionals are always aware of the medication and there have been local restrictions on the current TA132 which are incongruent to the TA.

Ezetimibe for treating primary (heterozygous-familial and non-familial) hypercholesterolaemia

Produced by Aberdeen HTA Group

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Declared competing interests of the authors

None.

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Rider on responsibility for report

The view expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Graham Scotland and Mehdi Javanbakht acted as health economists; critiqued and reviewed the cost-effectiveness evidence presented in the submission, checked and rebuilt the economic model, and carried out further sensitivity analyses. Neil Scott acted as statistician; critiqued the statistical methods presented in the submission, checked the numerical results, tables, and figures related to the review of the clinical effectiveness evidence. Moira Cruickshank and Pawana Sharma acted as systematic reviewers; critiqued the clinical effectiveness methods. Cynthia Fraser acted as information scientist; critiqued the methods used for identifying relevant studies in the literature and conducted additional searches. William Simpson acted as clinical expert; provided clinical advice and general guidance. Miriam Brazzelli acted as project lead for this appraisal; contributed to the critique and review of the clinical effectiveness methods, and supervised the work throughout the project. All authors contributed to the writing of the report and approved its final version.

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List of abbreviations

AE	Adverse Event
AHRQ	Agency for Healthcare Research and Quality
BMI	Body Mass Index
CAD	Coronary Artery Disease
CFB	Change From Baseline
CHD	Coronary Heart Disease
CI	Confidence Interval
CKD	Chronic Kidney Disease
CRD	Centre for Reviews and Dissemination
CTTC	Cholesterol Treatment Trialists' Collaboration
CV	Cardiovascular
CVD	Cardiovascular Disease
DM	Diabetes Mellitus
EAS	European Atherosclerosis Society
EQ-5D	EuroQol 5 dimensions
ERG	Evidence Review Group
ESC	European Society of Cardiology
FH	Familial Hypercholesterolaemia
HDL	High Fensity Lipoprotein
HeFH	Heterozygous familial hypercholesterolaemia
HMG-CoA	3-Hydroxy-3-Methyglutaryl Co-enzyme A
HR	Hazard Ratio
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
IDL	Intermediate Density Lipoprotein
JBS	Joint British Societies
LDL-c	Low Density Lipoprotein cholesterol
LMT	Lipid Monitoring Therapy
LY	Life Years
MD	Mean Difference
MI	Myocardial Infarction

NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network Meta-Analysis
OR	Odds Ratio
PAD	Peripheral Artery Disease
PAS	Patient Access Scheme
PSS	Personal Social Services
QALY	Quality Adjusted Life Years
QoL	Quality of Life
RCT	Randomised Controlled Trial
SD	Standard Deviation
SmPC	Summary of Product Characteristics
TA	Technology Assessment
TC	Total Cholesterol
TG	Triglycerides
TIA	Transient Ischaemic Attack
TTO	Time Trade Off
ULN	Upper Limit of Normal
VLDL	Very Low Density Lipoprotein

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The NICE scope considered the clinical and cost-effectiveness of ezetimibe (ezetrol, Merck, Sharp & Dohme Ltd, UK) within its licensed indication for the management of primary heterozygous familial and non-familial hypercholesterolaemia in adults for whom statins have been inadequately effective, not tolerated or contraindicated. The current approved indication for ezetimibe is "adjunctive therapy to diet for use in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia who are not appropriately controlled with a statin alone" (co-administered with a statin) or as monotherapy as "adjunctive therapy to diet for use in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia in whom a statin is considered inappropriate or is not tolerated".

The company's submission specifies the relevant population for this appraisal as people with primary heterozygous familial or non-familial hypercholesterolaemia, either (a) co-administered with a statin in people whose condition is not appropriately controlled with a statin alone, either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance, or (b) as monotherapy in patients where a statin is considered inappropriate or is contraindicated or not tolerated. It is assumed by the ERG that the company's specification of (a) above refers to co-administration of ezetimibe and a statin, and that (b) refers to ezetimibe as monotherapy.

The company's decision problem and the NICE final scope both specified optimal statin therapy as the comparator for people with primary heterozygous familial or non-familial hypercholesterolaemia whose condition is not appropriately controlled with a statin alone. For people with primary heterozygous familial or non-familial hypercholesterolaemia in whom a statin is not considered appropriate or is not tolerated, the company's submission specified no treatment as comparator, whereas the NICE final scope specified other lipid-regulating drugs. The company's justification was based on NICE guidance CG181 (lipid modification),[1] which does not recommend use of nicotinic acid, bile acid sequestrants or omega-3 fatty acid compounds, or routine use of fibrates.

The company's submission deviates from the final scope issued by NICE in that it does not include non-high density lipoprotein cholesterol (non-HDL-c) among the relevant outcome measures for this appraisal. The company maintains that non-HDL-c has not been routinely reported in ezetimibe clinical trials. The ERG is of the opinion that attempt to consider non-HDL-c should have been made by the company as this is one of the current recommended measures of lipid profiles.[1] The company included total cholesterol (TC) among the outcomes to assess, although TC was not specified in the final scope.

1.2 Summary of clinical effectiveness evidence submitted by the company

The clinical effectiveness evidences submitted by the company identified a total of 24 randomised controlled trials (RCTs) of either ezetimibe monotherapy versus placebo (n=13) or ezetimibe plus a statin versus a matching statin dose (n=19), with some RCTs relevant to several comparisons. The clinical trial report for the IMPROVE-IT trial, sponsored by Merck, was subsequently added to the selected set of 24 trials.

The ERG noticed that possible double counting of study data and some inconsistent inclusion of studies had occurred. The company confirmed these inconsistencies and, as a result, a corrected version of the analyses was provided by the company at clarification.

All trials included ezetimibe with a dose of 10 mg, but statin doses varied in the included trials and some studies included multiple arms comparing various doses of statin such as 10, 20, 40 and 80 mg. Studies with an active treatment duration of less than 12 weeks were not considered and included trials varied from 12 weeks to 2 years. Mean baseline LDL cholesterol (LDL-c) levels were generally balanced within individual trials but varied widely between trials.

Meta-analyses were conducted for percentage change from baseline in LDL-c and percentage change from baseline in TC for two comparisons: i) ezetimibe 10 mg monotherapy versus placebo ii) ezetimibe 10 mg plus statin versus matching statin dose. The pooled results show benefits of greater lowering of LDL-c and TC for both ezetimibe versus placebo and for ezetimibe plus statin versus matching statin dose.

Each of the four main meta-analyses, however, showed high levels of statistical heterogeneity (I^2>99%).

Subgroup analyses by the type of statin, by the dose of statin and by diabetes status for the percentage change in LDL-c and TC for ezetimibe plus statin versus matching statin dose broadly showed consistent results. The results of three further subgroup analyses (primary prevention in people with diabetes, people with CKD and heterozygous familial hypercholesterolaemia) were limited by the small number of available studies. Nevertheless, their results were broadly consistent with the main results.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

While the inclusion and exclusion criteria reported by the company appear comprehensive and appropriate, the consistency of application of these criteria raises some concerns about the reproducibility of the review process. A number of included studies did not fulfil entirely the eligibility criteria in terms of the population being included, but encompassed a broader definition, which was not necessarily limited to primary hypercholesterolaemia. The company confirmed that their definition could incorporate terms such as dyslipidaemia and that certain trials were included because they assessed high risk populations. The company did not, however, undertake appropriate literature searches to capture this broader definition.

Formal meta-analyses were performed only for LDL-c and TC, although data were extracted for apolipoprotein B and lipoprotein (a). Trials with 100% Japanese and Indian participants were excluded from the primary analyses, but the company did not provide a clear rationale for their exclusion. Moreover, the Cholesterol Treatment Trialists' Collaboration (CTTC) meta-analysis published in 2010[2] and used by the company for the economic model, included the MEGA trial with 100% Japanese patients.

No meta-analyses of clinical outcomes such as mortality or CV events were undertaken by the company. The ERG further noted that clinical outcomes were available in at least two of the included studies.[3, 4] The company opted to assess the effect of ezetimibe on clinical outcomes indirectly, using an external meta-analysis,

the CTTC meta-analysis, which assesses reductions in major CV events in people whose LDL-c is reduced by statin therapy. This approach had been used in the previous TA132 appraisal[5] but in the current company's submission, the decision to continue to use this meta-analysis, despite clinical outcome trial evidence now being available for ezetimibe specifically, is not fully justified. As supporting evidence in favour of ezetimibe, the company presents also, in a narrative fashion, the results of two studies comparing ezetimibe/simvastatin combination therapy versus placebo and assessing clinical outcomes.[6, 7] These studies (sponsored by Merck or conducted with Merck's collaboration) do not seem to have been identified through a systematic review process. A recently published meta-analysis by Battaggia and colleagues[8] has included further ezetimibe studies assessing clinical outcomes, although most of these fall outside the scope of this appraisal.

Despite the high levels of statistical heterogeneity between the trials, the company has made no attempt to investigate reasons for the variable effects of the studies and to discuss whether it is appropriate to use the point estimates and 95% CIs from the meta-analysis in the cost-effectiveness model.

Network meta-analyses (NMA) were not presented in the company submission. The ERG considered that NMA could potentially have been performed in this appraisal to incorporate a wider range of evidence on the effect of treatments (including ezetimibe, statins, combination therapies and placebo) on clinical outcomes.

1.4 Summary of cost effectiveness submitted evidence by the company

A de novo Markov model with annual cycle was developed by the company. The model simulates the occurrence of cardiovascular (CV) events for both primary and secondary prevention cohorts. Modelled CV events include stable angina (SA), unstable angina (UA), myocardial infarction (MI), stroke, transient ischaemic attack (TIA) and CV death. Stable angina and TIA are excluded from the company's base case analysis due to a lack of evidence demonstrating the effects of LDL-c reduction on these events.

For the primary prevention analyses, the cohort commences in a "well" state and can experience events as determined by the estimated baseline transition probabilities for

first CV events. Each CV event is modelled using two states, reflecting costs and utilities incurred within the first year of the event and then longer-term costs and utilities incurred in subsequent years (post-event health states). For the secondary prevention analyses, the cohort is initially distributed across the post-UA, post-MI and post-stroke states, and can experience any of these events in subsequent cycles of the model based on estimated transition matrices for secondary CV events. Apart from excluding stable angina and TIA health states from base case analysis, the structure of the model is generally in line with the previous NICE assessments, including TA94, TA132 and CG181.[1, 5, 9]

Treatment effects for statins and ezetimibe are incorporated as relative risks or rate ratios for non-fatal MI, unstable angina, stroke, CV deaths, and non-vascular deaths. The relative risks for statin treatment are taken directly from a previous meta-analysis conducted for NICE CG181[1], which estimated the direct effects of statin therapy on CV endpoints. The rate ratios associated with ezetimibe are derived indirectly through an estimated relationship between LDL-c reductions and relative reductions in the risk of CV events. The CTTC meta-analysis of 26 statin trials[2] provides estimated rate ratios expressed per 1 mmol/L reduction in LDL-c for MI, stroke and any vascular and non-vascular deaths. The company conducted a meta-analysis to estimate the effects of ezetimibe on LDL-c. For those unable to tolerate a statin, the effects of ezetimibe versus placebo were used to model the cost-effectiveness of ezetimibe monotherapy versus no treatment. The pooled effect of ezetimibe plus statin versus statin alone, expressed as an additive percentage reduction from baseline (pre-treatment LDL-c level), was used to model the cost-effectiveness of ezetimibe as an add-on on to statin.

The base case primary prevention analysis was carried out for a 60 year old cohort (46.4% female) with a ten-year CV risk of 20%. The base case secondary prevention analysis was carried out for a 69 year-old cohort (34.6% female). A mean pre-treatment LDL-c concentration of 4.32 mmol/L was applied for the primary and secondary prevention cohort to calculate the absolute further LDC-c reductions associated with ezetimibe use.

Health states utility values were identified based on an updated review of health related quality of life (HRQoL) studies. Most of the utility data used in the model were taken from previous technology appraisals and modelling conducted for clinical guidelines (TA94, TA132 and CG181). New utilities for the TIA and post TIA health states were identified from the updated review of the literature. The company also adjusted baseline health state utilities by age and sex, to reflect EQ-5D general population norms. A number of sources including NHS reference costs, drug cost databases, and a systematic review of previous economic evaluations, were used to identify values for all cost parameters in the model.

Cost-effectiveness was assessed from the perspective of the patient for health effects, and that of the NHS and personal social services for costs. Health benefits (Quality Adjusted Life Years (QALYs)) and costs were discounted at 3.5% per annum. The base case analysis was conducted over the life-time of patients (up to 100 years of age). Compliance and adherence are assumed to be 100% over the patient's life-time.

The company's base case results suggest that, for the 60 year old primary prevention cohort at 20% CV risk, ezetimibe monotherapy (in those who cannot tolerate a statin) has an ICER just above £30,000. Compared with atorvastatin (20mg) alone, ezetimibe as an add-on for primary prevention has an ICER of £58,473. In the secondary prevention cohort (age 69), ezetimibe monotherapy has an ICER of £17,553 compared with no treatment. As an add-on to atorvastatin (40mg) for secondary prevention, the ICER for ezetimibe is £30,940.

Table 1 Company's base case cost-effectiveness results

	Intervention/ comparator	**Total Costs**	**Total QALYs**	**Total LYs**	**Incremental Costs**	**Incremental QALYs**	**ICER***
Primary prevention– monotherapy	No treatment	£8,143	11.82	23.76	-	-	-
	Ezetimibe 10mg	£13,332	11.99	24.23	£5,188	0.172	£30,129
Primary prevention- add on to statin	Atorvastatin 20mg	£8,359	12.10	24.57	-	-	-
	Ezetimibe 10mg + Atorvastatin 20mg	£13,796	12.20	24.84	£5,437	0.093	£58,473
Secondary prevention – monotherapy	No Treatment	£31,072	13.80	5.76	-	-	-
	Ezetimibe 10mg	£34,957	14.49	5.98	£3,885	0.683	£17,553
Secondary prevention – add on to statin	Atorvastatin 40mg	£31,699	6.24	15.30	-	-	-
	Ezetimibe 10mg + Atorvastatin 40mg	£35,811	6.37	15.73	£4,113	0.422	£30,940

*Results are based on updated analysis provided by the company in response to the ERGs clarification letter

The company conducted subgroup analyses for primary prevention in those with type 2 diabetes and chronic kidney disease (CKD). The cost-effectiveness of ezetimibe was found to be improved in people with diabetes, with the ICERs for ezetimibe monotherapy and as an add-on estimated to be £20,294 and £31,352, respectively. The ICER for ezetimibe as an add-on to atorvastatin 20mg in people with CKD was also more favourable, at £30.939. Finally, whilst no specific subgroup analysis was conducted for people with heterozygous familial hypercholesterolaemia, results from sensitivity analysis suggest that the ICERs for ezetimibe will also be more favourable in this subgroup with high LDL-c at baseline.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The company conducted literature reviews of the cost effectiveness and quality of life in the area of hypercholesterolemia. The searches to identify economic evaluations

were not designed to retrieve evidence from the literature for all relevant events in the model (stroke, MI, angina, TIA) as was the case for the quality of life searches. Thus information relevant for health state costs may have been missed.

The economic model was generally appropriately structured and consistent with previous modelling work used to inform NICE guidance in the area of hypercholesterolemia and lipid modification. The ERG identified a number of issues as follows:

- A number of apparent bugs were identified throughout the model, but, once corrected, the ICERs for ezetimibe actually improved.
- Some of the model output appeared to lack face validity, particularly the modelled survival for the primary prevention (20% CV risk) cohort, where this exceeded the expectation for the age/sex matched general population. This appeared to be due to over-adjustment of background mortality for modelled CV deaths. Any bias associated with this may also depend on whether the inclusion of non-significant effects for lipid lowering on non-CV deaths is considered appropriate or not.
- Inconsistent with the modelling previously carried out for TA132, the new model included a non-significant effect for ezetimibe on non-CV deaths, with the point estimate favouring ezetimibe versus no treatment and statin alone. Whilst the effect is small, the point estimates of the ICERs are moderately sensitive to this assumption.
- Conversely, the effects of statin and ezetimibe on TIA and stoke were excluded from the base case model, rather than being assumed consistent with those observed for MI and stroke. The latter was assumed in the modelling for TA132 and CG181.
- The approach used to combine background utility values with CV event utilities did not appear to follow the NICE DSU recommendation to use age adjusted multipliers. In addition, some more up to date utility estimates were identified from a single UK source. However, implementation of these new utilities with age adjustment had little impact on the ICERs

- Compliance and adherence are assumed to be 100% over the patient's life-time. There was limited exploration regarding the importance of this assumption in sensitivity analysis.

A further issue in the economic modelling relates to the method used to estimate the effects of ezetimibe on CV endpoints and non-CV mortality. Based on exploratory analysis conducted by the ERG, the magnitude of the further reduction in LDL-c concentration (mmol/L), with ezetimibe as an add-on to statin, is sensitive to whether an estimated additive or multiplicative percentage reduction in LDL-c compared with that achieved on statin alone is applied. The company conducted a meta-analysis of the further additive percentage reduction in LDL-c from baseline (pre-treatment) for statin plus ezetimibe versus statin alone. This was the applied to the modelled baseline LDL-c value of 4.32 mmol/L, to estimate the absolute further reduction in LDL-c associated with ezetimibe as an add-on to statin. However, the company also estimated the weighted average multiplicative percentage reduction in LDL-c from post-statin LDL-c levels. When this is applied to typical LDL-c levels achieved by cohorts on high intensity statin treatment, the estimated absolute further reduction in LDL-c associated with ezetimibe as an add-on, is less than it is using the pooled additive effect. With the effects of ezetimibe on CV events modelled through the absolute reduction in LDL-c concentration (mmol/L), the overall cost-effectiveness results are moderately sensitive to the approach chosen.

For the secondary prevention cohort, there is also some direct evidence for the effect of ezetimibe (as an add-on to statin) on CV endpoints, albeit in a subgroup of the wider population and compared with simvastatin (40mg) rather than the currently recommended first line atorvastatin. However, applying these directly estimated relative risks in the secondary prevention cohort raises the ICER for ezetimibe (as an add-on) above £100,000 per QALY gained.

A number of issues were also identified with the company's probabilistic sensitivity analysis, which resulted in significant underestimation of the uncertainty surrounding the ICERs. The identified issues are outlined as follows:

- All the beta distributions for utility parameters appeared to be misspecified. They were treated as if the mean utility estimate represented a binomial probability, which was multiplied by N (the sample size for the estimate) to recover an estimate of alpha (i.e. a number of events). This is not the case, and the method of moments approach should have been used to derive the alpha and beta parameters for these utility distributions.
- An error was also identified in the formula used to recover the log scale standard error for the specification of lognormal distributions (used for risk ratios included in the model).
- For parameters representing the additional percentage reduction in LDL-c associated with ezetimibe use, which were incorporated as beta distributions, the alpha and beta parameters were not appropriately estimated using the method of moments approach.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

- The report was written in a clear manner.
- In general, the methods used in the clinical effectiveness section and in the cost-effectiveness section were appropriate.
- The economic model was appropriately structured.

1.6.2 Weaknesses and areas of uncertainty

- The search strategies included a restricted list of terms which would impact on sensitivity and the ERG noted a number of imprecisions, which may have impacted on the final retrieval of results.
- Uncertainty about the reproducibility of the systematic review of clinical effectiveness evidence due to following reasons:
    - Inconsistency of application of the inclusion/exclusion criteria in terms of patient population. Patient populations with mixed hyperlipidaemia, CKD or acute coronary syndrome rather than primary hypercholesterolaemia were deemed suitable for inclusion because considered at “high-risk”.

  - Lack of clarity on how and why studies were excluded on the basis of participant ethnicity.
- High levels of statistical heterogeneity (I^2>99%) in all main meta-analyses for LDL-c and TC outcomes with no attempt to investigate reasons for inconsistency between trials.
- A number of apparent data errors, although individually these were of minor concern.
- No attempt to perform a systematic review and meta-analyses of clinical outcomes.
- The company has excluded TIA and stable angina health states from the base case analysis, which is problematic for the model face validity.
- There are some deficiencies in the approach used to search for cost data pertaining to the health states.
- The estimated uncertainty surrounding the ICERs is likely to be underestimated due to misspecification of some distributions in the model.
- A number of apparent 'bugs' were identified throughout the model.
- Some of the model output appeared to lack face validity. In particular, the modelled survival for the primary prevention cohort, where this exceeded the expectation for the age/sex matched general population.
- In contrast with previous modelling approach used in TA132, the company's model includes a non-significant effect for ezetimibe on non-CV deaths which has significant impact on the estimated ICERs.
- The approach used to combine background utility values with CV events utilities did not appear to follow the NICE DSU recommendations on the use of age-adjusted multipliers.
- Up-to-date utility estimates for patients with a clinical history of CV events, derived from a patient population in the UK, were not taken into consideration by the company.
- There was limited exploration regarding the importance of full compliance and adherence assumptions in the sensitivity analyses.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

After making a series of stepped changes to the company's model – applying alternative utilities, removing the effect of ezetimibe on non-CV deaths, and including effects on TIA and stable angina – the ICERs for ezetimibe remained fairly consistent with the company's base case results. In the main primary prevention cohort the ICER for ezetimibe remained close to £30,000 per QALY gained for monotherapy, and substantially higher than £30,000 as an add-on to statin. In the secondary prevention cohort, the ICER for ezetimibe remained below £20,000 for monotherapy, but rose to ~£36,000 as an add-on to statin. The cost-effectiveness of ezetimibe clearly improves as the baseline CV risk and the baseline (pre-treatment) LDL-c level increases.

Exploratory analysis conducted by the ERG suggests that the cost-effectiveness of ezetimibe as an add-on to statin (in those inadequately controlled on statin alone), is moderately sensitive to whether the estimated additive or multiplicative percentage reduction in LDL-c (compared to statin) is used to model the effects of ezetimibe. With the latter approach, the magnitude of the absolute further reduction in LDL-c achieved with ezetimibe (versus statin alone) is dependent on the LDL-c level achieved on statin. With the additive approach, only the baseline (pre-treatment) LDL-c level is used to the estimate the absolute further reduction in LDL-c achieved with ezetimibe. By applying the multiplicative percentage reduction (for ezetimibe as an add-on to statin) to varying levels of LDL-c achieved on statin, and also using modelled LDL-c reductions to estimate the effects of statin alone on CV events, the ICER for ezetimibe falls below £30,000 when the post statin LDL-c level in the secondary prevention cohort is $\geq$ 3 mmol/L.

Finally, if directly estimated relative risks for the effect of ezetimibe (as an add-on to simvastatin 40mg) are applied (IMPROVE-IT trial) in the secondary prevention model, the ICER for ezetimibe rises above £100,000 per QALY.

2 BACKGROUND

Primary hypercholesterolaemia is a form of dyslipidemia characterised by abnormalities of lipoprotein transport associated with high concentrations of cholesterol in the blood. The five major classes of lipoproteins include high density lipoprotein (HDL), low density lipoprotein cholesterol (LDL-c), intermediate-density lipoprotein (IDL), very low-density lipoprotein (VLDL), and chylomicrons. LDL-c comprises of ~75% of cholesterol carried by non-HDL particles. Non HDL-c (calculated as total-C – HDL-c) is the total of cholesterol carried by all potentially atherogenic lipopoproteins such as LDL-c, IDL, Lipoprotein (a), VLDL, chylomicron particles.[10, 11] Typically, primary hypercholesterolaemia is associated with elevated LDL-c, which can be caused by a single genetic defect (*monogenic familial*) or by the interaction between a genetic predisposition and other environmental factors such as smoking, diet, or physical inactivity (*polygenic or non-familial*).[12] The term secondary hypercholesterolaemia refers to hypercholesterolaemia caused by the presence of concomitant clinical conditions or induced by drug therapies. Secondary hypercholesterolaemia is not relevant to the scope of this appraisal.

In familial hypercholesterolaemia (FH), people inherit an abnormal (mutant) gene that affects the rate at which cholesterol is cleared from the blood, giving rise to a high level of cholesterol in the bloodstream. An individual can inherit a mutant gene either from one parent (heterozygous FH) or from both parents (homozygous FH or compound heterozygous FH). Prevalence of heterozygous FH in UK is usually estimated at 1 in 500 and of homozygous FH 1 in million.[13] However, recent estimates suggest the increased prevalence of 1 in 200 for heterozygous and 1 in 640,000 for homozygous FH.[14] Polygenic (non-familial) hypercholesterolaemia, with an estimated prevalence of 20-80%, is the most common form of primary hypercholesterolaemia.[15]

Blood cholesterol may vary between people and there are no fixed normal ranges for blood lipids due to the differences in biological, methodological, genetic and enviromental factors.[16] In general, average plasma cholesterol concentration of more than 5 mmol/l (equivalent to LDL-c of 3 mmol/l) is considered to be hypercholesterolaemic.[17]

People with hypercholesterolaemia are at increased risk of cardiovascular disease (CVD) due to the fact that long-term high concentrations of cholesterol are known to accelerate atherosclerosis, the build-up of fatty deposits in the arteries.

Atherosclerosis is the cause of CVD events such as coronary heart disease, transient ischaemic attack (TIA) and stroke, and peripheral arterial diseases. Oxidised LDL-c in the blood is atherogenic and causes endothelial damage, alteration of vascular tone. There is robust and consistent evidence that reduction in low density lipoprotein cholesterol (LDL- c) can reduce the risk of atherosclerotic CVD, and, therefore, reduction in LDL-c has become the primary focus of many therapeutic studies.[18] However, the importance of non-HDL-c and its relation to risk of atherosclerotic CVD has also been recently acknowledged and supported by various guidelines.[10, 19, 20]

Cardiovascular disease (CVD) has a significant health implication accounting for more than a quarter of all deaths in the UK (approximately160,000 deaths each year). Recent statistics from British Heart Foundation (February 2015) suggest that about 7 million people are living with CVD in the UK and the total cost related to CVD (premature death, lost productivity, hospital treatment and prescriptions) is an estimated at £19 billion annually.[21] CVD is the major cause of death, disability and reduced quality of life in Europe and costs approximately Euro 196 billion to the European Union.[22] The American Heart Association has estimated that 83.6 million people in US are living with CVD (15.4 million with atherosclerotic CVD) which contributes to 32.3% of deaths.[23]

Various UK (and international) guidelines have set target lipid levels for people at risk of, or with CVD. The Joint British Societies guidelines indicate non-HDL-c of <2.5 mmol/L and/or LDL-c of <1.8 mmol/L[20] as achievable lipid targets while others technology assessments have suggested LDL-c less than 3 mmol/L.[15] It is estimated that over half of adults in the UK have high blood cholesterol levels (5mmol/l or above).[21, 24]

The current management of primary hypercholesterolaemia involves dietary and lifestyle modifications such as smoking cessation, weight loss and increase of physical

activity.The initiation of therapy with a lipid-regulating drug is generally based on an assessment of the person's cardiovascular risk.

Statins, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are usually the first-choice of drugs for modification of the lipid profile.[1] Statins act by inhibiting HMG CoA reductase, an enzyme responsible for cholesterol synthesis in the body. As a result, the concentration of LDL-c levels reduces due to the slower production of cholesterol and thereby increasing the liver's ability to clear LDL-c from the blood. [25] A meta-analysis of individual participant data from randomised trials of statins has shown that statin therapy can significantly reduce the incidence of major coronary events, coronary revascularisation, and stroke by about one fifth per mmol/L reduction in LDL cholesterol.[26, 27] At present, statins that have received approval from both the FDA and the European Medicine Agency are atorvastatin, fluvastatin, pravastatin, rosuvastatin, and simvastatin. NICE full guideline on lipid modification does not, however, recommend the use of rosuvastatin due to the lack of evidence of its superiority in terms of efficacy compared with atorvastatin.[1] Statins should only be started after an informed discussion between the clinician and patient about the risks and benefits of statin treatment considering factors such as benefits from lifestyle modifications, co-morbidities, general frailty and life expectancy.[28]

NICE TA132[5] in line with CG181, recommends ezetimibe as an option for treating primary (heterozygous familial or non-familial) hypercholesterolaemia, as a monotherapy when statins are contraindicated or not tolerated and in combination with statins when initial statin therapy does not provide appropriate control of LDL-cholesterol. Ezetimibe (Ezetrol, Merck Sharp and Dohme Limited and Schering-Plough Limited), a cholesterol absorption inhibitor, is a type of lipid modification therapy that acts by inhibiting the Niemann-Pick C1-like protein (NPC1L1) in the small intestine and thus preventing the uptake of cholesterol. This causes increased level of cholesterol production in the liver and uptake of LDL-c which ultimately results in the lowering of circulating LDL-c.

According to data from Health and Social Care Information Centre, in the primary care and hospitals of England, there were total 56,607 prescriptions of ezetimibe monotherapy dispensed and a total of 2,645 prescriptions of ezetimibe with statins

(Simvastatin) dispensed between 2013 and 2014.[29] The company maintains that "*the latest prescription data available for ezetimibe, year to January 2015, in the UK suggests that 38% of the patients receiving ezetimibe were on monotherapy and 62% co-prescribed with a statin*" (IMS Health, UK Disease Analyzer, MAT Jan 2015)

Other lipid-modifying therapy includes fibrates, nicotinic acid, bile acid sequestrants, and omega-3 fatty acids.

2.1 Critique of company's description of underlying health problems

The company's description of primary hypercholesterolaemia is accurate and appropriate to the decision problem.

2.2 Critique of company's overview of current service provision

At present there are currently four sets of NICE guidelines relating to lipid disorders and CVD prevention relevant to the purpose of this appraisal:

1. CG181 Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. Published in July 2014, this NICE guidelines updates and replaces the previous guideline on lipid modification (CG67, published September 2008)
2. CG71 Identification and management of familial hypercholesterolaemia. This guideline was published in August 2008 and will be updated in September 2016.
3. TA132 ezetimibe for the treatment of primary (heterozygous familial and non-familial) hypercholesterolaemia published in November 2007.
4. TA94 Statins for the prevention of cardiovascular events. This guidance was published in January 2006 and has been now updated and replaced by NICE clinical guideline CG181
5. Quality Standard 41 Familial hypercholesterolaemia issued in August 2013

The company adequately refers to the NICE lipid modification clinical guideline CG181,[1] NICE familial hypercholesterolaemia clinical guideline CG71[19] and NICE technology appraisal of ezetimibe for the treatment of primary hypercholesterolaemia TA132.[5]

In general, NICE CG181 recommends that statin treatment should be offered to patients for whom lifestyle modification is ineffective or inappropriate. Atorvastatin 20 mg is advised for the primary prevention of CVD to people who have a 10% or greater 10-year risk of developing CVD (estimated using the QRISK2 assessment tool).[30] For secondary prevention, in people with established CVD, statin treatment with atorvastatin 80 mg should be started. Recommended follow up is at 3 months after initiation of statin treatment and a reduction in non-HDL cholesterol greater than 40% should be expected. If such a reduction in non-HDL cholesterol is not achieved, an increase in the dosage of atorvastatin (if started on less than 80mg) should be considered. NICE CG 71 suggests that a high-intensity statin should be considered in people with FH to achieve a reduction in LDL-c concentration greater than 50% from baseline level. NICE CG181 (primary hypercholesterolaemia) and CG71 (familial heterozygous hypercholesterolaemia), in line with TA132, recommend ezetimibe as a possible option in adults with primary hypercholesterolaemia (familial and non-familial) who are either contraindicated or are intolerant to statins, or ezetimibe can be co-administered with statins in whom LDL-c concentration is not appropriately controlled.

The company also adequately refers to the Joint British Societies consensus recommendations for the prevention of cardiovascular disease (JBSIII)[20] and to a task force for the ESC/EAS,[18] which developed guidance for the management of dyslipidemias, published in 2014 and 2011, respectively.

Figure 1 presents the primary care clinical pathway of care for lipid modification therapy for preventing cardiovascular disease as described in the NICE pathway[28] and adapted by the ERG to include the likely position of statins and ezetimibe.

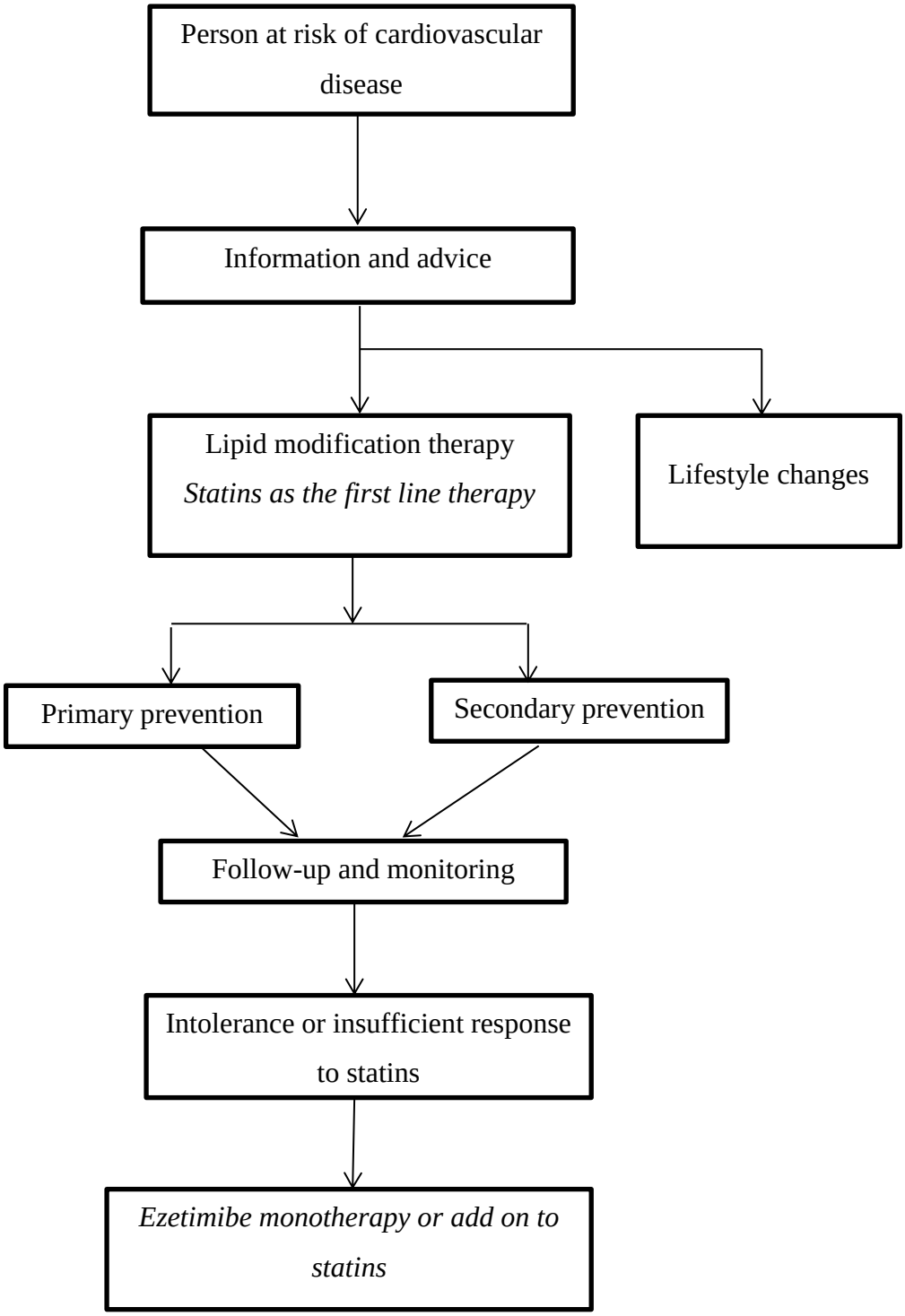


Figure 1 The primary care clinical pathway of care for lipid modification therapy for preventing cardiovascular diseases[28]

3 CRITIQUE OF THE COMPANY'S DEFINITION OF THE DECISION PROBLEM

3.1 Population

The company's submission specifies the relevant population for this appraisal as people with primary heterozygous familial or non-familial hypercholesterolaemia, either (a) co-administered with a statin in people whose condition is not appropriately controlled with a statin alone, either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance, or (b) as monotherapy in patients where a statin is considered inappropriate or is contraindicated or not tolerated. It is assumed by the ERG that the company's specification of (a) above refers to co-administration of ezetimibe and a statin, and that (b) refers to ezetimibe as monotherapy.

The company further specifies two populations for consideration: (i) primary prevention (10-30% 10-year risk of developing CVD) and (ii) secondary prevention (established CVD). The ERG assumes that these populations constitute sub-groups of the primary hypercholesterolaemia population specified above.

The NICE final scope specified the relevant population as people with primary heterozygous familial or non-familial hypercholesterolaemia, either (a) whose condition is not appropriately controlled with a statin alone, or (b) in whom a statin is considered inappropriate or is not tolerated.

The company's explanation for specification of the population co-administered with a statin is to consider people who are not appropriately controlled with a statin alone where up-titration is inappropriate or not tolerated. The company states that this practice is in accordance with clinical practice and NICE guidelines (CG181).[1] The ERG agrees that the company's specification of the population for this appraisal is appropriate.

3.2 Intervention

Ezetimibe (ezetrol, Merck, Sharp & Dohme Ltd, UK) is a lipid-lowering agent that inhibits absorption of dietary and biliary cholesterol and related plant sterols by the

intestines whilst not affecting the uptake of triglycerides or fat-soluble vitamins.[8, 15, 31] Ezetimibe localises in the brush border of the small intestinal enterocytes, reducing the uptake of cholesterol into the enterocytes. Thus, absorption of cholesterol is inhibited by retaining the cholesterol in the intestinal lumen, whereby it can be excreted[32, 33]. Ezetimibe has been available in England and Wales since 2003[15] and has a half-life of 24 hours, lending itself to administration once a day.[34]

Ezetimibe has marketing authorisation in the UK as monotherapy and in combination with a statin. As monotherapy, ezetimibe has marketing authorisation as an adjunctive therapy to diet for primary heterozygous familial or non-familial hypercholesterolaemia when a statin is considered inappropriate or is not tolerated. In combination with a statin, ezetimibe has marketing authorisation as adjunctive therapy to diet for primary heterozygous familial or non-familial hypercholesterolaemia that is not appropriately controlled with a statin alone. The current approved indication is "adjunctive therapy to diet for use in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia who are not appropriately controlled with a statin alone" (co-administered with a statin) or as monotherapy as "adjunctive therapy to diet for use in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia in whom a statin is considered inappropriate or is not tolerated" (Ezetrol, SmPC).[35]

Ezetimibe is formulated as tablets, each containing 10mg of ezetimibe. The recommended dose is one 10mg tablet daily, at any time of day, with or without food. If ezetimibe is co-administered with a statin, either the indicated usual dose of the statin or an already established higher dose should be continued (SmPC).[35]

The decision problem addressed by the company is in line with the final scope issued by NICE for this appraisal.

3.3 Comparators

The company's decision problem and the NICE final scope both specified optimal statin therapy as the comparator for people with primary heterozygous familial or non-familial hypercholesterolaemia whose condition is not appropriately controlled

with a statin alone. The company further specified the maximum tolerated dose for the pertinent statin therapy. This is considered appropriate by the ERG.
For people with primary heterozygous familial or non-familial hypercholesterolaemia in whom a statin is not considered appropriate or is not tolerated, the company's submission specified no treatment as comparator. The NICE final scope specified other lipid-regulating drugs. The company's justification for their choice of the 'no treatment' comparator was based on the NICE CG181 (lipid modification)[1] which does not recommend use of nicotinic acid, bile acid sequestrants or omega-3 fatty acid compounds, or routine use of fibrates.

3.4 Outcomes

The outcomes considered by the company were mean % change in LDL-c and total cholesterol, apolipoprotein B and lipoprotein A (amended to "lipoprotein (a)" at clarification); survival/mortality; fatal and non-fatal cardiovascular events (including coronary events); stroke; adverse effects of treatment; health-related quality of life
The outcomes specified in the NICE final scope include plasma lipid and lipoprotein levels, including LDL cholesterol, non-HDL cholesterol, apolipoprotein B and lipoprotein (a); requirement of procedures including LDL apheresis and revascularisation; fatal and non-fatal cardiovascular events; coronary events; stroke; mortality; adverse effects of treatment; health-related quality of life.

The company's justification for not considering non-HDL cholesterol as an outcome was that it is not routinely reported in clinical trials. NICE guidance CG181[1] recommends measurement of non-HDL cholesterol (among other measurements) both before starting lipid modification therapy and subsequently as the key marker of effectiveness of the therapy. Therefore, despite the lack of available trial data, non-HDL cholesterol should have been considered by the company among the relevant outcome measures for this appraisal.

The company did not include LDL apheresis as it is predominantly used in homozygous familial hypercholesterolaemia, and therefore not relevant to the remit of this appraisal.

The company included revascularisation in the health state costs applied in the cost-effectiveness analysis.

Although clinical outcomes (survival/mortality, CV events, stroke) and health-related quality of life were specified as outcomes in the decision problem addressed by the company, these were not reported in the company's systematic review of clinical evidence.

3.5 Other relevant factors

The decision problem addressed by the company for the economic analysis is consistent with the NICE final scope.

The NICE final scope specified the following subgroups for consideration if evidence allowed: presence or risk of cardiovascular disease; people with heterozygous familial hypercholesterolaemia; people with statin intolerance; severity of hypercholesterolaemia. The subgroups considered by the company are: primary prevention in people with diabetes; people with chronic kidney disease (CKD); people with heterozygous familial hypercholesterolaemia. The company considered that the presence or risk of cardiovascular disease was represented by the primary prevention population (10-30% 10-year cardiovascular risk) in this appraisal. The company considered severity of hypercholesterolaemia as part of the CV risk score and baseline LDL cholesterol values were modelled. Inclusion of the diabetes and CKD subgroups in the company's submission was considered following consultee feedback on the draft scope.

Table 2 illustrates the differences between the NICE final scope and the decision problem addressed by the company.

Table 3 (modified from Table 6 of the company's submission) illustrates the differences between the approach used for the previous TA132 and that used for the current submission.

Table 2 Comparison of NICE final scope and decision problem addressed by company

	Final scope issued by NICE	Decision problem addressed in the submission
Population	People with primary heterozygous familial or non-familial hypercholesterolaemia: • whose condition is not appropriately controlled with a statin alone or • in whom a statin is considered inappropriate or is not tolerated	People with primary heterozygous familial or non-familial hypercholesterolaemia: • co-administered with a statin in people whose condition is not appropriately controlled with a statin alone, either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance • as monotherapy in patients where a statin is considered inappropriate or is contraindicated or not tolerated **The following populations are considered:** • **Primary prevention (10-30% 10-year risk of developing CVD)** • **Secondary prevention (established CVD)**
Intervention	ezetimibe alone or in combination with a statin	• ezetimibe monotherapy • ezetimibe in combination with s statin
Comparator(s)	For people with primary heterozygous familial or non-familial hypercholesterolaemia	For people with primary heterozygous familial or non-familial hypercholesterolaemia

	Final scope issued by NICE	Decision problem addressed in the submission
	whose condition is not appropriately controlled with a statin alone: • Optimal statin therapy For people with primary heterozygous familial or non-familial hypercholesterolaemia in whom a statin is considered inappropriate or is not tolerated: • Other lipid-regulating drugs	whose condition is not appropriately controlled with a statin alone: • Optimal statin therapy (maximum tolerated dose) **For people with primary heterozygous familial or non-familial hypercholesterolaemia in whom a statin is considered inappropriate or is not tolerated:** • **No treatment**
Outcomes	The outcome measures to be considered include: • Plasma lipid and lipoprotein levels, including LDL cholesterol, **non-HDL cholesterol,** apolipoprotein B and lipoprotein a • **Requirement of procedures including LDL apheresis and revascularisation** • Fatal and non-fatal cardiovascular events • Coronary events • Stroke • Mortality • Adverse effects of treatment • Health-related quality of life	Outcome measures: • Mean % change in LDL-c and **TC**, apolipoprotein B and lipoprotein a • Survival/mortality* • Fatal and non-fatal cardiovascular events* • Stroke* • Adverse effects of treatment • Health-related quality of life*
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that	• The cost-effectiveness analyses is expressed as incremental cost per quality-adjusted life year (QALY) • Lifetime time horizon • NHS and Personal Social

	Final scope issued by NICE	Decision problem addressed in the submission
	the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	Services perspective
Subgroups to be considered	If the evidence allows, consideration will be given to the following subgroups: • Presence or risk of cardiovascular disease • People with heterozygous familial hypercholesterolaemia • People with statin intolerance • Severity of hypercholesterolaemia	Where evidence allows, analysis of subgroups will be considered in: • Primary prevention in people with diabetes • People with CKD • People with heterozygous-familial hypercholesterolaemia

*These outcomes were not addressed in the company's systematic review of clinical effectiveness

Table 3 Differences between the approach used for TA132 and that of the current company's submission

TA132 approach (Nov 2007)	Company's submission approach (June 2015)	Comments
Populations. TA132 considered five distinct populations for the cost-effectiveness analysis:	For the review of TA132:	
1. Ezetimibe co-administered with current statin therapy versus current statin therapy titrated to the next dose (generic simvastatin)	1. Not considered	1. This population was not considered, as according to clinical practice and NICE guidance (CG181) if a patient can tolerate up-titration of their statin to the next dose, this should be investigated prior to the addition of ezetimibe.[8]
2. Ezetimibe monotherapy versus no treatment	2. Ezetimibe monotherapy versus no treatment	2. Considered in this appraisal
3. Ezetimibe co-administered with non-proprietary simvastatin versus atorvastatin	3. Not considered	3. Atorvastatin is now generic and first-line option for treatment
4. Ezetimibe co-administered with current statin therapy versus current statin therapy alone	4. Ezetimibe co-administered with current statin therapy versus current statin therapy alone	4. Considered in this appraisal
5. Ezetimibe co-administered with rosuvastatin versus rosuvastatin monotherapy	5. Not considered	5. NICE concluded in CG181 that due to the availability of low cost statins, atorvastatin should be considered over rosuvastatin. There is however historical usage of ezetimibe in combination with rosuvastatin. The focus of this appraisal is on the first choice statin option (Atorvastatin).

TA132 approach (Nov 2007)	Company's submission approach (June 2015)	Comments
For the co-administration with a statin population in the 2007 appraisal of ezetimibe, up-titration of the statin dose was considered a comparator.	For the co-administration with a statin population, this review will only consider patients that cannot increase their statin dose due to intolerance or contraindication.	In the 2007 appraisal of ezetimibe, there were limited generic statin options, therefore it was appropriate to consider up-titration of the statin dose as a comparator to adding ezetimibe in the co-administer with a statin population. In today's environment there are many low-cost statin options, therefore increasing the dose of statin should always be considered before adding ezetimibe. For this reason MSD consider up-titration of a statin to not be a comparator to co-administration of ezetimibe with a statin.
Simvastatin was considered standard of care.	Atorvastatin 10 – 80 mg is considered standard of care depending on the population.	Since atorvastatin became generic in May 2012, it has replaced simvastatin as the first-line statin of choice, and is also the first statin of choice in CG181.
CV risk. Clinical practice and guidelines focused on a person's 10-year risk of CVD being over/equal to 20% before starting treatment with lipid-lowering therapy.	The appraisal will consider the use of ezetimibe with 10-30% 10-year risk of CVD to align with current guidance.	Since the original appraisal of ezetimibe (TA132), NICE Clinical Guideline CG181 has changed so that lipid modifying treatment can be considered for people whose 10-year risk of developing CVD is 10% or greater. Whilst the Marketing Authorisation for ezetimibe does not consider a person's risk of CVD for treatment with ezetimibe, this appraisal will consider people whose 10-year risk of developing CVD is 10-30% to reflect the evolution of clinical practice.

TA132 approach (Nov 2007)	Company's submission approach (June 2015)	Comments
Historically, in clinical practice Framingham risk scoring has been used to estimate a person's risk of CVD.	QRISK2 will be used.	In line with CG181, QRISK2 is the risk scoring tool of choice to assess CVD risk for the primary prevention.
Only Phase III RCTs were eligible for inclusion.	Any RCTs were eligible for inclusion.	
Comparators specified as: • 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.	Comparators specified as: • For people with primary heterozygous familial or non-familial hypercholesterolaemia whose condition is not appropriately controlled with a statin alone: Optimal statin therapy (maximum tolerated dose). • For people with primary heterozygous familial or non-familial hypercholesterolaemia in whom a statin is considered inappropriate or is not tolerated: No treatment.	

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

4.1.1 Searches

The company submission provides full details of the searches that were undertaken to identify the included studies for the clinical effectiveness review. The major relevant databases: MEDLINE (Ovid), EMBASE (Ovid) and CENTRAL (Cochrane Library) were searched on 9th March 2015 for publications written in English and published from 1990 onwards. Conference proceedings were not searched separately. However, EMBASE includes abstracts published in journals, so the contents of major conferences are likely to have been included.

The search strategies are documented in full in Appendix 4 and are reproducible. The MEDLINE and EMBASE strategies appropriately combined four search facets using the Boolean operator AND: hypercholesterolaemia; ezetimibe; statin or placebo; and randomised controlled trial. The search in the Cochrane Library for CENTRAL excluded the RCT facet, which was appropriate. Although both thesaurus terms (MeSH or EMTREE) and free text terms were used, the ERG does not consider that the search was as sensitive as it should have been (particularly for MEDLINE) and therefore cannot confirm that the company's approach was comprehensive in identifying relevant studies. The hypercholesterolaemia facet of the search was of particular concern:

- ***Hypercholesterolaemia*** is not the correct MeSH or Emtree term. While Emtree automatically maps to the correct term ***Hypercholesterolemia***, MEDLINE and the Cochrane Library, return no hits because this term is invalid.
- The MeSH term for familial hypercholesterolaemia (***Hyperlipoproteinemia Type II***) has not been included in the MEDLINE and Cochrane Library searches.
- The sensitivity of the search could have benefited by the inclusion of thesaurus and text terms related to the associated concepts of ***hyperlipidaemia*** and ***dyslipidaemia.***

- Not all included studies described their populations as having hypercholesterolaemia, hyperlipidaemia or dyslipidaemia but rather cardiovascular disease,[3] coronary disease[36] or kidney disease.[37] These studies were indexed in MEDLINE and EMBASE with these conditions and not with any terms associated with hypercholesterolaemia. Therefore sensitivity could have been further enhanced by including terms for these (and any other relevant) conditions.
- One study[37] was not retrieved by this facet when replicated by the ERG. It is unclear how this study was identified. Five further studies were only retrieved by the general text term **cholesterol.** It is unclear if using this term adequately compensated for the inaccurate and restricted range of terms that were used**.**

Additional comments on the search strategies are:

- Unlike EMBASE, MEDLINE does not have specific MeSH terms for most of the included statins. More general MeSH should have therefor been used - ***Hydroxymethylglutaryl-CoA Reductase Inhibitors/*** and **Anticholesteremic Agents/**
- The search for RCTs in MEDLINE and EMBASE includes the relevant thesaurus terms and a range of free text terms that are used in the Cochrane Highly Sensitive Search Strategy. However the MEDLINE search did not incorporate all the terms from the MEDLINE filter (***drug therapy.fs***, ***groups.ab***).

The ERG notes that there is a discrepancy in the number of hits obtained before removal of the duplicates in the flow diagram (N=1775) as compared to the total number of hits obtained by the searches as detailed in Appendix 4 (N=414 +1044+362= 1820). This difference may be due to restricting the searches to publications published after 1990, which has not been reported in Appendix 4.
The company submission states that no relevant ongoing studies were identified but no information was given as to what searching was undertaken to establish this.

4.1.2 Inclusion criteria

The company's systematic review of effectiveness involves two discrete comparisons: ezetimibe monotherapy versus placebo and ezetimibe in combination with a statin versus statin alone. There are, therefore, two distinct sets of inclusion criteria applied in the company's systematic review of clinical evidence. These are presented in Tables 4 and 5.

Table 4 Inclusion criteria used in the systematic review of clinical effectiveness: ezetimibe monotherapy (reproduced from Table 13 of the company's submission)

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Adults >18 years with primary hypercholesterolaemia	Adults with homozygous familial hypercholesterolaemia Adults with homozygous sitosterolaemia Secondary hypercholesterolaemia Paediatric populations
Intervention	Ezetimibe 10 mg (ezetimibe, ezetrol, zetia, vytorin, inegy)	Other lipid modifying therapy (nicotinic acid, bile acid sequestrants, fibrates, omega-3 fatty acids)
Comparators	Placebo	
Outcomes	LDL-c reduction (mean % change from baseline) TC reduction (mean % change from baseline) Apolipoprotein B Lipoprotein (a) Adverse Events (AEs and serious AEs)	
Study design	RCTs > 12 weeks	Non-RCTs
Language restrictions	English	
Other	Studies from 1990 onwards	

Table 5 Inclusion criteria used in the systematic review of clinical effectiveness: ezetimibe in combination with a statin (reproduced from Table 14 of the company's submission)

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Adults >18 years with primary hypercholesterolaemia	Adults with homozygous familial hypercholesterolaemia Adults with homozygous sitosterolaemia Secondary hypercholesterolaemia Pediatric populations
Intervention	Ezetimibe 10 mg + atorvastatin 10 -80 mg Ezetimibe 10 mg + simvastatin 10-80 mg Ezetimibe 10 mg + pravastatin 10-40 mg Ezetimibe 10 mg + fluvastatin 20-80 mg Ezetimibe 10 mg + rosuvastatin 5-40 mg	Other LMT (nicotinic acid, bile acid sequestrants, fibrates, omega-3 fatty acids)
Comparators	Matching statin dose: Atorvastatin 10 - 80 mg Simvastatin 10 - 80 mg Pravastatin 10 - 40 mg Fluvastatin 20 - 80 mg Rosuvastatin 5 - 40 mg	
Outcomes	LDL-c reduction (mean percentage change from baseline) TC reduction (mean percentage change from baseline) Apolipoprotein B Lipoprotein (a) Adverse Events (AEs and serious AEs)	
Study design	RCTs > 12 weeks	Non-RCTs
Language restrictions	English	
Other	Studies from 1990 onwards	

The company's inclusion criteria for the ezetimibe monotherapy population specify the intervention as "ezetimibe 10 mg (ezetimibe, ezetrol, zetia, vytorin, inegy)". However, both vytorin and inegy should be regarded as combination therapy rather than monotherapy since, according to the Summary of Product Characteristics (SmPC), they contain 10mg ezetimibe and 20mg simvastatin. The ERG assumes that inegy and vytorin have been included in Table 13 (page 62 of the company's submission) by mistake.

The inclusion criteria did not refer to various outcomes listed by the company in Table 1 (definition of the decision problem), page 12 of the company's submission such as survival, cardiovascular events, stroke and health-related quality of life. At clarification, the company confirmed that CV events and survival/mortality were eligible for inclusion in the systematic review of clinical effectiveness.

The company's systematic review of clinical evidence includes only RCTs published in English from 1990.

Within the eligibility criteria used for the systematic review of clinical evidence (Table 13, page 62 of the submission) the company indicates "*RCTs > 12 weeks*", which, in theory, would preclude inclusion of trials of 12 weeks duration. However, in the text of the submission (page 62 and then page 69) they state that "*RCTs with a treatment period of 12 weeks or greater were included*". Considering that a number of studies included in the systematic review of clinical evidence were of 12 weeks duration, the ERG assumes that the text of the submission reflects the correct approach.

4.1.3 Identified studies

From the results of the search strategies the company identified 26 relevant RCTs assessing either ezetimibe monotherapy versus placebo (n=15) or ezetimibe plus a statin versus a matching statin dose (n=20), with some RCTs relevant to more than one comparison. The clinical trial report from the IMPROVE-IT trial,[3] published on 3 June 2015, was subsequently added to the selected set of trials. It is worth pointing out that prior to the report of the systematic review of clinical evidence, the company describes (pages 52-61) three studies which assess the effectiveness of ezetimibe in

reducing CV events in distinct patient populations: the IMPROVE-IT trial (simvastatin plus ezetimibe versus simvastatin plus placebo in people with acute coronary syndrome),[3] the SHARP trial (simvastatin plus ezetimibe versus placebo versus simvastatin in people with CKD)[6] and the SEAS trial (simvastatin plus ezetimibe versus placebo in people with aortic stenosis).[7] Information on the way these studies were identified is not given. The SEAS trial would not have been retrieved by the company search strategy. It is worth noting that both the IMPROVE-IT and the SEAS studies were sponsored by Merck and that for the SHARP trial Merck is listed as collaborator.

The company explains (page 64 of the submission) that the clinical trial report (not the published study) of the IMPROVE-IT trial, sponsored by Merck, was added to the set of selected studies in order "*to complete the evidence base"* for this appraisal. However, the company cited the published study later in the text of the submission. No information is given on whether published data were available at the time of the original search (9 March 2015, Appendix 4), or if unpublished data were included in the systematic review of clinical evidence. The IMPROVE-IT trial does not fulfil the eligibility criteria specified by the company (i.e. the patient population does not necessarily have primary hypercholesterolaemia) but, nonetheless, appears to be relevant to clinical practice as focuses on prevention of CV events.

Explicit reasons why the SHARP and SEAS trials were not added to the set of initially selected studies were not provided.

The ERG noted that two of the studies selected from the literature[38, 39] were duplicate publications of original trials already included in the systematic review of clinical evidence. The study of Sager and colleagues[39] is a secondary analysis of the Davidson and colleagues trial.[40] The Knopp and colleagues 2001 abstract[38] appeared to report the same study as the Knopp and colleagues 2003 publication.[41] At clarification, the company confirmed that these two studies were duplicate publications and submitted revised meta-analyses in which these studies had been removed. Therefore, the studies by Knopp and colleagues[38] and Sager and colleagues[39] are no longer included or described in this report. The total number of assessed studies is therefore **25** (**24 selected studies plus the IMPROVE-IT trial**).

Sixty-three studies were excluded by the company during full-text assessment. Common reasons for exclusion are given in Appendix 4 of the company submission: study design (25 studies), population (14 studies), outcomes (12 studies), comparators (2 studies) and other reasons (10 studies).

A number of studies included in the systematic review of clinical effectiveness[3, 36, 37, 42-46] involve patients who do not necessarily have a diagnosis of primary hypercholesterolaemia and therefore do not fulfil the stated inclusion criteria for this appraisal. At clarification, the company justified their inclusion by arguing that these patient populations are at high risk of CVD and nonetheless relevant to clinical practice.

The ERG identified the 12-week RCT by Kerzner and colleagues[47] which compared ezetimibe versus lovastatin versus ezetimibe plus lovastatin versus placebo in people with primary hypercholesterolaemia. This study does not appear on the company's list of excluded studies and, therefore, the reason for its exclusion from the systematic review of clinical evidence is unclear. As this trial reports data for ezetimibe versus placebo, the ERG is of the opinion that it should have been included in the current review.

Similar to this appraisal, the previous TA132[15] excluded studies of less than 12 weeks and included trials that enrolled people with primary hypercholesterolaemia as well as mixed populations of people with and without a history of CVD. It is worth mentioning that the number of included studies differs between the two appraisals due to some differences in the stated inclusion criteria (see Table 6 of the company's submission). In particular, one study[43] included in the current appraisal was previously excluded because the patient population presented with mixed hyperlipidaemia. At clarification, the company justified inclusion of this study by stating that the patient population had *"mixed hyperlipidaemia (elevated LDL-c and TG) with/without diabetes and CV risk <20% with a mean baseline LDL-c of 4.2 and 4.1 mm/L in the placebo and ezetimibe arm, respectively".*

4.1.4 Characteristics of included RCTs

The majority of the included RCTs involved an active treatment duration of 12 weeks.[34, 36, 40-43, 46, 48-59] Active treatment in the remaining trials was 39 weeks,[44] 48 weeks,[60] 52 weeks[37, 45] or 2 years.[4] The IMPROVE-IT trial specified a minimum 2.5 year follow-up for each patient.[3]

Seven trials reported being single-centre studies (Clement 2014 [India],[42] Habara 2014 [Japan],[44] Kinouchi 2013 [Japan],[45] Krysiak 2012a [Poland],[53] Krysiak 2012b [Poland],[54] Stojakovic 2012 [Austria],[36] Zinellu 2012 [Italy].[37] Two trials did not report the number of centres involved.[52, 55] The remaining trials, including the IMPROVE-IT trial, were multi-centre.[3, 4, 34, 40, 41, 43, 46, 48-51, 56-60]

Thirteen trials in the company's submission involved a comparison of ezetimibe monotherapy to placebo.[34, 40-43, 49-54, 56, 59] Table 46 in Appendix 1 presents the study characteristics of the 13 ezetimibe monotherapy trials.

Thirteen studies in the company's systematic review of clinical evidence compared ezetimibe co-administered with simvastatin to matched simvastatin doses.[3, 4, 37, 40, 51-55, 57-60] A further seven studies compared co-administration of other statins and ezetimibe to matching statin doses; the alternative statins were atorvastatin,[49] fluvastatin[36, 44-46, 48] and pravastatin.[56] The study characteristics of these studies are presented in Table 47 in Appendix 1.

Table 6 presents baseline demographics of participants enrolled in ezetimibe monotherapy trials while Table 7 presents those on participants enrolled in ezetimibe/statin combination trials. Where baseline LDL-c values were reported in mmol/L, the formula recommended by Heart UK (http://heartuk.org.uk/files/uploads/documents/huk_fs_mfsP_cholestrigly_leverlsconversion.pdf) was used to convert to mg/dL (mmol/l x 38.6).

In general, mean baseline LDL-c levels were balanced within individual trials but there was wide variation between trials. In the 13 ezetimibe monotherapy trials, values in the ezetimibe groups ranged from 144.1 mg/dL[42] to 181.3 mg/dL.[40] In the placebo groups, values were between 133 mg/dL[42] and 179 mg/dL.[54] In the

ezetimibe/statin combination trials, LDL-c values in the ezetimibe/statin groups ranged from 93.8 mg/dL (IMPROVE-IT trial)[3] to 319 mg/dL (Kastelein and colleagues trial).[4] In the statin only groups, values ranged from 93.8 mg/dL (IMPROVE-IT trial)[3] to 317.8 mg/dL (Kastelein and colleagues trial).[4] It is worth noting that participants in the IMPROVE-IT trial had acute coronary syndrome, whilst those in the Kastelein and colleagues[4] trial had familial hypercholesterolaemia.

Table 6 Baseline characteristics of participants in ezetimibe monotherapy trials

Study ID	Mean (SD) age, years	Male, %	Mean (SD) BMI, kg/m^2	Ethnicity, %	Mean (SD) baseline LDL-c	CVD history/risk factors
Ballantyne 2003[49]				White, %	Mmol/L [mg/dl]	Hypertension/diabetes/CHD, %
Ezetimibe 10mg (n=65)	56.7 (11.7)	45	NR	88	4.53 (SEM 0.07) [174.9]	37/3/9
All atorvastatin (n=248)	57.8 (11.7)	38	NR	83	4.65 (SEM 0.04) [179.5]	32/4/9
All ezetimibe + atorvastatin (n=255)	58.7 (11.4)	42	NR	87	4.65 (SEM 0.04) [179.6]	33/7/9
Placebo (n=60)	56.9 (12.1)	48	NR	82	4.60 (SEM 0.07) [177.6]	38/2/8
Bays 2001[34]				White/black/ Asian, %	Mg/dL	
Ezetimibe 10mg (n=46)	58.7 (range 39-74)	43.5	NR	89.1/6.5/4.3	176.7	NR
Placebo (n=52)	57.1 (range 32-74)	59.6	NR	90.4/7/7/1.9	171.0	NR
Bays 2004[59]				White/black/ Hispanic, %	Mg/dL	
Ezetimibe 10mg (n=149)	55.5 (11.0)	45.6	28.4 (5.1)	89.3/2.7/2.7	179.9 (23.1)	NR
All simvastatin (n=62)	54.9 (11.2)	49.4	28.3 (5.1)	87/3.4/2.7	177.5 (25.3)	NR
All ezetimibe + simvastatin (n=609)	56.4 (10.6)	48.6	27.9 (4.6)	88.7/3.1/1.3	176.2 (24.8)	NR
Placebo (n=148)	56.0 (10.8)	43.9	28.0 (4.9)	89.2/3.4/1.4	177.9 (22.8)	NR
Clement 2014[42]						
Ezetimibe 10mg (n=22)	28.9	100	27	NR	144.1	NR
Simvastatin 20mg (n=20)	31.3	100	28.5	NR	134.4	NR
Placebo (n=21)	29.6	100	27.1	NR	133	NR
Davidson 2002[40]	Mean (range)			White/black/ Hispanic, %	Mg/dL	Hypertension/diabetes/CHD, %
Ezetimibe 10mg (n=61)	60.3 (35-84)	39	NR	95/2/3	181.3	

Study ID	Mean (SD) age, years	Male, %	Mean (SD) BMI, kg/m^2	Ethnicity, %	Mean (SD) baseline LDL-c	CVD history/risk factors
All simvastatin (n=263)	56.4 (25-87)	42	NR	90/5/5	178.5	30/8/5
Ezetimibe + all simvastatin (n=263)	57.6 (27-83)	46	NR	91/4/3	176.3	29/3/6 30/3/8
Placebo (n=70)	58.8 (25-84)	44	NR	96/1/1	177.4	30/9/7
Dujovne 2002[50]	Mean (range)		Mean (range)	White/black,/ Asian/hispanic	Mg/dL	Approx 1/3 had family history of coronary artery
Ezetimibe 10mg (n=666)	57.9 (18-85)	50	28.6 (17.5-47)	90/5/1/3	168	disease, and approx. 1/3 had
Placebo (n=226)	58.1 (30-85)	45	28.4 (19.4-49.5)	93/4/1/1	168	some degree of hypertension
Farnier 2005[43]					Mmol/L [mg/dl]	Diabetes/metabolic syndrome, %
Ezetimibe 10mg (n=187)	53.5 (9.2)	62.6	29.3 (4.5)	NR	4.1 [158.3]	18.8/54.6
Placebo (n=64)	54.5 (10.8)	62.5	29.7 (4.9)	NR	4.2 [162.1]	18.8/57.1
Goldberg 2004[51]	<65/≥65, %			White/black/ hispanic	<160/≥160, %	
Ezetimibe 10mg (n=92)	79/21	38	NR	77/7/10	32/68	NR
All simvastatin (n=349)	77/23	49	NR	79/4/10	31/69	NR
All ezetimibe + simvastatin (n=353)	75/25	48	NR	83/3/9	34/66	NR
Placebo (n=93)	71/29	41	NR	81/5/9	32/68	NR
Knopp 2003[41]	Mean (range)			White/black/ Asian/hispanic	Mmol/L [mg/dl]	Hypertension/diabetes/MI/CHD
Ezetimibe 10mg (n=622)	58.3 (20-86)	49	29.1 (17.8-49.6)	91/5/1/2	4.27 [164.8]	
Placebo (n=205)	57.6 (24-79)	46	29.6 (19.4-45.7)	88/6/<1/5	4.25 [164.1]	36/6/4/8 32/4/1/3
Krysiak 2011[52]					Mg/dL	HeFH/mild hypertension, %
Ezetimibe 10mg (n=33)	53.4 (3)	61	27.9 (2.3)	NR	178	6/24
Simvastatin 40mg (n=32)	54.3 (3.4)	56	27.6 (2.8)	NR	182	6/25
Ezetimibe + simvastatin (n=32)	54.5 (3.6)	59	28.1 (2.1)	NR	183	3/25
Placebo (n=30)	52.3 (2.4)	60	28.4 (2.5)	NR	175	3/23

Study ID	Mean (SD) age, years	Male, %	Mean (SD) BMI, kg/m^2	Ethnicity, %	Mean (SD) baseline LDL-c	CVD history/risk factors
Krysiak 2012a[53]					Mg/dL	Mild hypertension/stable coronary artery disease, %
Ezetimibe 10mg (n=24)	53.2 (3.2)	58.3	28.1 (2.4)	NR	177.8	25/16.7
Simvastatin 40mg (n=25)	53.9 (3.5)	56	27.9 (2.6)	NR	182	24/20
Ezetimibe + simvastatin (n=25)	54.2 (3.8)	60	28.3 (2.3)	NR	181.7	28/20
Placebo (n=24)	52.4 (2.2)	54.2	28.6 (2.3)	NR	174.9	25 20.8
Kyrsiak 2012b[54]Ezetimibe 10mg (n=43)	50 (3)	60	27.9 (2.8)	NR	Mg/dL 181	Mild hypertension, % 14
Simvastatin 40mg (n=44)	51 (4)	55	28.2 (3.2)	NR	183	16
Ezetimibe + simvastatin (n=42)	52 (4)	57	27.7 (2.5)	NR	182	12
Placebo (n=41)	51 (3)	56	27.8 (2.6)	NR	179	15
Melani 2003[56]	Mean (range)			White/black/ hispanic/Asian	Mmol/L [mg/dl]	Hypertension/diabetes/CHD, %
Ezetimibe 10mg (n=64)	52 (26-75)	36	NR	94/5/2/0	4.6 [177.6]	
All pravastatin (n=205)	55.1 (23-84)	49	NR	85/6/7/1	4.6 [177.6]	31/2/3
Ezetimibe + all pravastatin (n= 204)	56.9 (20-86)	41	NR	86/5/5/2	4.6 [177.6]	31/7/8 32/5/8
Placebo (n=65)	53.4 (32-76)	48	NR	80/9/2/9	4.6 [177.6]	23/3/3

Table 7 Baseline characteristics of participants in ezetimibe/statin combination trials

Study ID	Mean (SD) age, years	Male, %	Mean (SD) BMI, kg/m^2	Ethnicity	Mean (SD) baseline LDL-c	CVD history/risk factors
Atorvastatin studies (n=1)						
Ballantyne 2003[49]				White, %	Mmol/L [mg/dl]	Hypertension/diabetes/CHD, %
Ezetimibe 10mg (n=65)	56.7 (11.7)	45	NR	88	4.53 (SEM 0.07) [174.9]	37/3/9
All atorvastatin (n=248)	57.8 (11.7)	38	NR	83	4.65 (SEM 0.04) [179.5]	32/4/9
All ezetimibe + atorvastatin (n=255)	58.7 (11.4)	42	NR	87	4.65 (SEM 0.04) [179.5]	33/7/9
Placebo (n=60)	56.9 (12.1)	48	NR	82	4.60 (SEM 0.07) [177.6]	38/2/8
Fluvastatin studies (n=5)						
Alvarez-Sala 2008[48]					Mmol/L [mg/dl]	Hypercholesterolaemia/ hypertension/MI/diabetes, %
Ezemitibe + fluvastatin XL (n=38)	50.8 (13.5)	47.4	NR	NR	5.1 [196.9]	94.7/28.9/2.6/0
Fluvastatin XL (n=44)	49.3 (10.6)	40.9	NR	NR	5.6 [216.2]	90.9/36.4/2.3/2.3
Habara 2014[44]				Japanese, %	Mg/dL	Hypertension/diabetes, %
Ezetimibe + fluvastatin (n=32)	69.8 (7.8)	65	24.5 (3)	100	122.5	71/34
Fluvastatin (n=31)	68.8 (7.8)	83	23.5 (4)	100	109.1	58/41
Kinouchi 2013[45]				Japanese, %	Mg/dL	Hypertension/diabetes/ hyperuricaemia, %
Ezetimibe + fluvastatin (n=28)	55.2 (12)	71.4	24.7 (2.5)	100	159	64.3/3.6/42.9
Fluvastatin (n=26)	53.4 (11.4)	61.5	24.9 (7.2)	100	156	84.6/7.7/26.9
Stein 2008[46]				White, %	Mg/dL	High risk, %
Ezetimibe 10mg (n=66)	61.4 (10.1)	42	28.4 (4.8)	98	176.2	42
Ezetimibe + fluvastatin XL (n=64)	61 (10.5)	48	29.2 (4.4)	98	172.9	47
Fluvastatin XL (n=69)	60.6 (9.7)	52	28.2 (4.2)	100	174.2	48

Study ID	Mean (SD) age, years	Male, %	Mean (SD) BMI, kg/m^2	Ethnicity	Mean (SD) baseline LDL-c	CVD history/risk factors
Stojakovic 2010[36]					Mg/dL	CVD/diabetes/arterial hypertension, %
Ezetimibe + fluvastatin (n=56)	62 (9)	71	29.3 (4.7)	NR	112	34/88/82
Fluvastatin (n=28)	65 (9)	50	28.6 (5.2)	NR	102	54/96/93
Pravastatin studies (n=1)						
Melani 2003[56]	Mean (range)			White/black/ hispanic/Asian	Mmol/L [mg/dl]	Hypertension/diabetes/CHD, %
Ezetimibe 10mg (n=64)	52 (26-75)	36	NR	94/5/2/0	4.6 [177.6]	31/2/3
All pravastatin (n=205)	55.1 (23-84)	49	NR	85/6/7/1	4.6 [177.6]	31/7/8
Ezetimibe + all pravastatin (n= 204)	56.9 (20-86)	41	NR	86/5/5/2	4.6 [177.6]	32/5/8
Placebo (n=65)	53.4 (32-76)	48	NR	80/9/2/9	4.6 [177.6]	23/3/3
Simvastatin studies (n=13)						
Bays 2004[59]				White/black/ Hispanic, %	Mg/dL	
Ezetimibe 10mg (n=149)	55.5 (11.0)	45.6	28.4 (5.1)	89.3/2.7/2.7	179.9 (23.1)	NR
All simvastatin (n=62)	54.9 (11.2)	49.4	28.3 (5.1)	87/3.4/2.7	177.5 (25.3)	NR
All ezetimibe + simvastatin (n=609)	56.4 (10.6)	48.6	27.9 (4.6)	88.7/3.1/1.3	176.2 (24.8)	NR
Placebo (n=148)	56.0 (10.8)	43.9	28.0 (4.9)	89.2/3.4/1.4	177.9 (22.8)	NR
Davidson 2002[40]	Mean (range)			White/black/ Hispanic, %	Mg/dL	Hypertension/diabetes/CHD, %
Ezetimibe 10mg (n=61)	60.3 (35-84)	39	NR	95/2/3	181.3	30/8/5
All simvastatin (n=263)	56.4 (25-87)	42	NR	90/5/5	178.5	29/3/6
Ezetimibe + all simvastatin (n=263)	57.6 (27-83)	46	NR	91/4/3	176.3	30/3/8
Placebo (n=70)	58.8 (25-84)	44	NR	96/1/1	177.4	30/9/7
Goldberg 2004[51]	<65/≥65, %			White/black/ hispanic	<160/≥160, %	
Ezetimibe 10mg (n=92)	79/21	38	NR	77/7/10	32/68	NR
All simvastatin (n=349)	77/23	49	NR	79/4/10	31/69	NR
All ezetimibe +	75/25	48	NR	83/3/9	34/66	NR

Study ID	Mean (SD) age, years	Male, %	Mean (SD) BMI, kg/m^2	Ethnicity	Mean (SD) baseline LDL-c	CVD history/risk factors
simvastatin (n=353)						
Placebo (n=93)	71/29	41	NR	81/5/9	32/68	NR
IMPROVE-IT 2015[3]				White, %	Mg/dL	Diabetes/hypertension/ congestive heart failure/PAD/ previous MI/PCI/CABG, %
Ezetimibe + simvastatin (n=9067)	63.6 (9.7)	75.5	28.3 (5.2)	83.6	93.8	27.1/61.6/4.6/5.4/21.3/19.5/9.3
Simvastatin (n=9077)	63.6 (9.8)	75.9	28.3 (5.2)	84	93.8	27.3/61.3/4.1/5.7/20.7/19.8/9.3
Kastelein 2008[4]					Mg/dL	Diabetes/hypertension/MI, %
Ezetimibe + simvastatin (n=357)	46.1 (9)	53.5	27.4 (4.6)	NR	319	2.2/18.8/28.6
Simvastatin (n=363)	45.7 (10)	49.3	26.7 (4.4)	NR	317.8	1.4/14/28.7
Krysiak 2011[52]					Mg/dL	HeFH/mild hypertension, %
Ezetimibe 10mg (n=33)	53.4 (3)	61	27.9 (2.3)	NR	178	6/24
Simvastatin 40mg (n=32)	54.3 (3.4)	56	27.6 (2.8)	NR	182	6/25
Ezetimibe + simvastatin (n=32)	54.5 (3.6)	59	28.1 (2.1)	NR	183	3/25
Placebo (n=30)	52.3 (2.4)	60	28.4 (2.5)	NR	175	3/23
Krysiak 2012a[53]					Mg/dL	Mild hypertension/stable coronary artery disease, %
Ezetimibe 10mg (n=24)	53.2 (3.2)	58.3	28.1 (2.4)	NR	177.8	25/16.7
Simvastatin 40mg (n=25)	53.9 (3.5)	56	27.9 (2.6)	NR	182	24/20
Ezetimibe + simvastatin (n=25)	54.2 (3.8)	60	28.3 (2.3)	NR	181.7	28/20
Placebo (n=24)	52.4 (2.2)	54.2	28.6 (2.3)	NR	174.9	25/20.8
Krysiak 2012b[54]					Mg/dL	Mild hypertension, %
Ezetimibe 10mg (n=43)	50 (3)	60	27.9 (2.8)	NR	181	14
Simvastatin 40mg (n=44)	51 (4)	55	28.2 (3.2)	NR	183	16
Ezetimibe + simvastatin (n=42)	52 (4)	57	27.7 (2.5)	NR	182	12
Placebo (n=41)	51 (3)	56	27.8 (2.6)	NR	179	15

Study ID	Mean (SD) age, years	Male, %	Mean (SD) BMI, kg/m^2	Ethnicity	Mean (SD) baseline LDL-c	CVD history/risk factors
Krysiak 2014[55]					Mg/dL	Grade 1 hypertension, %
Ezetimibe + simvastatin (n=21)	52.5 (3.5)	57	26.9 (2.2)	NR	184	29
Simvastatin (n=23)	51.9 (2.7)	61	26.5 (2.6)	NR	186	22
Placebo (n=21)	51.1 (2.6)	57	27.2 (2.6)	NR	178	29
Masana 2005[60]				White/black/ hispanic/Asian	Mg/dL	
Ezetimibe + simvastatin (n=355)	59 (range 22-84)	57	29.2 (5.2)	91/6/2/<1	136.6	NR
Simvastatin + placebo (n=78)	61 (range 28-83)	55	29.6 (6.1)	94/3/1/3	131.4	NR
Rodney 2006[57]				Black, %	Mg/dL	Diabetes/CHD/CV risk≥2, %
Ezetimibe + simvastatin (n=124)	55.2 (11.6)	39	31.3 (5.9)	100	176.5	21/10/49
Simvastatin (n=123)	53.7 (11.5)	38	31 (5.7)	100	174.7	16/11/54
Shankar 2007[58]				Indian, %	Mg/dL	Metabolic syndrome/ hypertension/CHD
Ezetimibe + simvastatin (n=114)	52.2 (12.2)	61	NR	100	130.5	60/35/75
Simvastatin (n=116)	51.5 (10.1)	64	NR	100	125.5	61/33/73
Zinellu 2012[37]					Mg/dL	CKD, %
Ezetimibe + simvastatin 20mg (n=10)	58 (12)	60	NR	NR	230	100
Ezetimibe + simvastatin 40mg (n=10)	59 (9)	50	NR	NR	254	100
Simvastatin 40mg (n=10)	63 (11)	80	NR	NR	232	100

4.1.5 Critique of data extraction

The company followed the general principles recommended by the University of York Centre for Reviews and Dissemination (CRD) to assess current evidence. The ERG considers the methods described in this publication to be appropriate. Title/abstract screening and full text screening were carried out by two independent reviewers, with any disagreements resolved by discussion. The data extraction process used by the company and the number of reviewers involved are not detailed in the submission as well as the number of reviewers involved in the quality assessment of the selected studies.

4.1.6 Quality assessment

Risk of bias of included studies was based on an adaptation of the criteria specified in the CRD guidelines. The criteria involved assessment of selection bias, performance bias, detection bias, attrition bias and reporting bias and this is considered appropriate by the ERG.

A check by the ERG of the risk of bias of a sub-set of trials included in the submission revealed some inconsistencies. For example, randomisation in the Krysiak and colleagues 2014 study[55] was assessed as appropriate by the company whilst in fact "pseudorandomisation" was carried out, in which some participants self-selected into the placebo group and the remainder were allocated based on their date of birth. These methods of sequence generation are not considered appropriate (see the Cochrane Handbook of Systematic Reviews of Intervention).[61] A further assessment used by the company was, "*Were the care providers, participants, and outcome assessors blind to treatment allocation?"* The ERG noted that some studies which were assessed as fulfilling this criterion were, in fact, described as "double blind" and outcome assessors were not blinded.[4, 43, 49, 51]

According to the company's assessment of risk of bias, the majority of trials included in the systematic review of clinical evidence were conducted with appropriate randomisation and concealment of allocation methods, blinding procedures, balance of groups at baseline, and treatment of missing data and analyses.

The ERG conducted a broad assessment of the methods used by the company for the systematic review of clinical evidence using the CRD criteria. Results are presented in Table 8.

Table 8 Quality assessment of the company's systematic review of evidence

CRD quality item	Score
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes
2. Is there evidence of a substantial effort to search for all of the relevant research?	No
3. Is the validity of included studies adequately assessed?	No
4. Are sufficient details of the individual studies presented?	Yes
5. Are the primary studies summarised appropriately?	Yes

Overall, the inclusion and exclusion criteria reported by the company appear comprehensive and appropriate. However, the consistency of application of the inclusion criteria is questionable, with a number of studies not fulfilling entirely the eligibility criteria in terms of population being included in the review (i.e. patients do not have necessarily a diagnosis of primary hypercholesterolaemia). The ERG noted the apparent lack of CV outcomes but their inclusion was later confirmed by the company at clarification. In addition, the company's search strategies did not appear to be properly designed to identify additional trials focusing on prevention on CV events. These inaccuracies raise some concerns about the reliability of the systematic review process.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

Of the **25** included studies:

- 13 compared ezetimibe monotherapy to placebo
- 13 compared ezetimibe as an add-on to simvastatin
- 1 compared ezetimibe as an add-on to atorvastatin
- 5 compared ezetimibe as an add-on to fluvastatin
- 1 compared ezetimibe as an add-on to pravastatin

It worth noting that some multi-arm studies were included in more than one of these comparisons.

All trials included ezetimibe with a dose of 10 mg, but statin doses varied in the included trials and some studies included multiple arms comparing various doses of statin such as 10, 20, 40 and 80 mg.

Meta-analyses have been conducted for two comparisons:

- Ezetimibe 10 mg monotherapy versus placebo
- Ezetimibe 10 mg plus statin versus matching statin dose

The following outcomes have been assessed:

- Percentage change from baseline in LDL-c
- Percentage change from baseline in TC

Data for two additional outcomes, apolipoprotein B and lipoprotein (a), were also extracted and appear in Appendix 10 of the company's submission. Meta-analyses have not been conducted for these outcomes. No explicit reason for this choice is provided in the submission, although it appears from Appendix 10 that data were not always available and, in particular, standard deviations were often missing.

The pooled results from the four main conducted meta-analyses are shown in Table 9. The original results came from Figures 6-8 and 11 of the company's submission but updated analyses were presented in Figures 1-4 of the company's response to the ERG clarification letter (the ERG noticed that possible double counting of study data and inconsistent inclusion of studies conducted in India might have occurred). In each case a random effects model was used and meta-analyses were based on mean differences in percentage change scores. The results show evidence of benefits in favour of greater lowering of LDL-c and TC for ezetimibe versus placebo and for ezetimibe plus statin versus matching statin dose.

Table 9 Results of the meta-analyses for percentage change in LDL-c and TC (Figures 1-4 of the response to clarification)

	Ezetimibe versus placebo	Ezetimibe plus statin versus matching statin dose
	Mean difference (95% CI)	**Mean difference (95% CI)**
% change in LDL-c	-20.59 (-22.13 to -19.05)	-15.60 (-17.06 to -14.13)
% change in TC	-16.07 (-17.01 to -15.13)	-12.17 (-12.90 to -11.45)

Values less than zero favour ezetimibe or ezetimibe plus statin

Each of these meta-analyses showed high levels of statistical heterogeneity (I^2>99%). This means that there were very high levels of inconsistency between the trials included in the meta-analyses (95% confidence intervals for different trials rarely overlap).

For the percentage change in LDL-c and TC for ezetimibe plus statin versus matching statin dose three meta-analyses have been presented with studies split into subgroups: first by the type of statin, second by the dose of statin (for simvastatin studies only) and third by diabetes status (for studies reporting diabetic and non-diabetic subgroups). At clarification, the results by type of statin were updated to reflect the errors in the original submission. Broadly consistent results were shown in each of these subgroup analyses.

The ERG was somewhat concerned that some aspects of the systematic review process do not appear to be clearly reproducible. For example, there was no clear information about the handling of arms with different statin doses and the inclusion of data from different time points and this made it challenging for the ERG to double check a sample of the extracted data. At clarification, the company clarified that the statin arms had been pooled and that they had used the time point used in the primary analysis of the publication and that time points less than 12 weeks had not been used.

The ERG did not attempt to perform a systematic check of all data that had been extracted for the meta-analyses, but a small number of studies were checked and the following inconsistencies were noted:

- Alvarez-Sala 2008:[48] The number of patients in the treatment groups (N) provided for this study (38 in the ezetimibe + fluvastatin group and 44 in the fluvastatin group) do not match those presented in Figure 2 of the published paper (37 and 39, respectively). Additionally, apolipoprotein B is designated as "not reported" in Appendix 10 of the company's submission, even though data are apparently available in Figure 2 of the published paper.
- Bays 2001 arm A and Bays 2001 arm B:[34] There is an apparent inconsistency between the numbers of patients in the ezetimibe and placebo groups shown in Figure 6 of the submission and those reported in the table entitled 'Baseline LDL-c and mean % change' in Appendix 10 (numbers appear to have been swapped over).

The company's primary meta-analyses exclude trials with 100% Japanese or Indian participants. The results including these trials are reported in Appendix 11 of the submission and were subsequently updated during the clarification process. Results presented in Appendix 11 were broadly consistent with those reported in the main submission, which did not include these trials. The ERG noticed that only three of the four trials conducted in Japan or India had actually been excluded from the main analyses while the Clement 2014 study,[42] conducted in India, was still included. During the clarification process, the company agreed to exclude this study from the analyses. A further three studies including East Asian or South Asian populations had also been included in the analyses. At clarification, the company maintained that these trials had enrolled between 77% and 88% of people of white ethnicity and therefore representative of UK demographics.

Results of three subgroup analyses for three distinct patient subgroups are also presented, although, surprisingly, no meta-analyses have been performed. Only four studies could be included in the subgroup analyses for primary prevention in people with diabetes[41, 51, 57, 59] and only one each in the other two subgroups - people with

CKD[37] and people with HeFH.[4] The results of the subgroup analyses were broadly consistent with the main results.

An alternative way of reporting the results of the statin add-on analyses is presented in Appendix 12. This summary, referred to as the % incremental reduction for ezetimibe was calculated for each study. The reductions were then pooled using a weighted average. The resulting incremental reduction of 23.5% is reported in various places in the submission but is not used in the cost-effectiveness model. The ERG agrees with the formulae supplied by the company at clarification, but did not attempt to double check that the data for this calculation had been extracted correctly.

It is worth noting that the company does not present meta-analyses of clinical outcomes in their submission. Indeed, clinical outcomes were not part of the eligibility criteria given for the systematic review of clinical evidence (Tables 13 and 14 of the submission). However, at clarification, the company explained that cardiovascular and survival outcomes were considered eligible for inclusion. The ERG noted that the trial by Kastelein and colleagues[4] reported cardiovascular events but this was not mentioned in the company's submission. The ERG also identified a recent systematic review and meta-analysis published by Battaggia and colleagues.[8] This review had a wider scope than the company's systematic review and among others included the SHARP and SEAS trials (both ezetimibe plus simvastatin versus placebo), which were only described narratively by the company at the start of the submission. The IMPROVE-IT trial was not available at the time the Battaggia and colleagues' review was conducted.

The company has used the Cholesterol Treatment Trialists' Collaboration (CTTC) meta-analysis to link the effect of lipid reduction to clinical events. The CTTC is a large collaboration which has performed meta-analyses of statin RCTs to evaluate the association between lipid reduction and the risk of coronary events and mortality. The most recent CTTC meta-analysis was published in 2010[2] and included data from over 170,000 participants in 26 randomised trials. An earlier report of the CTTC meta-analysis[26] was also used in TA132.[15]

The data extracted from the CTTC meta-analysis and presented in Table 29 of the company's submission come from Figures 2 and 5 of the 2010 CTTC publication.[2] Results for non-fatal MI and any stroke come from Figure 2 and are based on results for a 1 mmol/l reduction in LDL-c. Mortality results come from Figure 5 and the risk ratios for any vascular death and any non-vascular death have been extracted. Table 10 shows a summary of the data extracted for use in the economic model.

Table 10 Extracted data from the CTTC meta-analysis (Table 29 of the company's submission)

Endpoint	RR (95% CI), 1 mmol/l reduction in LDL-c
Non-fatal MI	0.74 (0.69, 0.78)
Stroke	0.85 (0.80, 0.90)
Any vascular death	0.86 (0.82, 0.90)
All non-vascular deaths	0.97 (0.91, 1.03)

The ERG noticed two apparent errors in the data extracted into Table 29. In Figure 2 of the CTTC report[2] the risk ratio for non-fatal MI is expressed using a 99% confidence interval, but this has been reported as a 95% confidence interval in Table 29 of the company's submission. The heading of the table mentions 96% CIs but this is assumed to be a typographical error. There also appears to be a typographical error in the extracted confidence interval for any non-vascular death (0.91 to 1.03 instead of 0.92 to 1.03).

The risk ratios for statin versus not treatment have been presented in Table 30 of the company's submission (page 119) and sourced from the review of clinical evidence conducted as part of CG181.

The company presented a narrative summary of adverse events in each trial but has not performed any standard meta-analysis. When considering the rate of adverse events, there were no clear differences between groups.

4.3 Critique of trials identified and included in the indirect comparison and/ or multiple treatment comparison

No indirect comparisons and/or multiple treatment comparisons were conducted by the company.

4.4 Critique of the indirect comparison and/ or multiple treatment comparison

No indirect comparisons and/or multiple treatment comparisons were conducted by the company.

4.5 Additional work on clinical effectiveness undertaken by the ERG

None.

4.6 Conclusions of the clinical effectiveness section

The ERG thought that most aspects of the review had been conducted to a high standard but had concerns about the following aspects of the report.

4.6.1 Scope of the review

The decision problem specified by NICE included two distinct populations of people with primary heterozygous familial or non-familial hypercholesterolaemia: those whose condition is not appropriately controlled with a statin alone and those in for whom a statin is considered inappropriate or is not tolerated. The company has considered two clinical situations – primary prevention for those with a 10-30% risk of developing CVD and secondary prevention for those with established CVD. At clarification, the company stated that this was decided after discussions with NICE.

The ERG asked the company to clarify the definition of primary hypercholesterolaemia considered for the review and to justify the inclusion of specific studies. The company confirmed that their definition could incorporate terms such as dyslipidaemia and explained that certain trials[3, 36, 37, 43] were included in the review as they included high-risk patient groups. The ERG was concerned that some included trials did not meet the final scope specified by NICE but recognised that the assessment of lowering LDL-c in high risk groups is relevant to clinical practice.

For the comparison with ezetimibe monotherapy, the company has also used different comparators to those in the final scope issued by NICE. Other lipid-regulating drugs are not considered among the relevant comparators. Placebo or no treatment is considered as a comparator even though not specified in the NICE final scope.
Of the plasma lipid and lipoprotein levels specified by NICE, formal meta-analysis has been performed only for LDL-c, although data were also extracted for apolipoprotein B and lipoprotein (a). Non-HDL cholesterol was not considered by the company on the basis that this was not routinely reported in ezetimibe trials. Meta-analyses were, however, conducted for total cholesterol.

Clinical outcomes such as mortality and cardiovascular events were considered as part of the inclusion criteria for this appraisal (confirmed at clarification) but not reported, although an attempt was made to link these to lowering of LDL-c levels through an external meta-analysis.

No attempt was made to consider revascularisation or quality of life within the main outcomes for the systematic review of clinical evidence, even though these were stated in the NICE final scope. Adverse events of treatment were considered in the company's systematic review.

The search strategy developed by the company lacked sensitivity (in fact failed to identify the Kerzner and colleagues' trial)[47] and was not specifically designed to identify studies that focused on prevention of CV events.

4.6.2 Heterogeneity

Each of the meta-analyses conducted on the LDL-c and TC outcomes showed high levels of statistical heterogeneity (I^2>99%). The company has used random effects rather than fixed effect models for these analyses, which do not assume that every study has the same underlying effect size. Nevertheless, the high I^2 statistic suggests that heterogeneity has a large impact on the results obtained and it is arguable whether combining results from the included trials was appropriate in this situation. Although the company has referred to the heterogeneity, there was no attempt to investigate reasons for the variable effects of the studies and no discussion of whether it was appropriate to use the meta-analyses estimates in the cost-effectiveness model.

4.6.3 Imputation of standard deviations

The company stated that when the standard error of the mean percentage change was not reported, a correlation coefficient of 0.50 was used in the formula to estimate this according to the methodology reported in the Cochrane Handbook[61] given that intraclass correlation coefficients may not be available. At clarification, the company explained that this value was chosen as it was the most conservative approach. It is not made clear how often this approach had to be applied and no sensitivity analyses on this assumption were made.

4.6.4 Opportunity to perform a network meta-analysis (NMA)

The ERG is of the opinion that a network meta-analysis (NMA) could have been performed for the purpose of this appraisal - this could have included different statin doses as separate treatments within the network as well as ezetimibe/statin combination therapy, placebo and other lipid-regulating drugs.

Instead, the company's analyses are restricted to two distinct questions on the benefit of ezetimibe over placebo and the extra benefit of ezetimibe over stain.

4.6.5 Exclusion of Asian studies

Even though Asian participants were not explicitly excluded according to the inclusion criteria for the review of clinical evidence (Tables 13 and 14 of the company's submission), the company chose to exclude studies with 100% Japanese and Indian participants from the primary analyses. These studies were later included in a sensitivity analysis presented in Appendix 11 of the submission. The company did not seem to apply this strategy consistently and one Indian study[42] was excluded from the analyses at clarification.

The ERG was concerned that the decision to exclude these studies may have been formulated after the formal exclusion criteria had been finalised and the rationale for excluding these patient populations was not backed up with appropriate references. The company argued that multicentre studies with Asian populations were not excluded as overall these included mainly people of white ethnicity. The CTTC meta-

analysis used in the economic model includes also studies conducted in Asia (e.g. the MEGA trial, which was based on an adult Japanese population).

4.6.6 Exclusion of studies < 12 weeks

Only studies of 12 weeks' duration or greater have been included in the review. The company stated (page 65 of the submission) that many studies were excluded *due to study length of fewer than 12 weeks*. At clarification, the company explained that this approach is consistent with previous TAs (e.g. TA132) and guidelines that focused on the efficacy of lipid-modifying therapy. Moreover, the company maintains that this allows the effects of the therapy to stabilise so that they can be adequately evaluated.

4.6.7 Data errors

The original submission included two instances where data from the same trial had been included twice in a meta-analysis. This was corrected at clarification. The inconsistent exclusion of only one of two Indian studies was also corrected at clarification.

The ERG found a number of discrepancies when checking the quality assessment, the extraction of data from the published articles and from the CTTC meta-analysis article. Individually each of these was generally minor and would be unlikely to affect the interpretation of the results, but the number of discrepancies found in the articles checked leads to some concerns about the robustness of the company's analyses.

4.6.8 Use of the CTTC meta-analysis

One of the reasons for revisiting this assessment after completion of TA132 was the current availability of clinical data from the IMPROVE-IT trial and other relevant trials. However, the way that the company has incorporated this evidence was not straightforward. Narrative results for three recent trials, IMPROVE-IT, SHARP and SEAS, which assess clinical outcomes, are provided at the start of Chapter 4, before the methods and results of the systematic review of clinical evidence are presented. The ERG was, therefore, unable to assess whether these studies were identified as part of a systematic review process or included in the submission because known by the company (the trials were either sponsored by Merck or conducted with Merck's collaboration). These three trials examine specific clinical populations and two of

them (SHARP and SEAS) do not meet the eligibility criteria for the company's main systematic review as they compare a combination of ezetimibe and simvastatin versus placebo. At clarification, the company stated that CV outcomes and survival/mortality were considered eligibility criteria for inclusion and that the IMPROVE-IT, SHARP and SEAS trials report relevant clinical outcomes for ezetimibe.

The ERG believes that it is regrettable that no attempt to perform a systematic review and meta-analysis of clinical outcomes was made. Instead, the company has assessed the effect of ezetimibe on clinical outcomes indirectly by using an external meta-analysis linking cholesterol lowering to clinical outcomes. This is the approach already used in the previous TA132.[15] In TA132, however, the decision to use the CTTC meta-analysis was based on the fact that no clinical data for ezetimibe were available. In addition, a formal process (Strategic Choice Approach) was used to identify the most appropriate method to evaluate the effects on clinical outcomes after considering competing approaches such as the Framingham model.

In contrast, the approach used by the company seems to lack some clarity. No formal meta-analysis of clinical outcomes is reported, although a narrative review of three trials is presented before the start of the formal literature searches. Unlike TA132, the decision to use the CTTC meta-analysis is not fully justified and no search of other external meta-analyses of clinical outcomes is attempted or discussed.

The company did perform a sensitivity analysis using the clinical outcome results derived from the IMPROVE-IT trial. This sensitivity analysis led to very different conclusions about the cost-effectiveness of ezetimibe compared with the company's primary approach.

In summary, the data on clinical outcomes used in the cost-effectiveness modelling are not derived directly from a systematic review of the effects of ezetimibe on these outcomes, but indirectly from a systematic review of the effects of ezetimibe on LDL-c and from an external systematic review of the effect of lowering the LDL-c on clinical outcomes for statins. Although a direct meta-analysis of clinical outcomes would have involved relaxation of the inclusion criteria of the review, this would have provided clinically more relevant information.

5 COST EFFECTIVENESS

5.1 ERG comment on company's review of cost-effectiveness evidence

5.1.1 State objectives of cost effectiveness review. Provide description of company's search strategy and comment on whether the search strategy was appropriate. If the company did not perform a systematic review, was this appropriate?

The manufacturer updated the systematic review of economic evaluations that was conducted for TA132. MEDLINE (Ovid), EMBASE (Ovid), NHS Economics Evaluation Database (NHS EED) and the HTA Database (both the CRD and Cochrane Library interfaces) were searched on 4th March 2015 for publications in English from 2006 onwards to identify studies published since TA132. In addition recent relevant conference proceedings from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), European Atherosclerosis Society (EAS), American College of Cardiology (ACC) and European Society of Cardiology (ESC) were searched from 2013.

The searches are documented in full in Appendix 14 of the submission and are fully reproducible. The MEDLINE and EMBASE search strategies included both thesaurus terms (MeSH or EMTREE) and free text terms and combined the concepts of hypercholesterolaemia and cost effectiveness while for NHS EED and the HTA database only the concept of hypercholesterolaemia was included.

The inclusion of additional terms would have been beneficial. As was the case with the clinical effectiveness searches, the sensitivity of the hypercholesterolaemia facet could have been enhanced by the inclusion of related terms such as *hyperlipidaemia* and *dyslipidaemia* and associated conditions, particularly *cardiovascular* and *coronary diseases*. However, unlike the clinical effectiveness searches, the correct MeSH and Emtree terms for hypercholesterolaemia were used.

For the cost effectiveness facet the inclusion of the following could have been beneficial

- MeSH term ***Exp "costs and cost analysis"***
- Emtree term ***Exp economic evaluation/***
- MeSH ***Technology Assessment, Biomedical/*** and Emtree ***Biomedical technology assessment/***

In addition, there was inconsistency whereby the MEDLINE search did not use terms relating to Monte Carlo methods and Markov models while the EMBASE search did.

Key conference abstracts for 2013-5 were searched and employed a keyword search to identify relevant studies. Keywords used related to the clinical condition and included hypercholesterolemia as well as stroke, myocardial infarction and angina.

5.1.2 State the inclusion/ exclusion criteria used in the study selection and comment on whether they were appropriate.

The scope of the review was defined in terms of population (adults age 18 or older with primary hypercholesterolemia), intervention/comparator (ezetimibe, statins, other lipid lowering drugs), outcomes (inputs and outcomes reported in economic evaluations) and study design (cost-effectiveness analyses and cost-utility analyses). Models that assessed the cost-effectiveness of ezetimibe and or other lipid lowering drugs versus an appropriate comparator were included. Restrictions were made to include only studies conducted for UK populations and those published in English language. These restrictions appear appropriate for identifying studies to inform the specific question of whether ezetimibe offers a cost-effective option from the UK NHS perspective. However, some of the exclusion criteria may have ruled out studies potentially relevant for informing model structure.

5.1.3 What studies were included in the cost effectiveness review and what were excluded? Where appropriate, provide a table of identified studies. Please identify the <u>most important</u> cost effectiveness studies.

Seven full cost-effectiveness and cost-utility analyses were identified in line with the original scope of the review,[15, 62-67] and a further two cost-effectiveness models were deemed relevant because they described model structures and inputs that were utilised by included economic studies.[9, 68] It was stated that these two studies originally fell

outside the scope of the review because they did not focus specifically on patients with hypercholesterolemia or ezetimibe as a primary intervention. However, a number of the seven originally included studies also did not include ezetimibe as an intervention or comparator, and so it is not entirely clear why the two additional models were deemed to be outside the original scope. The table of included studies presented in the company's submission is reproduced below (Table 11).

Table 11 Company's summary of studies included in the review of cost-effectiveness studies

Study	Summary of model	Health States	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (cost (£) per QALY gained)
Davies *et al.* 2006[65]	Combination of a titration model and a long-term Markov model with 9 health states and a cycle length of 4 years.	1 CHD free 2 Existing CHD 3 Angina 4 MI – year 1 5 Post-MI 6 Other CVD: Stroke (mild, 7 moderate, severe), CHF, PVD 8 Secondary CHD 9 Dead	NR	NR	NR	ICER (men/ women) Rosuvastatin/ vs. Simvastatin: 9,735/ 15,184 Atorvastatin/ vs. Rosuvastatin: Dominated/dominated Simvastatin/ vs. Pravastatin: 6,883/10,790 Fluvastatin/ vs. Simvastatin: Dominated/dominated Pravastatin/ vs. No treatment: 296/779
NICE TA132 2007[5] Company's submission; Cook model [64]	Cook Markov model including 9 health states. Cycle length is not reported.	1 Event free 2 Primary MI 3 Primary angina 4 Primary stroke 5 Secondary M	NR	NR	NR	ICER Ezetimibe plus current statin: range from just under 8,000 to just under 122,000

Study	Summary of model	Health States	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (cost (£) per QALY gained)
		6 Secondary angina 7 No event in previous 12 months 8 CHD death 9 Non-CHD death				Ezetimibe monotherapy versus no treatment, ranged from just under 10,000 to just over 131,000
Ara *et al.* 2008b [62]	Modified Markov model based on the original model by Ward S *et al.* with a cycle length of 1 year.	1 New unstable angina 2 New nonfatal MI 3 New nonfatal stroke 4 Post-stable angina 5 Post-unstable angina 6 Post-MI 7 Post-TIA 8 Post-stroke 9 Fatal CHD 10 Fatal stroke 11 Death other causes	NR	Lifetime Ezetimibe: 8.400 No treatment: 8.189	£, UK, 2006 Lifetime Ezetimibe: 14,458,088 No treatment: 9,597,278	Lifetime ICER for Ezetimibe in comparison to no treatment: 23,026 (22,979-23,074)
Ara *et al.* 2008c[63]	Adapted version of the original Markov model developed by Ward *et al.* with a	1 New unstable angina 2 New nonfatal MI 3 New nonfatal stroke 4 Post-stable angina	NR	Lifetime Ezetimibe co-administered with statin: 8.386	£, UK, 2006 Lifetime Ezetimibe co-administered with statin: 16,560,000	ICER for ezetimibe co-administered with statin in comparison to statin monotherapy Mean (95% CI) Lifetime:

Study	Summary of model	Health States	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (cost (£) per QALY gained)
	cycle length of 1 year	5 Post-unstable angina 6 Post-MI 7 Post-TIA 8 Post-stroke 9 Fatal CHD 10 Fatal stroke 11 Death other causes		Statin monotherapy: 8.252	Statin monotherapy: 12,867,000	27,475 (27,331-27,620)
Ara *et al.* 2008[15]	A new Markov model with a cycle length of 1 year	1 Event free 2 Stable angina 3 Post-stable angina 3 Unstable angina 4 Post-unstable angina 5 Non-fatal MI 6 Post-non-fatal 7 MI 8 TIA 9 Post-TIA 10 Non-fatal stroke 11 Post-non-fatal stroke 12 Fatal CHD event	NR	NR	NR	ICER range: Ezetimibe to ongoing statin treatment compared with maintaining statin treatment at the current dose: 19,000 to 48,000 Ezetimibe to ongoing statin treatment compared with a switch to a more potent statin: 1,500 to 116,000

Study	Summary of model	Health States	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (cost (£) per QALY gained)
		13 Fatal CVD event 14 Death from other causes				
Nherera *et al.* 2010 [66]	Lifetime Markov model. Cycle length is not reported.	1 Well 2 MI – year 1 3 MI – subsequent 4 Stroke – year 1 5 Stroke – subsequent 6 PVD – year 1 7 PVD- subsequent 8 HF – year 1 9 HF – subsequent 10 REV – year 1 11 REV – subsequent 12 Unstable angina – year 1 13 Unstable angina – subsequent 14 Death	NR	High-intensity statin: 12.44 Low-intensity statin: 12.02	£, UK, 2008-2009 values High-intensity statin: 14,095 Low-intensity statin: 9,448	ICER for high-intensity statin in comparison to low-intensity statin: 11,103
Reckless *et al.* 2010[67]	Markov- decision-analytic model, based on the Cook model with 5	1 No event 2 MI 3 Angina 4 CHD death	Ezetimibe/Simvastatin (10/40 mg) group (mean, SD): 63.3 (10.5) Double statin dose	Pooled baseline (mean) Ezetimibe-Simvastatin (10/40 mg): 6.82	£, UK, 2004 values, inflated to 2009 costs Pooled baseline	ICER for Ezetimibe/Simvastatin in comparison to doubling the statin dose: 11,571

Study	Summary of model	Health States	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (cost (£) per QALY gained)
	health states and a cycle length of 1 year.	5 Non-CHD death	group (mean, SD): 63.6 (10.9)	Doubling the statin dose: 6.94	(mean) Ezetimibe-Simvastatin (10/40 mg): 4,602 Doubling the statin dose: 4,763	
Ward *et al.* 2007[68]	Markov model with 10 health states and a cycle length of 1 year.	1 Event free 2 Remain event free 3 Stable angina 4 Unstable angina 5 Non-fatal MI 6 Fatal CHD event 7 TIA 8 Non-fatal stroke 9 Fatal CVD event 10 Death from other causes	Range, starting age: 45 – 85	Discounted incremental QALYs Secondary prevention (M/F) 45 yrs.: 462/493 55 yrs.: 410/452 65 yrs.: 314/387 75 yrs.: 193/248 85 yrs.: 103/132	Discounted incremental costs Secondary prevention (M/F) 45 yrs.: £4,732/£4,966 55 yrs.: £4,109/£4,432 65 yrs.: £3,310/£3,660 75yrs: £2,455/£2,799 85 yrs.: £1,615/£1,853	Discounted ICERs Secondary prevention (M/F, £,000) 45 yrs.: £10.2/£10.1 55 yrs.: £10.0/£9.8 65 yrs.: £10.5/£9.5 75 yrs.: £12.7/£11.3 85 yrs.: £15.7/£14.0
NICE CG181 2014 (Appendix L)[1]	Markov models based on Ward. including 15	1 Well 2 MI 3 Post-MI	Range, starting age: 40 – 70	NR	NR	Discounted ICERs: Secondary prevention: (£,000)

Study	Summary of model	Health States	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (cost (£) per QALY gained)
	health states and a cycle length of 1 year. Low, medium vs. high intensity statins	4 HF 5 Post-HF 6 TIA 7 Post-TIA 8 Stroke 9 Post-stroke 10 PAD 11 Post-PAD 12 Stable angina 13 Post-stable angina 14 Unstable angina 15 Post-unstable angina 16 CV Death 17 Non-CV Death				60 yrs., male, Med – Low: dominates 60 yrs., male, High – Medium: £1.4 Primary prevention: (Male, £,000), 60 yrs., 10% QRISK2 S20 vs NT: £4.3 A20 vs S20: £3.2 A80 vs S20: £13.3

5.1.4 What does the review conclude from the data available? Does the ERG agree with the conclusions of the cost effectiveness review? If not, provide details.

The included studies were each summarised narratively, tabulated for comparison and quality appraised using the Drummond checklist (Appendix 15 of company's submission). No overarching conclusion was drawn regarding the cost-effectiveness of ezetimibe as a monotherapy or as an add-on to statin therapy based on the reviewed studies. Rather, the key objective of the review (although not specially stated) appears to have been to identify appropriate modelling frameworks for addressing the current decision problem. Based on consideration of all the models appraised, the company favours a Markov model structure based on the modelling approaches developed by Ward et al.2007[68] for NICE TA94[9] and Ara and colleagues 2008[15] for TA132[5] and further adapted for NICE CG181[1] on lipid modification. The overall approach is consistent with the majority of published cost-effectiveness studies in the clinical area. These models simulate the incidence of cardiovascular events for primary and secondary prevention cohorts, and apply costs and utilities associated with these events in the first year and subsequent years following events.

The effects of lipid lowering therapy are incorporated as risk ratios that are applied to annual baseline probabilities of CV events. These risk ratios can either be estimated directly from trials assessing effectiveness in terms of clinical endpoints (i.e. CV events) or indirectly via estimated relationships between cholesterol reductions and CV event rates (e.g. Baigent, et al[2]). The company's model (described in detail below) adopts a combination of the two approaches, with the effects of statin on baseline pre-treatment risks being estimated directly from statin trials including clinical end-points, and the effect of ezetimibe being modelled through its effect on LDL-c.

5.2 Summary and critique of company's submitted economic evaluation by the ERG suggested research priorities

5.2.1 NICE reference case checklist (Table only)

Table 12 NICE reference case checklist

Attribute	Reference case and TA Methods guidance	Does the *de novo* economic evaluation match the reference case
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	Yes. The comparators are: **Optimal statin therapy** (maximum tolerated dose) for those people with primary heterozygous familial or non-familial hypercholesterolaemia whose condition is not appropriately controlled with a statin alone; and **no treatment** For people with primary heterozygous familial or non-familial hypercholesterolaemia in whom a statin is considered inappropriate or is not tolerated. The omission of other lipid lowering medications is justified by NICE clinical guideline CG181[1]
Patient group	As per NICE scope. *"People with primary heterozygous familial or non-familial hypercholesterolaemia:* • *whose condition is not appropriately controlled with a statin alone* ***or*** *in whom a statin is considered inappropriate or is not tolerated"*	Yes
Perspective costs	NHS & Personal Social Services	Yes
Perspective benefits	All health effects on individuals	Yes
Form of economic evaluation	Cost-effectiveness analysis	Yes. Cost-utility analysis
Time horizon	Sufficient to capture differences in costs and outcomes	Yes
Synthesis of evidence on outcomes	Systematic review	Yes. The effects of ezetimibe versus statin and no treatment (in terms of LDL-c total cholesterol lowering) are derived from a

		systematic review. Systematic searches are also used to inform health state utilities and costs in the model. The effects of statins on baseline CV event rates are taken from a recently conducted systematic review for CG181[1]
Outcome measure	Quality adjusted life years	Yes
Health states for QALY	Described using a standardised and validated instrument	Yes, health states defined by CV events (first year and subsequent years following events)
Benefit valuation	Time-trade off or standard gamble	Yes, generally based on EQ-5D responses of appropriate UK populations, scored using the UK time trade-off tariff.
Source of preference data for valuation of changes in HRQL	Representative sample of the public	Yes, generally. Stroke and post stroke utilities are an exception. These are based on a meta-regression of 20 studies, adjusted for severity of stroke, assessment method, respondents, and bounds of the scale. Values reflect EQ-5D TTO values, but not necessarily those that would be obtained using the UK population tariff.
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Probabilistic modelling	Probabilistic modelling	Yes, the base cases were modelled deterministically and probabilistically. However, several probability distributions were misspecified in the model leading to significant underestimation of uncertainty in the model outputs.
Sensitivity analysis		Yes, the impact of varying a number of parameters is assessed through one-way deterministic sensitivity analysis, with results presented as tornado diagrams. Various scenario analyses are also presented for alternative assumptions and baseline input values.

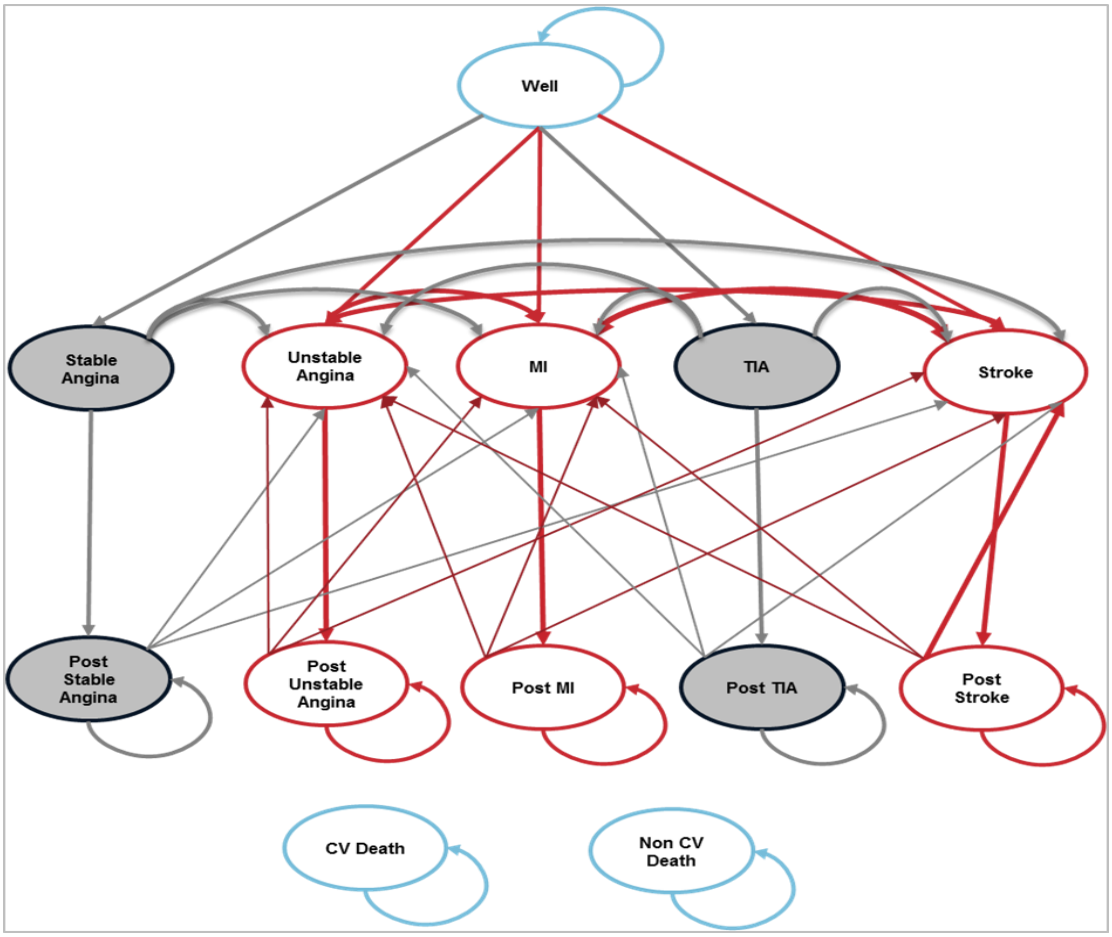
5.2.2 Models structure

A de novo Markov model with annual cycle was developed by the company. A copy of the model schematic provided in their submission is reproduced in Figure 2. The model simulates the occurrence of cardiovascular (CV) events for both primary and secondary prevention cohorts. Modelled CV events include those included in datasets used to derive the Q-Risk prediction algorithm[69] i.e. stable angina (SA), unstable angina (UA), myocardial infarction (MI), stroke, transient ischaemic attach (TIA) and CV death. Stable angina and TIA are excluded from the company's base case analysis due to a lack of direct evidence demonstrating the effects of statins on these events, or evidence linking the effects of LDL-c reduction to relative reductions in the incidence of these events. There is an option to include SA and TIA in scenario analysis, with treatment effects modelled to be equivalent to those observed for MI (stable angina) and Stroke (TIA). Note, however, that the omission of risks for stable angina and TIA will have knock-effects on the risk of subsequent events and CV mortality. Thus it seems inappropriate to exclude any risk of these events from the model in the base case analysis. If it is considered appropriate not to model any effects of ezetimibe and/or statins on these events, then the relevant treatment effects should be switched off in the model, and not the baseline risks of these events. This latter specification was however included as a scenario analysis by the company.

For the primary prevention analyses, the cohort commences in a "well" state, and can experience events as determined by the estimated baseline transition probabilities for first CV events. Each CV event is modelled using two states, reflecting costs and utilities incurred within the first year of the event and then longer-term costs and utilities incurred in subsequent years (post-event health states). For the secondary prevention analyses, the cohort is initially distributed across the post-UA, post-MI and post-stroke states, and can experience any of these events in subsequent cycles of the model based on estimated transition matrices for secondary CV events.

Treatment effects for statins and ezetimibe are incorporated as relative risks or rate ratios for non-fatal MI, unstable angina, stroke, any vascular death and non-vascular deaths. The relative risks for statin treatment are taken directly from a previous meta-analysis conducted for NICE CG181[1] which estimated the direct effects of statin therapy on CV endpoints (MI, Stroke, CV death). Since unstable angina was not

included as an outcome in the meta-analysis for CG181, the associated relative risk for unstable angina is assumed to be equal to that observed for MI. The rate ratios associated with ezetimibe use are derived indirectly through an estimated relationship between LDL-c reductions and relative reductions in the risk of the defined CV events. The Cholesterol Treatment Trialists' Collaboration (CTTC) meta-analysis of 26 statin trials provides estimated rate ratios per 1 mmol/L reduction in LDL-c for MI, stroke, any vascular death and non-vascular death. Thus modelled reductions in LDL-c associated with ezetimibe use (as monotherapy or add-on to statin), were linked to reductions in CV events through these estimated relationships. Again, the rate ratio for MI was also assumed to apply for the effects of ezetimibe on unstable angina.[2]



NB. Stable angina and TIA health states (grey coloured) are additional health states explored in scenario analyses. All non-fatal health states can transition at any point to the absorbing fatal health states, CV death and Non-CV death.

Figure 2 Copy of the model schematic provided in the company's submission

5.2.3 Population

The populations modelled in base case analyses include:

- A primary prevention population with a 10 year CV risk of 20%, starting age 60, 46.4% female.
- Secondary prevention population with baseline CV event risks derived from reviews of published literature, starting age 69, 34.6% female.

The primary prevention baseline characteristics represent those of a large UK primary care cohort (n=300,914) without existing CVD and on statin therapy[70] and are applied both for cohorts in whom a statin is considered inappropriate, contraindicated or not tolerated, and for those whose condition is not appropriately controlled with a statin

alone. Whist this appears generally appropriate, it does assume that age, sex, and pre-treatment CV risk are independent of the appropriateness / tolerance and response to statin therapy. The model also allows the baseline age, CV risk and sex distribution to be modified. The baseline characteristics of the secondary prevention cohort come from a coronary heart disease (CHD) subgroup (n=1773) of a retrospective UK observational study of patients with an atorvastatin prescription and should be applicable.[71]

A further important baseline parameter that is used in the model to calculate absolute LDC-C reductions associated with ezetimibe (and in turn associated relative risk reductions for CV events) is the baseline pre-treatment LDL-c level. The applied value of 4.32 mmol/L is the mean value observed within one year of initiating statin therapy in the UK primary prevention cohort reported by Van Staa et al[70] (mean Q-risk score at initiation of statin therapy was 17.8%). This seems generally appropriate for representing baseline (off-treatment) LDL-c for the modelled primary prevention cohort. Incidentally, for those with a repeat (post-statin) LDL-c measurement, the mean reduction reported by Van Staa et al[70] was 1.57 mmol/L at 6-12 months. It is more challenging to assess the validity of the mean pre-treatment LDL-c level for higher/lower risk cohorts. This makes risk specific scenario analyses (where baseline risk is modified but baseline LDL-c is not) more difficult to interpret.

Given a lack of available data on the pre-treatment LDL-c levels for a secondary prevention cohort, the same 4.32 mmol/L was applied in the company's secondary prevention base case analysis. The validity of this assumption is difficult to assess. However, in the cohort study by Jameson et al[71] the LDL-c value achieved by patients on a high intensity atorvastatin dose (20, 40, 88 mg) was ~2.10 mmol/L, which would represent a 51.4% reduction from baseline level of 4.32 mmol/L. This is consistent with the estimated mean percentage reductions in LDL-c associated with high intensity atorvastatin doses (43-55%)[72] so a baseline figure of 4.32 mmol/L for the secondary prevention population does seem reasonable.

5.2.4 Interventions and comparators

For both the primary and secondary prevention cohorts, ezetimibe is modelled as monotherapy for patients in whom a statin is considered inappropriate or is

contraindicated or not tolerated, and as an add-on to statin therapy for those whose condition is not appropriately controlled with a statin alone.

5.2.5 Perspective, time horizon and discounting

The perspective is that of the patient for health effects, and that of the NHS and personal social services for costs. Health benefits and costs are discounted at 3.5% per annum. The base case analysis is conducted over the life-time of patients (up to a maximum of 100 years of age). Compliance and adherence are assumed to be 100% over the patient's life-time. This latter assumption is in keeping with base case analyses for TA132[5] and the modelling conducted for CG181[1] However, there was limited exploration regarding the importance of this assumption in sensitivity analysis.

5.2.6 Treatment effectiveness and extrapolation

The modelled treatment effects (in terms of CV events averted and QALYs gained) are a function of the baseline risk of CV events (off treatment), and the relative risks applied for statin and ezetimibe therapy. As mentioned above, the effects of statin treatment on baseline (off-treatment) event risks are derived from a previous meta-analysis which estimated the direct effects of statin therapy versus placebo on CV endpoints (CG181). The effects of ezetimibe therapy are calculated via their estimated additive effect on percentage LDL-c reductions from baseline pre-treatment levels compared to placebo (for monotherapy) or statin alone (as an add-on to statin).

These additive percentage reductions are translated into absolute further reductions in LDL-c (mmol/L) in the model, and combined with published relative rate ratios for CV events per mmol/L reduction in LDL-c.[2] Further details and a critique of the approach are provided below.

Baseline CV risks (primary prevention)

For the primary prevention model, the 10 year CV risk at baseline (prior to any treatment) can be specified at various levels defined by a Q-risk score (e.g. 10%, 20%, 30%), and 20% is selected for the base case analysis. The base case cost-effectiveness results are therefore intended to be applicable to a cohort of 60 year old adults with a 20% 10-year risk of suffering any CV event included in the Q-risk assessment tool

(i.e. any fatal or non-fatal angina, MI TIA or stroke). The pre-treatment LDL-c level is assumed to be 4.32 mmol/L.[70]

The 20% ten year risk is first transformed it into a constant one-year probability (2.21%) in keeping with the Markov cycle. The following equations are appropriately applied:

Average Rate (r) = -[ln(1-P)]/t
One-year probability = 1-exp(-r)

Where P is the probability (0.2) and t is the time in years to which that probability relates (i.e. 10). Within the model, this probability is then combined with published data on the relative incidence of different types of CV event in different age bands (40-54; 55-64; 65-74; 74-84; 85+) from men and women.[15, 68] This yields baseline one year transition probabilities from "well" to "stable angina", "unstable angina", "MI", "TIA", "stroke", and "CV death".

These one-year transition probabilities (reflective of the stated 10-year baseline risk) are then assumed to apply to the mid-point within each age band (47, 60, 70, and 80 and 85). The annual overall risk of a CV event is then adjusted downwards below the mid-point in each age band, and upwards above it, keeping the relative distribution of events within the age-band constant. Annual risk increments are applied to account for increasing risk with age, and are implemented as additive percentage increases in the risk per year increase in age. These are taken from a previous HTA that estimated an approximate linear relationship between increasing age and the risk of angina, MI, or CV death.[68] Based on an analysis of Health Survey for England data, Ward et al estimated an annual increase in the risk of experiencing any of these events of 0.03% for men and 0.008% for women.[68] The risk of TIA and stroke (which were not factored into the analysis by Ward et al)[68] are also increased each year in the model, in proportion to their relative frequency in relation to the CHD events. Table 13 below outlines the resultant 1st cycle risks for men in the age band 55-64, with TIA and stable angina included in the model.

Table 13 Baseline risks for men aged 55 to 64

Age	Stable angina	Unstable angina	MI	TIA	Stroke	CV death	SUM
55	0.65%	0.14%	0.34%	0.18%	0.41%	0.27%	1.99%
56	0.67%	0.14%	0.35%	0.18%	0.42%	0.27%	2.04%
57	0.68%	0.15%	0.36%	0.19%	0.43%	0.28%	2.08%
58	0.70%	0.15%	0.36%	0.19%	0.44%	0.28%	2.12%
59	0.71%	0.15%	0.37%	0.19%	0.45%	0.29%	2.16%
60	**0.72%**	**0.16%**	**0.38%**	**0.20%**	**0.45%**	**0.30%**	**2.21%**
61	0.74%	0.16%	0.39%	0.20%	0.47%	0.30%	2.27%
62	0.77%	0.17%	0.40%	0.21%	0.48%	0.31%	2.34%
63	0.79%	0.17%	0.41%	0.21%	0.49%	0.32%	2.40%
64	0.81%	0.17%	0.42%	0.22%	0.51%	0.33%	2.46%

These values are used as the lookup risks for the first cycle of the model, given the selected age and 10-year CV risk for the cohort. Note that if a 60 year cohort with a 20% 10-year risk is chosen, the selected first year risk for any CV event included in the Q-risk will be 2.21%, which is then increased annually in the model. This results in a modelled 10 year cumulative risk of any Q-risk event that is slightly greater than 20%. Whilst the modelled risks therefore do not appear to precisely match the stated risk, the differences are small, and unlikely to lead to significant bias. Furthermore, it is noted from Table 13 that the first cycle risk of any CHD event (any angina, MI, CV death) increases by more than the stated 0.03% (for men) per one year increase in the starting age. This appears to be due to a minor bug in the formula used to age adjust the starting risks in the model.

Another complicating assumption is the exclusion of any risk of stable angina or TIA in the base case analysis. These events appear to have been omitted due to lack of evidence for the effect of lipid lowering therapy on their incidence. Thus, the compounded 10-year risk of any included CV event (unstable angina, MI, stroke, or CV death) is less than 20% over ten years in the base case. It seems inappropriate to assume zero risk of these events, as even if they are assumed not to be reduced by lipid lowering therapy, the morbidity, costs and downstream risks associated with their occurrence may still influence the comparisons.

Once the appropriate first cycle risks (specific to the chosen age and risk level) are defined for men and women, these are weighted by the baseline sex distribution in the model; to generate the 1st cycle risks for each included CV event for the primary prevention cohort as a whole. These risks are then increased in each subsequent cycle of the model to account for increasing risk with age (using a similar approach as described above to adjust the first cycle risks by starting age). This is done by estimating the increase in risk (accounting for proportionally similar increases in the risk of non CHD events) based on the modelled age for men and women, and then taking the weighted average of these based on the estimated sex distribution (which updates annually in the model). It should also be noted that by excluding the risk of stable angina and TIA in the base case analysis, this influences slightly the rate at which the risk of included events increase in the model, which does not seem appropriate. Moreover, when the risk increase is applied to the previous cycle's risk in the model, it appears to be inflated (to account for proportional increases in non CHD events) a second time. This was flagged for clarification with the company, but the company stated that this inflation was occurring only once.

The ERG maintains that there is a second inflation to account for the annual increase in the risk of stroke and TIA occurring in the model, which has not been fully explained or justified. However, the ERG also has concerns relating to the face validity of resultant increases in CV risk with age. With the applied approach, the baseline risk of any CV event (included in Q-risk) increases over ten years in the model from 2.21% (20% 10y risk) at age 60 to 2.67% (23.7% 10y risk) at age 70. This equates to relative risk of 1.21 for a ten year increase in age. However, reviewing the modelling used to derive the Q-risk algorithm, the adjusted hazard ratio for a 10% increase in age (e.g. from age 60 to 66), was 1.66 for women and 1.59 for men.[69] This would suggest that the risk of primary CV events may not be increasing sharply enough with age in the model. This may also explain some counterintuitive output of the primary prevention model, whereby the modelled ratio of CV to non-CV deaths falls as the cohort ages, and overall mortality appears low for a high risk cohort (see section 5.2.12 below).

A primary prevention subgroup analysis was also conducted for individuals with type-2 diabetes, for those with a 20% (also 10 and 30%) CV risk based on the UKPDS risk

equation. The UKPDS risk equation predicts the risk of experiencing non-fatal MI, fatal MI or stroke events - just three of the types of CV event included in the distribution of modelled CV events (Table 13). Therefore, the other types of CV event were assumed to occur at rates consistent with the proportional distributions (by age and sex) for all the modelled CV events. The same proportional distributions as used for the main primary prevention model were applied. Thus, the 10-year baseline risk of any modelled CV event is appropriately higher than 20% for a diabetes cohort with a 20% ten-year risk based on the UKPDS risk equation. Note that the diabetes subgroup analysis was conducted for a 67 year-old cohort (44.3% female), based on data reported by Jameson et al.[71] The same baseline LDL-c level of 4.32 mmol/L was assumed.

Baseline CV risks (secondary prevention)

The baseline risks of CV events for the secondary prevention cohort are more straight forward, in that they are adapted from those used in the modelling conducted for NICE CG181[1] and are also reflective of those used by Ward et al[68] for TA94.[9] These are incorporated as matrices of age dependent transition probabilities between the modelled event and post-event states. They were originally derived by Ward et al[68] from the analysis of registry data (Nottingham Heart Attack Register; South London Stroke Register) and a review of published studies relevant to UK cohorts in the pre-statin era. These were updated in CG181 to account for the risk of stroke from unstable angina.[73] Risks for peripheral arterial disease (PAD) and heart failure (HF) were also included in the model for CG181, but these have not been included in the current model. The original sources for the secondary event risks in the company model are the Nottingham Heart Attack Register[74] (for MI, Strokes, unstable angina, and CVD death following CHD), the South London Stroke Register[75] for strokes, TIA and CV death following stroke), Juul-Moller et al.[76] (for stable angina), and the CURE study[73] (for risks following unstable angina). It appears generally appropriate that PAD and HF are not included the current model, given a lack of clear evidence linking LDL-c reductions to reductions in the risk of these events.

Treatment effects (ezetimibe monotherapy)

The effect of ezetimibe monotherapy therapy (versus no treatment) is incorporated in the company's model as an additional percentage reduction from baseline LDL-c

levels compared with that achieved on placebo. This is derived from the meta-analysis of 15 trials of ezetimibe monotherapy versus placebo included in the systematic review of clinical effectiveness (Figure 6 of company's submission). This is applied to the estimated baseline LDL-c value of 4.32 mmol/L to estimate a total additional reduction in LDL-c of 0.88 mmol/L versus no treatment. This absolute estimated reduction in LDL-c is then combined with estimated risk ratios for CV events expressed per 1 mmol/L reduction LDL-c, to estimate the relative risk of CV events associated with ezetimibe monotherapy. Table 14 outlines the calculations in the model, and the resultant relative risks applied to baseline CV event risks. These relative risks were applied to the annual age dependent baseline transition probabilities, to model the impact of treatment on events.

Table 14 Estimation of rate ratios for ezetimibe as monotherapy versus no treatment

Event	RR (per mmol/L reduction in LDL-c)	Percentage reduction (per 1 mmol/l reduction LDL-c)	Percentage change based on LDL-c reduction (x 0.88)	RR based on LDL-c reduction
Non-fatal MI	**0.74**	0.26	0.23	0.77
Stable Angina	**0.74**	0.26	0.23	0.77
Unstable angina	**0.74**	0.26	0.23	0.77
Non-fatal stroke	**0.85**	0.15	0.13	0.87
TIA	**0.85**	0.15	0.13	0.87
CVD death (Vascular death)	**0.86**	0.14	0.12	0.88
Other non CVD Death (non-Vascular death)	**0.97**	0.03	0.03	0.97

The approach of estimating relative risks through estimated reductions in LDL-c, rather than using directly estimated relative risks for CV events, appears justified for ezetimibe monotherapy on the grounds that there have been no trials of ezetimibe versus placebo with CV endpoints in general primary or secondary prevention populations.

Treatment effects (ezetimibe as an add on to statin therapy)

The approach to estimating treatment effects for ezetimibe as an add-on to statin therapy is modelled in two stages. The effects of statin therapy versus no treatment are modelled using relative risks for CV events (derived from trials with CV events as endpoints). These relative risks come from a meta-analysis of the effects of different intensities of statin dose (low, medium, high) on CV events, conducted for the NICE CG181[1] (Table 15). In the base case analysis, atorvastatin (20mg) is assumed for primary prevention, and atorvastatin 40mg is assumed for secondary prevention. Both these statins were grouped in the high intensity category in the meta-analysis for CG181, and so equivalent effects are modelled for these different doses.

Table 15 Risk ratios for statin treatment

	Risk Ratios		
Health state	**Low-intensity**	**Medium-intensity**	**High-intensity**
Unstable angina (non-fatal)	Same as MI	Same as MI	Same as MI
MI (non-fatal)	0.78 (0.72 to 0.84)	0.61 (0.55 to 0.68)	0.46 (0.37 to 0.59)
Stroke (non-fatal)	0.84 (0.75 to 0.94)	0.73 (0.66 to 0.81)	0.80 (0.70 to 0.91)
CV death	0.84 (0.78 to 0.91)	0.81	0.72
Non-CV death	0.96 (0.90 to 1.02)	0.96 (0.90 to 1.02)	0.96 (0.90 to 1.02)
Low-, medium- and high-intensity category definitions sourced from NICE CG181 Lipid Modification Guideline: Low-intensity statins include simvastatin 10 mg Medium-intensity statins include simvastatin 20 mg, simvastatin 40 mg & atorvastatin 10 mg High-intensity statins include simvastatin 80 mg, atorvastatin 20 mg, atorvastatin 40 mg & atorvastatin 80 mg			

Ezetimibe benefit is then modelled indirectly through its pulled additive effect on baseline LDL-c (versus statin alone) via the published CTT meta-analysis.[2]

The pooled additive effect on baseline LDL-c (-15.52% versus statin alone) comes from the meta-analysis of trials of ezetimibe + statin versus statin alone. These trials reportedly all required a wash out period prior to randomisation, and so the additive percentage reduction is applicable to the baseline LDL-c value (off-treatment), and not to the LDL-c value achieved with statin alone. Therefore, in the model this is applied to the pre-statin LDL-c value of 4.32 mmol/L, to estimate the absolute

incremental reduction in LDL-c associated with ezetimibe (as an add-on) versus statin therapy alone (4.32x0.1552=0.67 mmol/L).

The company justify modelling the effects of ezetimibe through changes in LDL-c on the following grounds: 1) This approach was used in the original cost-effectiveness analysis for TA132;[5] 2) since the trials demonstrating direct effects of ezetimibe on CV event rates are in subpopulations of the ezetimibe license (with different baseline characteristics and CV risks), the extrapolation of these CV event reductions to the wider population is challenging. Whilst the second point may be valid for modelling the effects of ezetimibe monotherapy (in those who cannot tolerate a statin), and ezetimibe as an add-on to statin in the primary prevention cohort, we are not convinced this approach is justified in the case of modelling the effects of ezetimibe as an add on to statin in the secondary prevention cohort. The IMPROVE-IT trial[3] assessed the effectiveness of ezetimibe as an add-on in a sub-group of patients within the wider secondary prevention cohort. Whilst the company have submitted a scenario analysis whereby they apply the IMPROVE-IT relative risks to a cohort with baseline characteristics matching those of patients included in the IMPROVE-IT trial, it could be argued that the relative risks form IMPROVE-IT are the most appropriate source of effectiveness data for the secondary prevention cohort as a whole.

The ERG has further concerns relating to the different ways in which the effects of statin (on baseline pre-treatment CV risks) and then ezetimibe (as an add-on) are modelled:

1 By modelling reductions in baseline CV risk using pooled relative risks derived from a meta-analysis of different statin regimens versus placebo, this could potentially underestimate the CV risk for patients who are inadequately controlled on statin alone (i.e. those who will be considered potential candidates for ezetimibe as an add-on to statin therapy).
2 The additive difference in percentage LDL-c reduction (between ezetimibe + statin versus statin alone) may be sensitive to the baseline LDL-c (off-treatment) value, and also the percentage reduction from baseline achieved with statin therapy alone. Thus, in modelling conducted for TA132, Ara and colleagues[15] did in fact apply an estimate of the multiplicative effect of

ezetimibe in terms of percentage reduction from LDL-c levels achieved on statin.

3 The approach adopted by the company makes assessment of cost-effectiveness by level of LDL-c control achieved on statin alone difficult, which is the starting point for considering the appropriateness of ezetimibe as an add-on therapy.

If the effects of ezetimibe (as an add-on to statin) are to be modelled through their additional effects on LDL-c, it may be more appropriate to apply a multiplicative percentage reduction in LDLC-C from the post statin LDL-c level. The company has estimated this multiplicative percentage reduction in the clinical effectiveness review (23.5%), and states that this is a more meaningful representation of clinical efficacy. However, it has not been used in the modelling.

Typical levels of LDL-c achieved on different doses of statin are available from observational studies[70, 71] and percentage reductions from baseline (pre-treatment) levels achieved with different doses of statin are available from a previous systematic reviews.[72] This provides a means for estimating typical post statin LDL-c levels for different doses of statin given a baseline (pre-treatment) level of 4.32 mmol/L.

Then applying the multiplicative percentage reduction in LDL-c from this post statin level provides an estimate of the absolute further reduction in LDL-c with ezetimibe. Such an approach would also provide the flexibility to model ezetimibe as an add-on versus various scenarios reflective of inadequate control on statin alone, such as achievement of LDL-c levels of 2, 2.5, 3 or 3.5 mmol/L. Using this approach, the effects of statin could also be modelled through their impact on LDL-c (i.e. taking the difference between the baseline and modelled post statin LDL-c level for each scenario).

Treatment effects and aging

A point to note for the effects of ezetimibe and statins in the primary prevention model is that an assumption appears to have been made that the effects of lipid lowering therapy are only applied to the baseline component of CV event risk (i.e. the equivalent annual probability for a 20% CV risk). The increases in risk with age

appear to have been treated as being independent of LDL-c, and are applied incrementally regardless of treatment. This may not be the case if there is an interaction between LDL-c control and the effect of aging on CV risk. It is also worth noting that this approach does not seem to be mirrored in the secondary prevention model, where the risks of events also increase with age, but treatment effects are applied to the whole risk. It is difficult to verify which approach is correct.

5.2.7 Health related quality of life

MEDLINE (Ovid), EMBASE (Ovid), NHS Economics Evaluation Database (NHS EED, Database of Abstracts of Effects (DARE) and the HTA Database (both the CRD and Cochrane Library interfaces) were searched on 22nd February 2015 for publications in English from 2006 onwards to identify studies published since TA 132. In addition recent relevant conference proceedings were searched from 2013. The searches are documented in full in Appendix 17 of the submission and are fully reproducible. All strategies combined two search facets: Conditions included in the analysis (hypercholesterolaemia, unstable angina, myocardial infarction and stroke); and quality of life measures or utilities. The search terms used included a range of both thesaurus and free text terms and were appropriate.

Studies in the UK were preferred and included study designs were cost-effectiveness, cost-utility analysis and observational studies reporting HRQoL data. Finally, to be consistent with the NICE reference case, only studies that reported quality of life scores using the EQ-5D questionnaire were included. Most of the utility data were derived from previous technology appraisals and modelling conducted for clinical guidelines (TA94,[9] TA132[5] and CG181.[1]) New studies identified in the updated systematic review were only used to estimate health state utilities for the TIA and post TIA states.[77] Based on the inclusion and exclusion criteria, the systematic review identified 18 publications that reported utility values for patients with hypercholesterolaemia-related symptoms, including angina, stroke, MI and TIA. The company assessed the quality of included studies using the quality checklist developed by the NICE Decision Support Unit.[78] The methods and findings of all the identified studies were tabulated by the company and utility values from those studies deemed to be inconsistent with the NICE reference case were not included in the cost-

effectiveness model. The final values selected for inclusion in the model are provided in Table 16.

Whilst the utility values assigned to most health states are reasonably well justified, there are a number of issues worth noting.

Table 16 Summary of utility values used by the company in the base case cost-effectiveness analyses

State	Utility value: mean	Standard error	Reference in submission
Well	1	n/a	By definition
Unstable angina	0.770	0.038	Goodacre 2004[79]
Post-unstable angina	0.80	Not reported	NCCPC[80] Ara 2008[15]
MI	0.760	0.018	Goodacre 2004[79]
Post-MI	0.80	Not reported	MI plus Lacey 2003[81]
Stroke	0.50	Not reported	Tengs 2003[82] weighted by stroke severity from Youman 2003[83]
Post-stroke	0.628	Not reported	Tengs 2003[82] weighted by stroke severity from Youman 2003[83]
CV death	0	n/a	By definition
Non-CV death	0	n/a	By definition
Stable angina	0.808	Not reported	Melsop 2003[84]
Post-stable angina	0.808	Not reported	Assumption based on Melsop 2003[84]
TIA	0.76	0.017*	6 months data point, Luengo-Fernandez, 2013[77]
Post TIA	0.76	0.020*	24-month data point, Luengo-Fernandez, 2013[77]

Well health state

To estimate age and sex adjusted baseline health state utility multipliers for the "well" state of the primary prevention model, the company used a published equation reported by Ara and Brazier.[85]

$$General\ population\ EQ-5\text{D} = 0.9508566 + 0.0212126 * male - 0.0002587 * age - 0.0000332 * age^2$$

This yields general population EQ-5D norms given the age and sex distribution of the modelled cohort, and updates annually in the model with increasing age. Whilst this is

generally an appropriate approach, Ara and Brazier[85] have published a second algorithm to estimate age and sex adjusted EQ-5D utilities among those in the general population who have no reported history of cardiovascular disease. Since by definition in the current submission people in the well state are those who have no history of CVD, the ERG believes this second algorithm may have been more appropriate for estimating the baseline utilities in primary prevention model. The equation for this alternative approach is as follows:

$$\text{No CVD } EQ-5D = 0.9454933 + 0.0256466 * male - 0.0002213 * age - 0.0000294 * age^2$$

CVD event health states

Within the model, heath utility weights identified for CV events (and post-event states) were multiplied by corresponding age related utilities to estimate the QALYs accruing over time. Whilst this approach is consistent with descriptions of prior modelling conducted in the area, it has been noted in the literature that when multiplying health state utilities together, it is preferable to use age adjusted health state multipliers to improve accuracy.[85] For example, if the identified utility for the MI health state is 0.76 based on reported values in a cohort with a mean age of 65 years, and age-adjusted multiplier is derived by dividing this by the age matched utility in the absence of MI. For the current example, using the estimated UK EQ-5D age relate norm for people with no CV event, this would be 0.82. Thus the ae-adjusted multiplier would be 0.76/0.82 = 0.923. Thus, when applied multiplicatively to the baseline age related utility, the occurrence on an MI in a 65 year-old would result in a drop in utility from 0.82 to 0.76 (=0.82*0.923). However, this is not the case in the company's model. Instead, the age related baseline utilities are being multiplied by the raw utility values identified from alternative sources for cohorts of varying age. This may lead to inappropriate age adjustment of health state utilities in the model.

A further point worth noting, is that since the publication of TA132[5] Ara and colleagues (who conducted the original modelling for TA132), have published a methodological paper proposing alternative utility values for this very clinical area.[85] Based on an analysis of EQ-5D values reported by participants in the Health Survey

for England (HSE), they were able to estimate mean EQ-5D utility weights for members of the general population (N = 26,679) experiencing different types of CVD, within a year of a primary event, and in subsequent years following an event. They were also able to estimate values for those experiencing multiple events, although the current model does not track multiple event histories. Given that these health state utilities (Table 17) are from a single source and are representative of the population with and without CVD in England, these are arguably more coherent and suitable for the modelling conducted here.

Table 17 Health states utilities form the analysis of Health Survey for England data

Health State	Utility multiplier	N	SE	Reference	Age	Age-adjusted multipliers
Angina*	0.615	271	0.019	Ara R, Brazier JE, 2010.[85]	68.8	0.782
Post angina*	0.775	246	0.015	Ara R, Brazier JE, 2010[85].	68	0.986
MI	0.721	31	0.045	Ara R, Brazier JE, 2010[85]	65.4	0.901
Post MI	0.742	206	0.02	Ara R, Brazier JE, 2010[85]	65.1	0.927
Stroke	0.626	76	0.038	Ara R, Brazier JE, 2010.[85]	67.9	0.791
Post Stroke	0.668	291	0.018	Ara R, Brazier JE, 2010[85]	66.8	0.839
TIA	0.68		0.0413	Ratio from Luengo -Fernandez, 2013[77]	66.09	0.854
Post TIA	0.73		0.0195	Ratio from Luengo -Fernandez, 2013[77]	65.02	0.906

* The same utility values are assumed for stable and unstable angina

Minor points relating to selected health state utility values

Some further minor points relating to the utility values selected for use in the company's economic model are discussed below:

Unstable angina & post unstable angina

To estimate the health state utility associated with unstable angina, two relevant published studies[79, 86] were considered by the company. It was mentioned in the company submission that the values reported by Kim et al[86] (average 0.731 at 4 months; 0.744 at 12 months) were rejected because the surveyed a cohort included

more severe patients with NSTEMI. Instead, a value of 0.77 (obtained by Ara and colleagues from personal communication with Goodacre) was selected for unstable angina in the first year, with the assumption that this would improve in subsequent years to 0.8. This was stated as being consistent with Ara et al,[15] Ward et al[68] and CG181.[1] Whilst this seems justified, it is worth noting the Ara et al. updated their utility value for unstable angina in the first year from 0.77 to 0.73 and this is the value that appears in their final HTA report.[15]

MI & post MI

It was also mentioned by the company that a utility value of 0.76 was applied for MI in the first year, to be consistent with the modelling conducted for TA132.[5] However, whilst the original value in the modelling for TA132 was 0.76, it was changed to 0.7 in an addendum based on data reported by Lacey et al.[81] The value of 0.7 appears in the final HTA monograph.[15] The value of 0.76 appears to have come from the study by Goodacre et al,[79] which reported 6 month utility data for a cohort with undifferentiated chest pain. Thus, the value of 0.76 may overestimate the health state utility for patients with true MI. The utility value for the post MI state was taken to be 0.8, which is consistent with the TA132, but it is not entirely clear how this value was derived.

Stroke & post stroke

Health utility associated with the post stroke state was derived from Tengs et al.[82] which reports a meta-regression of health state utilities from 20 studies. This source was again chosen to be in line with the previous TA132. As Tengs et al.[82] reported different utilities for mild, moderate and severe stroke, a mean weighted estimate of 0.628 was calculated using proportions, reported by Youman et al,[83] of patients experiencing stroke of different severity (0.19 mild, 0.27 moderate, 0.54 severe). However, the meta-regression by Tengs et al.[82] included utility values obtained from a number of difference countries using a number of different instruments. Whilst the predicted results are expressed for the Time trade-off method, there is uncertainty as to how values obtained from other instruments and tariffs might have affected the results. In addition, the follow-up time to which the estimated values should apply is unclear, but they are assumed to apply to the post stroke state (i.e. subsequent years

following the event). A lower value of 0.5 was then assumed for the first year post stoke.

Given the availability of more recent EQ-5D estimates reported by severity of stroke and follow-up time for a UK cohort,[77] the ERG requested an additional analysis using this data. The manufacture subsequently supplied this, and it was found to have minimal impact on the ICERs.

Stable angina & post stable angina

Although not included in the base case analysis, the company assigned a value of 0.808 for first and subsequent years following onset of stable angina. Whilst this is consistent with the value applied in the first year following onset in the modelling for TA132, a value of 0.9 was ultimately assumed in subsequent years.[15]

5.2.8 Resources and costs

Different sources of data including health care resource use and drug cost databases, and the systematic review of economic evaluations, were used by the company to identify values for all cost parameters in the model. These included drug costs, monitoring costs, and costs associated with CV events. For CV events, higher costs were applied in the first year following the event than in subsequent years, to reflect the higher costs associated with the acute episode and immediate rehabilitation. All costs were expressed in 2013/2014 values using, where necessary, the Hospital & Community Health Services (HCHS) Pay and Prices Index[87] to adjust values. Below, each of the main cost categories is discussed in turn.

Intervention and comparator cost

Drug costs associated with the intervention and comparators were taken from the drug and pharmaceutical electronic market information tool (eMit) or the Monthly Index of Medical Specialties (MIMs). Both are appropriate sources for drugs prescribed in the England and Wales, but it is noted in the NICE methods guide [88] that the preferred source for drugs prescribed predominantly in primary care is the NHS Drug Tariff[89]
No administration costs were included as both the intervention and the comparators are administered orally via one tablet per day. Annual costs were calculated based on the unit cost per pack of 28 tablets, assuming no wastage. In the primary prevention

cost-effectiveness analysis, the company has assumed that those patients who experience a CV event will be switched to atorvastatin 80mg which is in line with NICE CG181.[1] The company also considered a scenario where the price of ezetimibe drops by 75% following patent expiry. This is due to occur in April 2018, and was applied in the scenario analysis from year 3 of the model. Tables 18 and 19 below reproduce the unit costs for drugs used in the model and estimated annual costs for the comparator and intervention regimens.

Table 18 Drug cost estimation

Drug	mg	Cost (£)	SD	Cost annual (£)	Cost per 28 day pack (£)
Atorvastatin	10	0.74	1.33	9.65	0.74
Atorvastatin	20	1.02	1.39	13.31	1.02
Atorvastatin	40	1.05	0.23	13.70	1.05
Atorvastatin	80	1.90	0.25	24.78	1.90
Simvastatin	10	0.17	0.07	2.22	0.17
Simvastatin	20	0.48	1.18	6.26	0.48
Simvastatin	40	0.36	0.11	4.70	0.36
Simvastatin	80	1.90	-	24.78	1.90
Ezetimibe	10	26.31	-	343.20	26.31
Ezetimibe once generic	10	6.58	-	85.80	-

Table 19 Estimated annual costs of the comparators and interventions for the base-case analysis

Strategy	Annual cost of comparator (£)	Annual cost of intervention (ezetimibe) (£)	Annual cost of intervention (Anticipated price with generic cost of ezetimibe) (£)
Primary prevention - monotherapy	0.00	343.20	85.80
Primary prevention - add on to Atorvastatin 20 (mg)	13.31	356.51	99.11
Secondary prevention– monotherapy	0.00	343.20	85.80
Secondary prevention- add on to Atorvastatin 40 (mg)	13.70	356.90	99.50

Monitoring cost

All resource use associated with monitoring of treatment were obtained from CG181.[1] The company has assumed that patients within the first year of treatment would have increased monitoring requirements compared to subsequent years (Table 20). Monitoring costs include appointments to take blood samples for biochemistry tests, GP visits, and lab costs for total and LDL-c, and Liver transaminase (ALT or AST).

Based on deliberations of the Guideline Development Group (GDG) for CG181[1] it was assumed that total and HDL cholesterol tests would be performed at 3 months and annually thereafter. It was also assumed that a liver transaminase enzymes test would be performed at 3 and 12 months following initiation of treatment with a statin, and then annually from the second year onwards. Unit costs for the monitoring tests were taken from the NHS Reference cost 2013-2014.[90] It was also assumed that patients would have an annual medication review via a face-to-face appointment with a GP and one additional consultation in the first year of treatment. From the explanation it appears that the company has assumed two GP visits in the first year of treatment and one per year in subsequent years. However, 2.2 GP visits are applied in the first year of the model and 2 visits are applied in subsequent years. This is consistent with CG181 but is not explained in the text. Costs associated with consultations are sourced from the PSSRU Unit Costs of Health and Social Care.[87]

The ERG had some concerns relating to the appropriateness of assuming equal monitoring costs between the ezetimibe and comparator arms in the first cycle where higher costs associated with the first year of treatment are assumed. This seems inappropriate for the comparator arms, since individuals who either remain on statin alone or on no treatment are not in the first year of treatment. Apart from this issue which would result in only minor changes to monitoring costs in the first cycle of the model, the monitoring assumptions and costs seem appropriate. Based on the above assumptions, total annual monitoring costs in first and subsequent years of treatment are estimated to be £120.12 and £101.46 respectively.

Table 20 Monitoring resources use and costs

	Usage - 1st year	Usage further years	Unit Cost (£)
Routine Appointments:			
Appointment to take blood sample (with health care assistant)	2	1	£6.46
Appointment with GP	2.2	2	£46.00
Blood tests:			
Total cholesterol	2	1	£1.00
HDL cholesterol	2	1	£1.00
Liver transaminase (ALT or AST)	2	1	£1.00

Health state costs

The company identified cost studies from the formal searches undertaken to retrieve economic evaluation and utility studies. In addition four relevant studies were identified by hand searching. No further details of the hand searching undertaken are provided although the source of two of the studies was the NICE website. The identification of additional studies reinforces the opinion of the ERG that searches undertaken for cost effectiveness studies were too precise and excluded terms that would have benefited the sensitivity. In particular, hypercholesterolemia was the only condition included in the search, rather than widening the scope to include studies on dyslipidaemia and cardiovascular and coronary diseases. Thus, whilst cost studies relating to CV events were considered relevant, they were not searched for in a systematic manner.

Based on the review of 10 studies identified as being relevant for informing health state costs, the company estimated first and subsequent year costs for inclusion in their model. The ten studies included 6 of the studies included in the review of economic evaluations (i.e. those where a cost for at least one of the health states was estimated based on assumptions, clinical expert opinion, specific resource use breakdown) and the four additional studies identified through hand searching.[1, 91-93] The final selected values for the modelled health states are reproduced in Table 21. Some specific points relating to the selected values are discussed below.

Table 21 Health state costs

Health state	Annual cost used in the model	Original value	Reference
Well	£0.00	£0.00	By definition
Unstable angina	£575.21	£477.00	Ara et al.[15]
Post unstable angina	£285.52	£226.59	CG94[94] (costs in 2010 prices inflated to 2014)
MI	£6,154.50	£3,966.00	Palmer 2002 + primary care and medication costs as UA[93]
Post MI	£625.27	£500.00	CG18 (costs in 2005 prices inflated to 2014)
Stroke	£14,151.26	£10,059.33	Youman 2003[83] costs in 2002 prices inflated to 2014)
Post stroke	£3,927.73	£2,792.00	Youman 2003[83] (costs in 2002 prices inflated to 2014)
CV death	£5,697.23	£0.00	Clarke 2003, Youman 2003[83]{ inflated to 2014 and weighted by fatal CHD and fatal Stroke
Non-CV death	£0.00	£0.00	By definition
Stable angina	£242.38	£201	TA132[5] costs in 2006 prices inflated to 2014)
Post stable angina	£242.38	£201	TA132[5] costs in 2006 prices inflated to 2014)
TIA	£3,982.31	£3,660	Luengo-Fernandez 2012[91] (costs in 2009 prices inflated to 2014)
Post TIA	£1,386.22	£1,274	Luengo-Fernandez 2012[91] (costs in 2009 prices inflated to 2014)

Stroke and TIA

One of the studies identified through hand searching was a UK based cohort study which estimated costs of stoke and TIA over a period of 5 years.[91] This provided a breakdown of average costs by stroke severity and time since the event. Whilst the costs associated with TIA were sourced from this study, the stroke estimates were rejected in favour of those estimated by Youman and colleagues in 2003,[83] which were also adapted for use in TA132[5] and in the NICE guidelines on the management of hypertension.[94] This was done because the costs estimated by Luengo-Fernandez et

al.[91] included only hospital costs, and not wider social care and primary care costs associated with stroke management. Whilst the ERG understand the decision, the data from Youman is now quite old and reliance on inflation indices to cover such a long time period may lead to inaccuracy in this parameter. It is possible that a more up to date estimate of stroke costs could have been calculated using reported data on resources use (such as length of stay) coupled with up to date reference costs covering the acute admission, excess bed days, and rehabilitation period.[90]

Myocardial Infarction (MI)

Regarding the costs of the MI health state, acute first year hospital costs were taken from an older study by Palmer et al 2002 (£3,966), inflated to 2013/2014 values and updated to incorporate primary care and drug costs. This seems generally appropriate for the first year costs but, again, applying inflation indices over such a long time period will lead to inaccuracies and may fail to account for the influence of changes in management practice on costs. For the post MI health state, a value of £500 per year was taken from NICE CG18[94] which was also applied in CG127[95] and CG172.[96] The long-term annual post-MI hospital cost estimated by Palmer et al. (£1,587) was rejected on the grounds that it was considered very high. This seems appropriate as this cost will likely include costs associated with subsequent CV events which are already being counted explicitly in the model.

Adverse event costs

Based on review of adverse event rates in RCTs included in the clinical effectiveness review, ezetimibe as monotherapy and ezetimibe co-administered with a statin were found to have similar adverse event profiles compared with placebo and statin alone. Whilst the reported ranges of adverse event rates in included trials do appear similar, these outcomes have not been meta-analysed so it is difficult to make a judgement on the conclusion that there are no important differences. However, based on the data reported, the ERG agrees that any differences in adverse event rates are likely to be small and so have little impact on the overall costs of strategies.

5.2.9 Cost effectiveness results

All estimated costs and outcomes were summarized in the results section of the company's submission. A breakdown of total drug costs, health state costs and monitoring costs was provided for each strategy and presented with and without discounting. Total Life-years and QALYs accrued in the different health states were also summarised for the intervention and comparator.

For each scenario in the base-case analysis the company reported total costs and QALYs, incremental costs, incremental QALYs and the ICER (Table 22). To illustrate the flow of patients through the model for each comparator, Markov traces were provided to illustrate the proportion of patients in each health state for each cycle over the modelled time horizon.

The company base case results suggest that for a 60 year old primary prevention cohort with a 20% Q-risk, ezetimibe monotherapy (in those who cannot tolerate a statin) has an ICER just above £30,000. Compared with atorvastatin (20mg) alone, ezetimibe as an add-on for primary prevention has an ICER of £58,473. In the secondary prevention cohort (age 69), ezetimibe monotherapy has an ICER of £17,553 compared with no treatment. As an add-on to atorvastatin (40mg) for secondary prevention, the ICER for ezetimibe is £30,940.

Table 22 Company's base case cost-effectiveness results

	Intervention/ comparator	Total Costs	Total QALYs	Total LYs	Incremental Costs	Incremental QALYs	ICER*
Primary prevention– monotherapy	No treatment	£8,143	11.82	23.76	-	-	-
	Ezetimibe 10mg	£13,332	11.99	24.23	£5,188	0.172	£30,129
Primary prevention- add on to statin	Atorvastatin 20mg	£8,359	12.10	24.57	-	-	-
	Ezetimibe 10mg + Atorvastatin 20mg	£13,796	12.20	24.84	£5,437	0.093	£58,473
Secondary prevention – monotherapy	No Treatment	£31,072	13.80	5.76	-	-	-
	Ezetimibe 10mg	£34,957	14.49	5.98	£3,885	0.683	£17,553
Secondary prevention – add on to statin	Atorvastatin 40mg	£31,699	6.24	15.30	-	-	-
	Ezetimibe 10mg + Atorvastatin 40mg	£35,811	6.37	15.73	£4,113	0.422	£30,940

*Results are based on updated analysis provided by the company in response to the ERGs clarification letter

Cost-effectiveness for subgroups

The company has identified three relevant subgroup analyses to conduct on patients with type 2 diabetes, chronic kidney disease (CKD) and Heterozygous familial hypercholesterolaemia (HeFH) due to the differences in the baseline CV risk and the lipid-modification management strategies in these patients compared to general population.

Primary prevention for people with diabetes

To conduct cost-effectiveness analysis for the primary prevention among type 2 diabetes patients the company has taken the baseline risks from the type 2 diabetes specific risk assessment tool (UKPDS) and baseline characteristics were derived from a UK observational study.[71] Mean age and female ratio were assumed to be 67 years and 44.3% respectively based on this study.[71] The baseline pre-treatment LDL-c level was assumed to be 4.32 mmol/L based on the study by Van Staa et al.[70]

The company has used the same Markov model and comparator and interventions as used for the base–case analysis for this sub-group analysis with only changing the baseline characteristics, the baseline risks and the clinical effectiveness. 10-year CVD risk was estimated using UKPDS risk assessment tool. The company has conducted a separate meta-analysis to determine the change in LDL-c for people with diabetes. Among patients with diabetes, the mean difference for ezetimibe plus statin vs statin monotherapy was estimated to be -18.8% (95% CI -20.7 to -17.0). The estimated effect was incorporated into the cost-effectiveness model for the sub-group analysis. The company has also applied the same costs and utility data as used in the base-case scenario in this sub-group analysis. Results for the primary prevention population with diabetes at a 10-year CV risk of 20%, when ezetimibe is prescribed as a monotherapy are summarised in Table 23.

Table 23 Cost effectiveness results for sub-group analysis: primary prevention with diabetes, monotherapy

	Total Costs	Total QALYs	Total LYs	Incremental Costs	Incremental QALYs	ICER
No treatment	£8,709	9.36	18.00	-	-	-
Ezetimibe 10mg + Atorvastatin 20mg	£12,815	9.56	18.47	£4,106	0.202	£20,294

*Results are based on updated analysis provided by the company in response to the ERGs clarification letter

Also results for the primary prevention population, for diabetic patients receiving add-on therapy are summarised in Table 24.

Table 24 Cost effectiveness results for sub-group analysis: primary prevention with diabetes, add-on to statin

	Total Costs	Total QALYs	Total LYs	Incremental Costs	Incremental QALYs	ICER
Atorvastatin 20mg	£8,483	9.72	18.87	-	-	-
Ezetimibe 10mg + Atorvastatin 20mg	£12,843	9.86	19.20	£4,360	0.139	£31,352

*Results are based on updated analysis provided by the company in response to the ERGs clarification letter

People with Chronic Kidney Disease (CKD)

A subgroup analysis using a maximum atorvastatin dose of 20mg has been evaluated by the company among people with CKD for the secondary prevention population only, because the base case results for primary prevention evaluated the same dose. The same baseline risks as the base-case population were applied. Results from subgroup analysis for the secondary prevention of CVD for people with CKD, who are limited to atorvastatin 20 mg are summarized in Table 25.

Table 25 Sub-group results for people with CKD, secondary prevention – add-on to statin

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
Atorvastatin 20mg	£31,694	15.30	6.24	-	-	-	-
Ezetimibe 10mg + Atorvastatin 20mg	£35,807	15.73	6.37	£4,112	0.422	0.133	£30,939

People with HeFH

The company has not conducted separate cost-effectiveness analyses among people with HeFH due to the extremely limited data on the baseline risks of this group. As the patients with HeFH have extremely high LDL-c of at least 8 mmol/L[97] the company provided the ICER in different level of LDL-c and believed that at such high levels of LDL-c, ezetimibe is a highly cost-effective option (Figure 3).

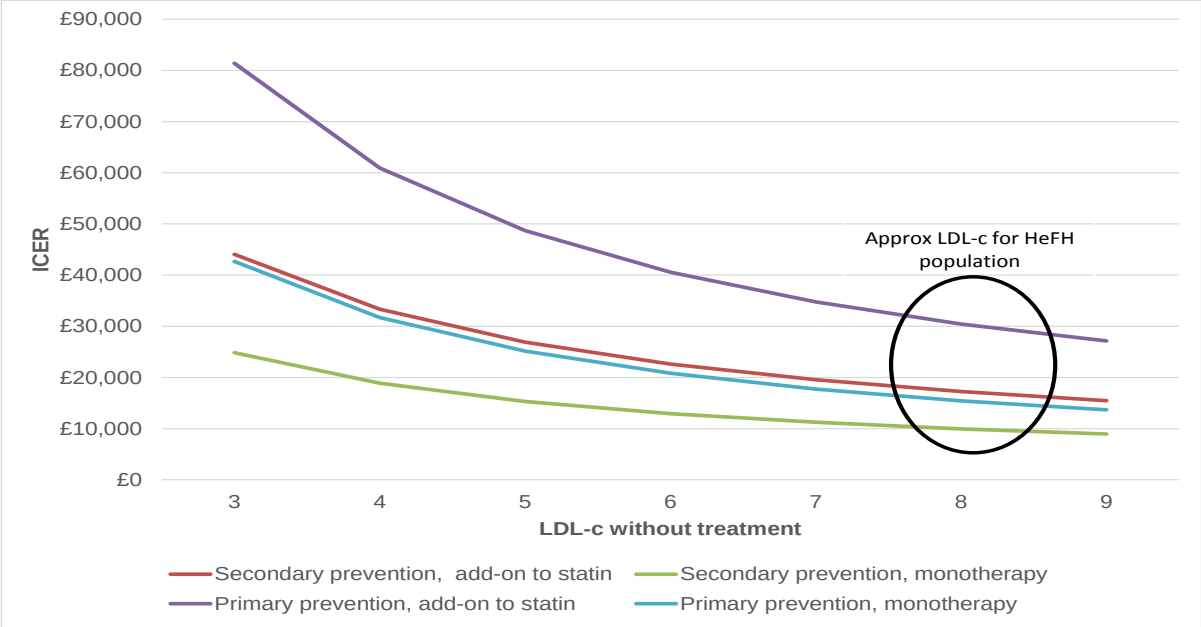


Figure 3 Incremental cost-effectiveness ratios (ICERs) for base populations, by varying baseline LDL-c levels

5.2.10 Sensitivity analyses

The company conducted both deterministic and probabilistic sensitivity analysis to evaluate the uncertainty surrounding different parameters and assumptions used in the model. For probabilistic sensitivity analyses (PSA) all relevant parameters were defined as distributions to be used in the Monte Carlo simulation for PSA. Results were presented as scatter plots on the incremental cost-effectiveness plane and cost-effectiveness acceptability curves (CEACs). A number of issues were identified with the PSA, which resulted in significant underestimation of the uncertainty surrounding the ICERs. The identified issues are outlined as follows:

- In the "parameters" sheet of the model, all the beta distributions for utility parameters appeared to be misspecified. They were treated as if the mean utility estimate represented a binomial probability, which was multiplied by N (the sample size for the estimate) to recover an estimate of alpha (i.e. a number of events). This is not the case, and the method of moments approach should have been used to derive the alpha and beta parameters for these utility distributions.
    - Alpha= (((mean)^2)*(1-mean))/((SE^2)-(mean))
    - Beta= ((1-mean)*((1-mean)*(mean))/((SE^2)-1))
- An error was also identified in the formula used to recover the log scale standard error for the specification of lognormal distributions (used for risk ratios included in the model). This resulted in significant underestimation of uncertainty surrounding all the risk ratios. It was apparent from examining the random draws from these distributions, that the range of values did not cover the reported confidence limits.
- For parameters representing the additional percentage reduction in LDL-c associated with ezetimibe use, which were incorporated as beta distributions, the alpha and beta parameters were not appropriately estimated using the method of moments approach. This again resulted in an underestimation of the associated uncertainty.

The above inconsistencies were identified after the clarification letter was sent to the company, and so these were not amended in a subsequent probabilistic analysis that the company provided. Another source of uncertainty which was not originally

included in the PSA was the initial distribution of the secondary prevention cohort across the post-CV event states included in the model, and the ERG requested if this could be addressed at the clarification stage. The company duly incorporated this uncertainty using a Dirichlet distribution. Whilst the response indicated that the event numbers behind the proportional distribution were not available, the company did manage to recover approximate estimates of what these might be, and so incorporated this source of uncertainty in an updated probabilistic analysis. This significantly increased the spread of points on the incremental cost-effectiveness plane for the secondary prevention cohort. Given the errors identified in the PSA, the company's results are not reproduced here.

Deterministic sensitivity analysis

The company performed some scenario and one-way sensitivity analyses around relevant model parameters to evaluate their impact on the ICER. Key parameters including risk ratios, discount rates, post stroke utility values and health state costs were varied by the upper and lower bounds of their confidence limits, with results presented as tornado diagrams.

This analysis illustrated that the ICERs are most sensitive to changes in the rate ratio applied for non CV deaths per one mmol/L reduction in LDL-c, and the discount rate for QALYs. This is potentially important, since rate ratio per mmol/L reduction in LDL-c (sourced from the CTT meta-analysis) is not significantly different from one (0.97 95% CI 0.92-1.03). However, the estimate is included in the model as log-normal distribution, with the point estimate providing reduced non-CV mortality compared with no treatment or statin therapy alone. Thus, removing this non-significant effect from the model increases the ICERs for ezetimibe. In addition, since the distribution assigned to this parameter was miss-specified in the company's model, the sampled estimates for the PSA were all less than one. Thus, the uncertainty surrounding this input was not appropriately propagated through the PSA (see 5.3 for exploratory sensitivity analysis conducted by the ERG).

Scenario analysis

In addition to the one-way sensitivity analysis, the company conducted some scenario analyses. The scenarios assessed and their impacts on the cost-effectiveness findings are summarised below.

Scenario A: Application of alternative pre-treatment LDL-c levels:

The pre-treatment LDL-c levels were varied between 3 and 9 mmol/L, with the results indicating that with higher pre-treatment LDL-c levels the ICERs improve for ezetimibe monotherapy and ezetimibe as an add-on in both the primary and secondary prevention cohorts. This is as expected, since the pre-treatment LDL-c level drives the absolute magnitude of the additional LDL-c reduction achieved with ezetimibe, and in turn the size of effects on CV events.

Scenario B1 & B2: Applying alternative 10-year CV risk levels

For the base case the company modelled a 20% 10-year risk of CV events based on the Q-RISK assessment tool (note that the risk of events included in modelled base case is lower than this). The impact of changing the baseline 10-year Q-risk to 30% and 10% were assessed for the primary prevention cohort. For ezetimibe monotherapy the ICERs at a 10% and 30% 10-year risk were estimated to be £47,067 and £21,187 respectively. This compares with a base case estimate of £29,286. For ezetimibe as an add-on to statin, the ICER was £84,752 at the 10% risk level, and £41,783 at the 30% risk level. The comparable base case ICER was £56,394 (at 20% ten year risk).

Scenario C: Application of costs for generic ezetimibe from year 3 onwards

The effect of applying a 75% cost reduction for ezetimibe from year three in the model was explored. This was done to factor in the impact of patent expiry which is due to occur in April 2018. This decreased the ICER in the primary prevention cohort to £10,146 for ezetimibe monotherapy and £20,540 for ezetimibe as an add-on. The respective ICERs for the secondary prevention cohort were £8,140 and £13,874.

Scenario D1 & D2: Including TIA and stable angina states in the model

In the base case, the company included only unstable angina, MI, Stroke and death (CV and non-CV related) states. In this scenario the company investigated effect of including TIA and stable angina without and with and without treatment effects for

ezetimibe and statin. For the analysis with effects, the same risk ratios for MI were applied stable angina, and risk ratios for stroke were applied for TIA. Under these scenarios the ICERs decreased for the primary prevention cohort, but increased slightly for the secondary prevention cohorts (Table 26).

Table 26 Impact of including TIA and stable angina states, with and without treatment effects

Scenario	ICER for ezetimibe
Primary prevention ezetimibe monotherapy (base case)	**£29,286**
Addition of TIA and stable angina health states (with no treatment benefit)	£26,224
Addition of TIA and stable angina health states (with treatment benefit)	£22,426
Primary prevention ezetimibe as add-on to statin (base case)	**£56,394**
Addition of TIA and stable angina health states (with no treatment benefit) (A20 + E10 vs. A20)	£48,090
Addition of TIA and stable angina health states (with treatment benefit) (A20 + E10 vs. A20)	£45,608
Secondary prevention ezetimibe monotherapy (base case)	**£17,553**
Addition TIA and stable angina health states (with no treatment benefit)	£18,951
Addition of TIA and stable angina health states (with treatment benefit)	£18,951
Primary prevention ezetimibe as add-on to statin (base case)	**£30,940**
Addition TIA and stable angina health states (with no treatment benefit) (A40 + E10 vs. A40)	£34,730
Addition of TIA and stable angina health states (with treatment benefit) (A40 + E10 vs. A40)	£34,730

Scenario E: Applying no treatment effect on unstable angina

As unstable angina was not evaluated in the CTTC meta-analysis, the company explored a scenario where the risk ratio for unstable angina was set to 1 for both ezetimibe and statin. This change had very little impact on the ICERs.

Scenario F: Applying results from IMPROVE-IT trial

In this scenario the relative risk reductions from IMPROVE-IT trial[3] were applied by the company to estimate the transition probabilities when ezetimibe is added-on to simvastatin (40mg). Based on the events observed in the IMPROVE-IT trial the relative risks (RR) were estimated and applied as follows: non-fatal MI (RR: 0.871, 95% CI: 0.798–0.950), non-fatal stroke (RR: 0.802, 95% CI: 0.678–0.949) CV death (RR: 1.0, 95% CI: 0.887–1.127). A relative risk of 1 was applied for non-CV deaths, and the cohort age (64 years) and sex distribution (24.3% female) were updated to match the characteristics of the IMPROVE-IT cohort. Under this scenario there is a significant jump in the ICER, from £30,940 to £137,642 (secondary prevention, add-on to statin).

Scenario G: Applying alternative doses of atorvastatin as background therapy

To reflect the variation in clinical practice the company has investigated a scenario to explore the impact of adding ezetimibe to alternative doses of statin in the primary and secondary prevention cohorts:

- Primary prevention (atorvastatin 10 mg and 40 mg)
- Secondary prevention (atorvastatin 10 mg, 20 mg & 80 mg)

Note that in the model, the same effects are modelled for atorvastatin 20mg, 40mg and 80mg. So changes between these doses result in very small changes in the ICERs (due to very small differences in cost alone). However, when the lower atorvastatin (10mg) is applied (with lower effects on baseline pre-treatment risks) the ICERs for ezetimibe (as an add-on) improve somewhat: from £56,394 to £51,558 for primary prevention, and from £30,940 to £28,256 for secondary prevention.

Scenario H: Applying alternative time horizons

In the base case analysis a lifetime time horizon was adopted by the company. The company has assessed the effect of applying different time horizons of 10, 20 and 30 years on the estimated ICERs. By decreasing the time horizon of the analysis to 10 years the ICER increased as follows: to £101,898 (primary prevention, monotherapy), to £199,460 (primary prevention, add-on to statin), to £30,858 (secondary prevention, monotherapy), and to £61,766 (secondary prevention, add-on to statin). Note that the impact of modelling discontinuation with a life-time horizon was not explored.

Scenario I: *Results by age and sex*

Finally the company estimated results for primary and secondary prevention by sex and starting age of the cohort (with the ten-year CVD risk set t0 20%). The results of this analysis show that the estimated ICERs all decrease with increasing starting age. This is likely a reflection of differences in the relative distribution of types of CV event with increasing age, and also the increased risk of secondary CV events in older age groups. Hence, the ratio of increased costs to additional benefits will decrease as the risks increase.

5.2.11 Model validation and face validity check

The company's submissions states that the economic model was quality assured by the internal processes of the external economists who produced it. This involved an economist not involved in the model's development reviewing it for coding errors, inconsistencies and the plausibility of inputs. It is also stated that the modelling approach used in this submission is consistent with the modelling for previous technology assessments conducted by Ward et al and Ara et al.[15, 68] However, as noted in the previous section, there are some inconsistencies with these prior models.

The company also attempted to validate the model using data from the IMPROVE-it trial. To do so the model time horizon was set to 5 years in accordance with IMPROVE-IT trial and the estimated average number of the CV events per patient year in the model was compared with the numbers observed in the IMPROVE-IT trial. The table from the company's submission showing the results of this comparison is reproduced below (Table 27). Based on these results, the company's submission concluded that the model results are similar in scale to the IMPROVE-IT results, with no obvious directional bias. It was noted that the incidence of events such as MI, stoke and on-CV death were under predicted by the model, whilst CV deaths were somewhat over predicted. No attempts were made to assess the external validity of the primary prevention model.

Table 27 Comparison of events in IMPROVE-IT and the cost-effectiveness model

Events	Mean number of events per patient			
	Cost-effectiveness model		IMPROVE IT trial	
	Ezetimibe + simvastatin 40mg	simvastatin 40mg monotherapy	Ezetimibe + simvastatin 40mg	simvastatin 40mg monotherapy
MI	0.098	0.113	0.104	0.119
Stroke	0.012	0.015	0.027	0.034
CV death	0.071	0.072	0.059	0.059
Non CV death	0.046	0.046	0.056	0.055

The ERG carried out a number of checks to assess the face validity of the model output. Comparing the modelled survival of the 60 year-old primary prevention cohort (20% CV risk) to the age/sex weighted population norms, it was noted that overall mortality was slightly higher in the first few cycles of the model (due to a higher proportion of CV deaths) but that the rate of increase in mortality slowed with age relative to the rate of increase in the general population over time. These results indicate greater overall survival in the modelled cohort compared with the age/sex matched general population (Figure 3). It was also noted that the ratio of CV to non-CV deaths (by annual cycle) decreases over time in the model. This appears inconsistent with UK mortality data, which suggests that the proportion of deaths attributable to vascular causes keeps increasing with age, whilst the annual proportion of deaths from ischaemic heart disease and cerebrovascular disease remains fairly constant from age 60 upwards. This suggests that the age related rate of increase in CV events (and CV deaths) may not be increasing sharply enough in the model.

The overall increased survival relative to the general population, may be partly related to the way in which vascular deaths have been adjusted out of the background (non-CV) mortality in the model. To estimate background mortality, UK life tables 1980-82 to 2011–2013 (Office of National Statistics (ONS)[98] were used to obtain age and sex- specific probabilities of death. The life table data were adjusted by excluding the proportion of deaths (by age and sex) attributable to all diseases of the circulatory

system (ICD-10 codes I00-I99); the rationale behind this being that CV deaths are explicitly modelled through the CV event risks. However, the CV deaths that are modelled explicitly only include deaths attributable to ischaemic coronary heart disease and cerebrovascular disease. The impact of this is that the overall mortality for the cohort in question may be underestimated in the model, with all circulatory deaths taken out of the background mortality, and only deaths from ischaemic heart disease and stoke put back in. This, in turn, may lead to overestimation of estimated LYs and QALYs in the model.

It is difficult to predict what impact the above inconsistencies might have on the modelled cost-effectiveness results. If the increase in CV risk associated with aging in the primary prevention model is progressing too slowly, this might act against ezetimibe. This is because the effects of lipid lowering therapy are not applied to the component of CV risk attributable to ageing. Conversely and somewhat counterintuitively, increasing other cause mortality could act in favour of ezetimibe, since a small additional effect on other cause mortality is modelled for ezetimibe through is further lowering of LDL-c.

A reproduction of the Markov trace is provided in Figure 4, which shows the proportion of the 60 year old primary prevention cohort under no treatment in the different states of the model over a 40-year time horizon. Note, this figure was modified to include the proportion of the cohort in the well state, which was not included in the original primary prevention traces provided in company's submission.

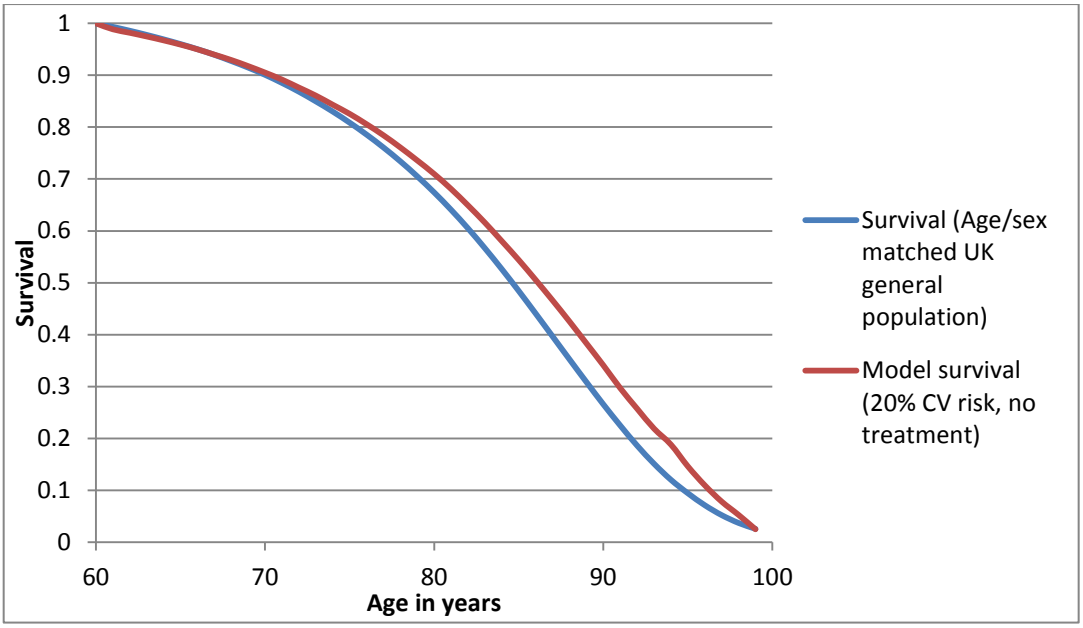


Figure 4 ERGs estimates of overall survival in the primary prevention cohort (age 60, 20% CV risk) compared with the age/sex matched UK general population

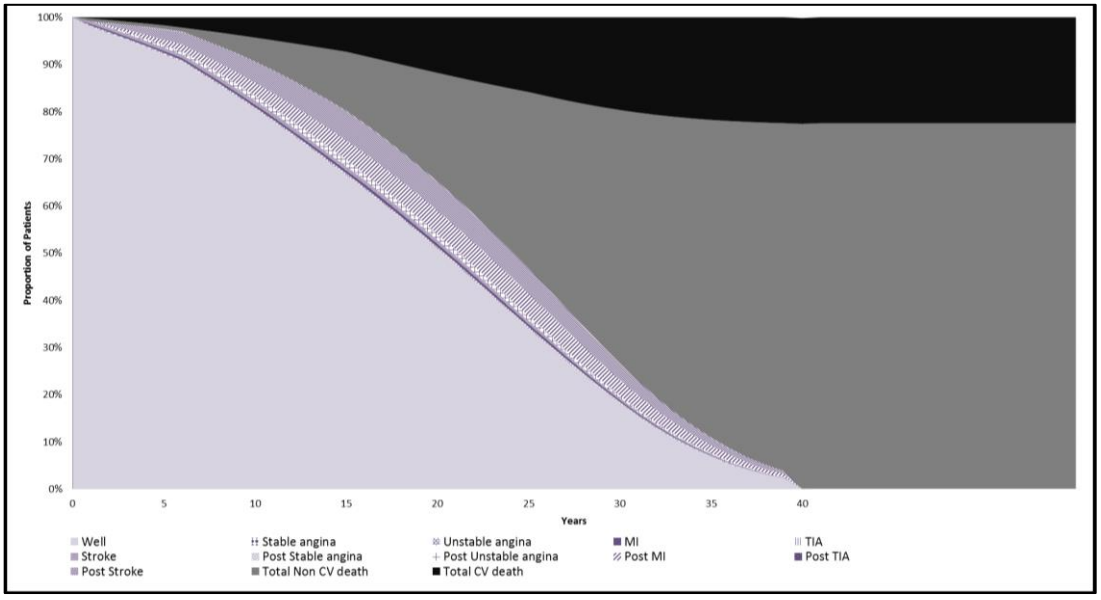


Figure 5 Markov trace: primary prevention, no treatment for 60 year-old cohort with 20% CV risk

5.3 Exploratory and sensitivity analyses undertaken by the ERG

Step 1: Correction of apparent bugs

Whilst undertaking the review of the model, the ERG identified a number of apparent bugs with potential to influence results. These were amended as follows:

- The half cycle correction, which did not appear to be implemented appropriately in the original model, was adjusted to reflect the assumption that on average, transitions occur at the midpoint within each cycle.
- Alteration to the increasing annual risk of CV events for age. This involved altering a formula where the annual increase in risk applied in the model appeared to be adjusted upwards a second time, to account for proportional increases in non CHD events (worksheet "Age adjusted PP risks, from cell J81 down"). This was not consistent with the description in the text of the submission.
- A minor bug in the formula used to estimate the risk and proportional distribution of the first CV event by starting age in the model ("Age adjusted PP risks spreadsheet" Columns I and R, rows 12 through to 72).
- Amendment of distributions specified for utilities, risk ratios, and percentage reductions in LDL-c.

An update of the company's base case deterministic results, following correction of the identified bugs, is presented in Tables 28 to 31. Overall, this has resulted in modest reductions in the ICERs for ezetimibe, particularly in the primary prevention cohort. Cost-effectiveness acceptability curves from the updated PSA are provided in Figure 6. The updated probabilities of cost-effectiveness at a threshold of £30,000 per QALY, are: (a) 71% for ezetimibe monotherapy as primary prevention; (b) 4% for ezetimibe as an add-on to statin for primary prevention; (c) 93% for ezetimibe monotherapy as secondary prevention; and (d) 53% for ezetimibe as an add-on to statin for secondary prevention

Table 28 Results with bugs fixed: primary prevention, monotherapy (a)

	Total Costs	Total QALYs	Total LYs	Incremental Costs	Incremental QALYs	ICER
No Treatment	£7,593	11.13	23.07	-	-	-
Ezetimibe	£12,533	11.31	23.57	£4,940	0.188	£26,253

Table 29 Results with all bugs fixed in the model: primary prevention, add on to statin (b)

	Total Costs	Total QALYs	Total LYs	Incremental Costs	Incremental QALYs	ICER
Atorvastatin (20mg)	£7,199	11.48	24.02	-	-	-
Ezetimibe + Atorvastatin (20mg)	£12,422	11.59	24.31	£5,223	0.107	£48,886

Table 30 Results with all bugs fixed in the model: secondary prevention, monotherapy (c)

	Total Costs	Total QALYs	Total LYs	Incremental Costs	Incremental QALYs	ICER
No Treatment	£24,239	5.22	12.80	-	-	-
Ezetimibe	£27,905	5.44	13.49	£3,666	0.221	£16,563

Table 31 Results with all bugs fixed in the model: secondary prevention, add on to statin (d)

	Total Costs	Total QALYs	Total LYs	Incremental Costs	Incremental QALYs	ICER
Atorvastatin (40mg)	£24,874	5.70	14.30	-	-	-
Ezetimibe + Atorvastatin (40mg)	£28,775	5.83	14.73	£3,901	0.133	£29,351

Figure 6 Cost effectiveness acceptability curve for primary prevention-monotherapy (a), primary prevention-add on to statin (b), secondary prevention-monotherapy (c) and secondary prevention-add on to statin (d)

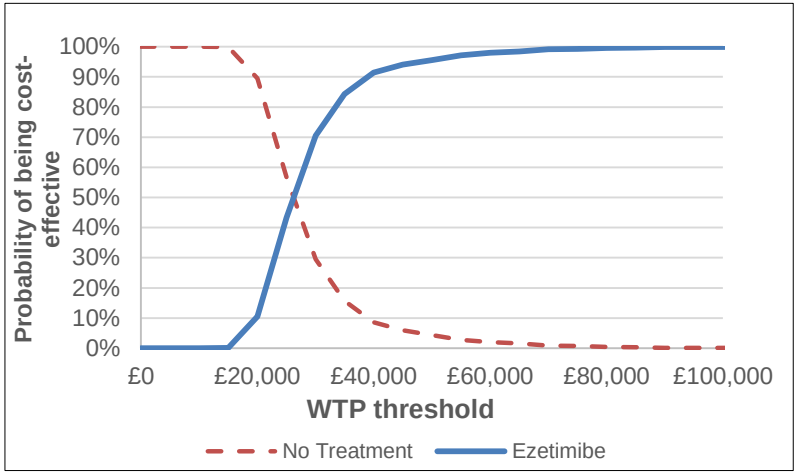


Figure (a)

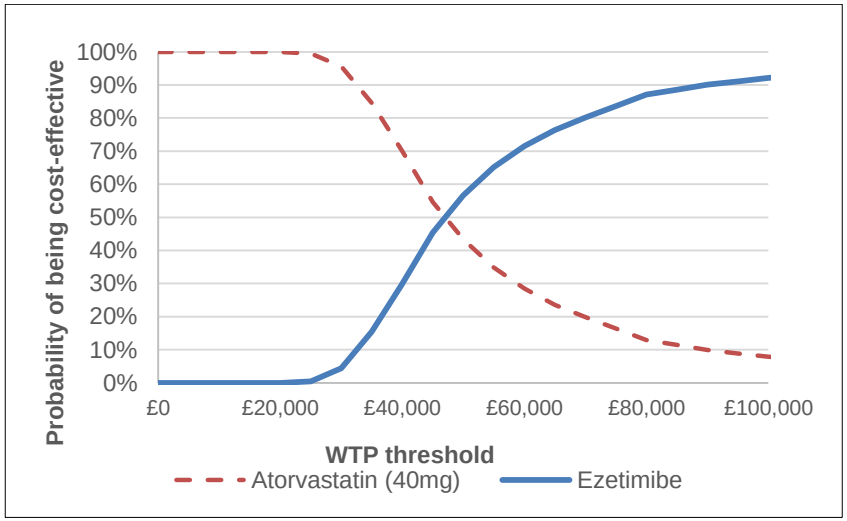


Figure (b)

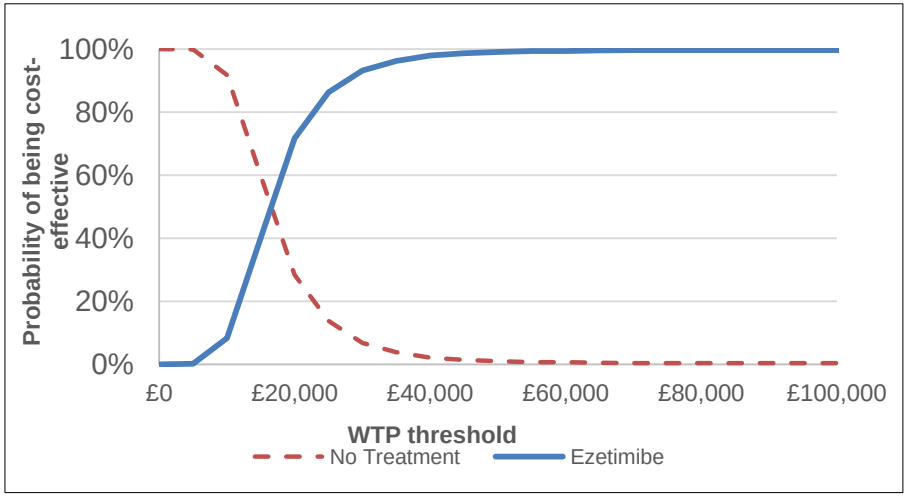


Figure (c)

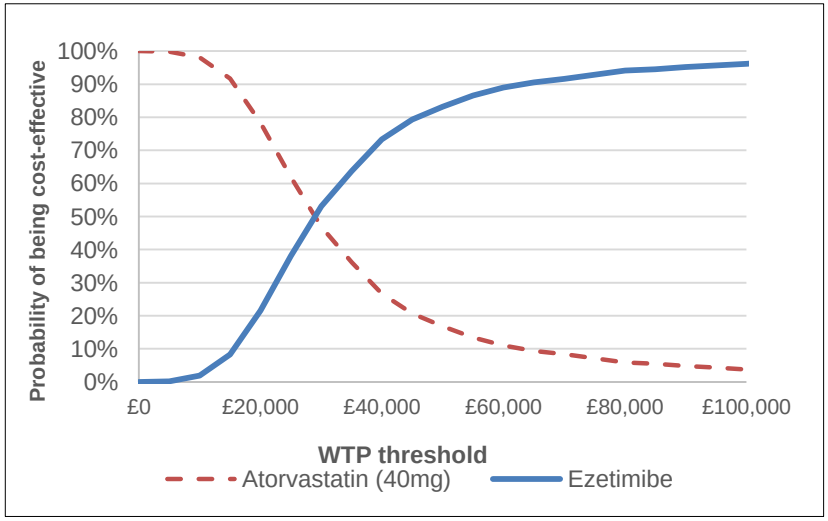


Figure (d)

Step 2: Including TIA and stable angina states in the model without treatment effects for these events

The company excluded risks of TIA and stable angina from their base case model analysis. The ERG believes that it is more realistic to include these events so that the modelled risks are consistent with stated baseline risk of 20% (based on a Q-risk score). Therefore, on top of the changes implemented above, we have included the risks of TIA and stable angina in the model, with treatment effects for statin or ezetimibe switched off. This has limited impact on the ICERs (Tables 32 to 35).

Table 32 Results with bugs fixed and including risks of TIA and stable angina without treatment effects for these events: primary prevention, monotherapy

	Total Costs	Total QALYs	Total LYs	Incremental Costs	Incremental QALYs	ICER
No Treatment	£7,913	10.93	23.00			
Ezetimibe	£12,821	11.13	23.54	£4,908	0.194	£25,274

Table 33 Results with bugs fixed and including risks of TIA and stable angina without treatment effects for these events: primary prevention, add on to statin

	Total Costs	Total QALYs	Total LYs	Incremental Costs	Incremental QALYs	ICER
Atorvastatin (20mg)	£7,313	11.31	24.06			
Ezetimibe + Atorvastatin (20mg)	£12,493	11.42	24.38	£5,181	0.111	£46,479

Table 34 Results with bugs fixed and including risks of TIA and stable angina without treatment effects for these events: secondary prevention, monotherapy

	Total Costs	Total QALYs	Total LYs	Incremental Costs	Incremental QALYs	ICER
No Treatment	£18,870	5.67	13.65			
Ezetimibe	£22,511	5.88	14.27	£3,640	0.204	£17,871

Table 35 Results with bugs fixed and including risks of TIA and stable angina without treatment effects for these events: secondary prevention, add on to statin

	Total Costs	Total QALYs	Total LYs	Incremental Costs	Incremental QALYs	ICER
Atorvastatin (40mg)	£19,031	6.11	15.00			
Ezetimibe + Atorvastatin (40mg)	£22,967	6.23	15.37	£3,936	0.119	£32,970

Step 3: Application and age adjustment of alternative health state utility values
The ERG also assessed the impact of applying a new set of utilities derived by Ara and Brazier from an analysis of Health Survey for England (HSE) data.[85] The study reflects mean EQ-5D values of individuals in England who have experienced different types of CV event (see Table 17). In addition the baseline EQ-5D utilities in this model are based on the published equation from Ara and Brazier[85] which estimates age and sex specific EQ-5D utilities for members of the general population who have no reported history of cardiovascular disease. The ERG has also followed the approach suggested by Ara and Brazier[85] of age-adjusting the health state utility multipliers to improve accuracy. The following results are based on applying these changes to the utility parameters on top of all the changes in steps 1 and 2 above. Whilst overall the QALYs increase when applying these alternative utility assumptions, they have limited impact on incremental differences between strategies, and thus little impact on the ICERs. In fact the ICERs for secondary prevention improve somewhat (Tables 36 to 39).

Table 36 Results with alternative age adjusted health state utility values, on top of changes made in steps 1 and 2 above: primary prevention, monotherapy

	Total Costs	Total QALYs	Total LYs	Incremental Costs	Incremental QALYs	ICER
No Treatment	£7,913	11.56	23.00			
Ezetimibe	£12,821	11.75	23.54	£4,908	0.193	£25,479

Table 37 Results with alternative age adjusted health state utility values, on top of changes made in steps 1 and 2 above: primary prevention, add on to statin

	Total Costs	Total QALYs	Total LYs	Incremental Costs	Incremental QALYs	ICER
Atorvastatin (20mg)	£7,313	11.93	24.06			
Ezetimibe + Atorvastatin (20mg)	£12,493	12.04	24.38	£5,181	0.110	£47,045

Table 38 Results with alternative age adjusted health state utility values, on top of changes made in steps 1 and 2 above: secondary prevention, monotherapy

	Total Costs	Total QALYs	Total LYs	Incremental Costs	Incremental QALYs	ICER
No Treatment	£18,870	6.27	13.65			
Ezetimibe	£22,511	6.51	14.27	£3,640	0.243	£14,988

Table 39 Results with alternative age adjusted health state utility values, on top of changes made in steps 1 and 2 above: secondary prevention, add on to statin

	Total Costs	Total QALYs	Total LYs	Incremental Costs	Incremental QALYs	ICER
Atorvastatin (40mg)	£19,027	6.80	15.00			
Ezetimibe + Atorvastatin (40mg)	£22,963	6.94	15.37	£3,936	0.141	£27,937

Step 4: Assigning no effect of further LDL-c reductions on non-CV deaths (RR=1) but applying relative treatment effects for TIA and stable angina

Since the results of the CTTC meta-analysis show a non-significant effect for LDL-c lowering on non-CV deaths (RR 0.97 (95% CI: 0.91-1.03), the ERG assessed the impact of setting this to one in the model. This is consistent with the modelling for TA132[5] and the modelling conducted for CG181[1] In the review for CG181, more intensive statin doses (which result in further reductions in LDL-c) were not found to be associated further significant reductions in non-CV deaths compared with less intensive doses. However, the previous modelling for TA132 and CG181 did assume treatment effects of lipid lowering on TIA and stable angina, and these were assumed to be the same as those observed for stroke and MI respectively. Thus, in this exploratory analysis, treatment effects for TIA and stable angina are included for

statin and ezetimibe. The results show that the ICERs for ezetimibe increase under this scenario, particularly as an add-on to statin (Tables 40 to 43).

Table 40 Results with all changes in steps 1-4: primary prevention, monotherapy

	Total Costs	Total QALYs	Total LYs	Incremental Costs	Incremental QALYs	ICER
No Treatment	£7,913	11.56	23.00	-	-	-
Ezetimibe	£12,683	11.71	23.38	£4,770	0.149	£31,939

Table 41 Results with all changes in step 1-4: primary prevention, add on to statin

	Total Costs	Total QALYs	Total LYs	Incremental Costs	Incremental QALYs	ICER
Atorvastatin (20mg)	£7,243	11.86	23.77	-	-	-
Ezetimibe + Atorvastatin (20mg)	£12,307	11.92	23.93	£5,064	0.067	£75,950

Table 42 Results with all changes in step 1-4: secondary prevention, monotherapy

	Total Costs	Total QALYs	Total LYs	Incremental Costs	Incremental QALYs	ICER
No Treatment	£18,870	6.27	13.65			
Ezetimibe	£22,375	6.47	14.15	£3,505	0.203	£17,279

Table 43 Results with all changes in step 1-4: secondary prevention, add on to statin

	Total Costs	Total QALYs	Total LYs	Incremental Costs	Incremental QALYs	ICER
Atorvastatin (40mg)	£18,852	6.73	14.79			
Ezetimibe + Atorvastatin (40mg)	£22,635	6.84	15.06	£3,783	0.105	£36,042

Scenario A: Multiplicative effects of ezetimibe (as an add-on) on post-statin LDL-c levels

All the above analyses retain the same approach to estimating the effects of ezetimibe as an add-on to statin treatment; i.e. applying the additive further percentage reduction in LDL-c (for ezetimibe versus statin alone) to the baseline level (4.32 mmol/L), to estimate the absolute further LDL-c reduction in mmol/L.

The ERG have also undertaken some exploratory analysis to assess the impact of modelling reductions in LDL-c associated with statin therapy, and then applying the estimated further multiplicative proportional reduction in LDL-c with ezetimibe (23.5%) from post statin LDL-c levels. With this approach, the cost-effectiveness of ezetimibe as an add-on to statin is modelled for varying levels of LDL-c achieved on statin alone. This accounts for variability in the response to statin therapy, and recognizes the fact that some people will fail to achieve the mean response, and so remain at higher risk of CV events following statin therapy. For this analysis, it becomes necessary to tie the relative risks associated with statin therapy to modeled reductions in LDL-c. So for example, the LDL-c reduction for those assumed to achieve a post-statin level of 3 mmol/L would be 1.32 mmol/L (4.32-3). These reductions are then converted into relative risks using the CTTC meta-analysis, as they are for ezetimibe. The further absolute reduction in LDL-c using the new post statin LDL-c level, would then be 0.705 mmol/L (=3x0.235). Tables 44 and 45, and Figure 7, present the results of these further scenario analyses for the primary and secondary prevention cohorts, assuming a baseline LDL-c level of 4.32 mmol/L. All these scenarios are conducted using the model with all the incorporated changes in steps 1 to 4 above.

Table 44 Results incorporating changes in step 1-4 above, and multiplicative effect of ezetimibe on post-statin LDL-c levels: primary prevention, add on to statin

Post statin LDL-c attainment	Alternatives	Total Costs	Total QALYs	Total LYs	Incremental Costs	Incremental QALYs	ICER
2	Atorvastatin (20mg)	£6,665	11.89	23.84	-	-	-
	Ezetimibe (10mg) + Atorvastatin (20mg)	£11,861	11.93	23.95	£5,196	0.045	£116,243
2.5	Atorvastatin (20mg)	£6,939	11.83	23.70	-	-	-
	Ezetimibe (10mg) + Atorvastatin (20mg)	£12,039	11.90	23.85	£5,100	0.063	£81,021
3	Atorvastatin (20mg)	£7,237	11.77	23.54	-	-	-
	Ezetimibe (10mg) + Atorvastatin (20mg)	£12,227	11.85	23.75	£4,990	0.085	£58,522
3.5	Atorvastatin (20mg)	£7,560	11.70	23.36	-	-	-
	Ezetimibe (10mg) + Atorvastatin (20mg)	£12,425	11.81	23.64	£4,865	0.113	£43,230

Table 45 Results incorporating changes in step 1-4 above, and multiplicative effect of ezetimibe on post-statin LDL-c levels: primary prevention, add on to statin

Post statin LDL-c attainment	Alternatives	Total Costs	Total QALYs	Total LYs	Incremental Costs	Incremental QALYs	ICER
2	Atorvastatin (40mg)	£18,669	6.75	14.84	-	-	-
	Ezetimibe (10mg) + Atorvastatin (40mg)	£22,471	6.82	15.02	£3,801	0.073	£51,975
2.5	Atorvastatin (40mg)	£18,727	6.66	14.62	-	-	-
	Ezetimibe (10mg) + Atorvastatin (40mg)	£22,477	6.76	14.87	£3,751	0.099	£37,755
3	Atorvastatin (40mg)	£18,792	6.56	14.38	-	-	-
	Ezetimibe (10mg) + Atorvastatin (40mg)	£22,485	6.69	14.71	£3,693	0.130	£28,496
3.5	Atorvastatin (40mg)	£18,865	6.46	14.12	-	-	-
	Ezetimibe (10mg) + Atorvastatin (40mg)	£22,493	6.62	14.53	£3,629	0.165	£22,056

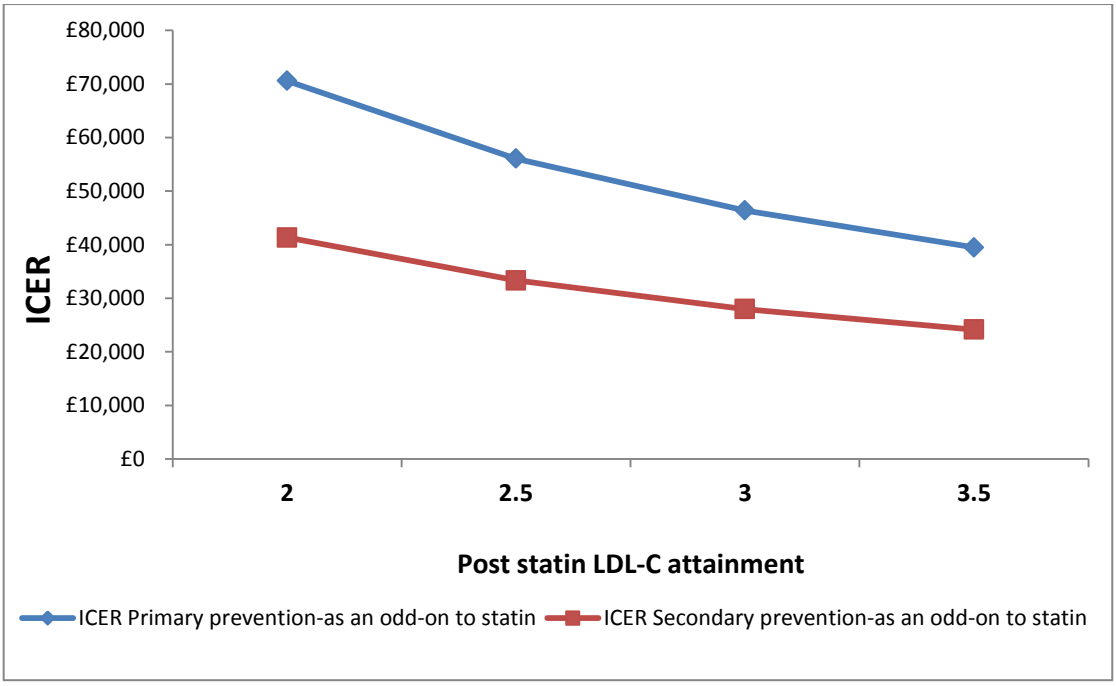


Figure 7 Incremental cost-effectiveness ratios for ezetimibe as an add-on to statin, using the multiplicative effect of ezetimibe on post-statin LDL-c levels

Scenario B: Using the results from the IMPROVE-IT trial for the secondary prevention, add-on to statin analysis

Using the updated model from step 4 above, the ERG finally investigated the effect of applying the directly estimated relative risks for ezetimibe from the IMPROVE-IT trial. This was done only for secondary prevention as an add-on to statin, using Simvastatin (40mg) as the comparator (the comparator in IMPROVE-IT). The results are provided in Table 46.

Table 46 Results from scenario A: secondary prevention, add on to Simvastatin (40mg)

	Total Costs	Total QALYs	Total LYs	Incremental Costs	Incremental QALYs	ICER
Simvastatin (40mg)	£18,496	6.60	14.44			
Ezetimibe + Simvastatin (40mg)	£21,831	6.62	14.49	£3,335	0.029	£115,354

5.4 Conclusions of the cost effectiveness section

The company conducted literature reviews of the cost effectiveness and quality of life literature in the area of hypercholesterolemia. In identifying economic evaluations, sensitivity of the searches may have been enhanced by the inclusion of additional terms, both for the clinical conditions and economic data relevant to the assessment.

The economic model is generally appropriately structured and consistent with previous modelling work used to inform NICE guidance in the area hypercholesterolemia and lipid modification. The ERG identified a number of issues as follows:

- A number of apparent bugs were found throughout the model, but once corrected the ICERs for ezetimibe actually improved.
- Some of the model output appeared to lack face validity, particularly the modelled survival for the primary prevention (20% CV risk) cohort, where this exceeded the expectation for the age/sex matched general population. This appears to be due to over-adjustment of background mortality for modelled CV deaths. Any bias associated with this may also depend on whether the effects of lipid lowering on non-CV death are considered appropriate or not.
- The approach used to combine background utility values with CV event utilities did not appear to follow NICE DSU recommendations to use age adjusted multipliers, and some more up to date utility estimates were identified from a single UK source. However, implementing these new utilities with age adjustment had little impact on the ICERs.
- Inconsistent with the modelling previously carried out for TA132, the new model included a non-significant effect for ezetimibe on non-CV death, with the point estimate favouring ezetimibe versus no treatment and statin alone. Whilst the effect is small, the ICERs are moderately sensitive to this assumption.
- Conversely, effects of statin and ezetimibe on TIA and stoke were excluded from the base case model, rather than being assumed consistent with those observed for MI and stroke. The latter was assumed in the modelling for TA132 and CG181.

A key issue in the economic model relates to the method for estimating the effects of ezetimibe on CV endpoints and non-CV mortality. The main areas of uncertainty are as follows:

- Based on exploratory analysis conducted by the ERG, the magnitude of the further reduction in LDL-c concentration (mmol/L), with ezetimibe as an add-on to statin, is sensitive to whether the estimated additive or multiplicative percentage reduction in LDL-c from post statin levels is applied. With the effects of ezetimibe on CV events modelled through the absolute reduction in LDL-c concentration (mmol/L), the overall cost-effectiveness results are moderately sensitive to the approach chosen.
- For the secondary prevention cohort there is some direct evidence for the effect of ezetimibe (as an add-on to statin) on CV endpoints, all be it in a subgroup of the wider population and compared with simvastatin (40mg) rather than the currently recommended first line atorvastatin. However, applying these directly estimated relative risks in the secondary prevention cohort raises the ICER for ezetimibe (as an add-on) above £100,000 per QALY gained.

6 OVERALL CONCLUSIONS

The company considered only two comparisons: ezetimibe 10 mg monotherapy versus placebo and ezetimibe in combination with a statin versus matching statin dose. Formal meta-analyses were conducted for only two outcomes: change in LDL-c and total cholesterol.

The company's search strategies identified 24 studies comparing ezetimibe 10 mg monotherapy versus placebo or ezetimibe in combination with a statin versus matching statin dose. The clinical trial report from the IMPROVE-IT trial[3] was subsequently added to the selected set of trials.

The results provided evidence that ezetimibe is effective compared with placebo in reducing LDL-c (mean difference in % change: -20.59 (95% CI: -22.13 to -19.05)) and that ezetimibe in combination with a statin is effective compared with the matching statin dose alone (mean difference in % change: -15.60; 95% CI: -17.06 to -14.13). Similar benefits were found for total cholesterol.

The company did not conduct a meta-analysis of clinical outcomes. Instead, an external meta-analysis of statin trials (2010 CTTC meta-analysis) has been used to link the LDL-c results indirectly.

There was no clear evidence of differences between groups in the rates of adverse events.

Although the ERG felt most aspects of the company's systematic review of clinical evidence were adequate, there were some concerns about the following aspects:

- The differences between the scope of the systematic review of clinical evidence and that issued by NICE.
- Use of a restricted set of terms in the literature search strategies that could have impacted on the sensitivity of the searches.
- Uncertainty about the reproducibility of the decision rules for inclusion/exclusion of relevant studies.

- Use of meta-analyses with high rates of statistical heterogeneity (I^2>99%).
- No attempt to perform a systematic review and meta-analysis of clinical outcomes.
- The use of the CTTC meta-analysis of statin studies to derive clinical outcomes data for the cost-effectiveness modelling is open to question.

With regard to the economic model, the company's base case results suggested that for a 60-year old primary prevention cohort with a 20% Q-risk score, ezetimibe monotherapy (in those who cannot tolerate a statin) has an ICER just above £30,000. Compared with atorvastatin (20mg) alone, ezetimibe as an add-on for primary prevention has an ICER of £58,473. In the secondary prevention cohort (age 69), ezetimibe monotherapy has an ICER of £17,553 compared with no treatment. As an add-on to atorvastatin (40mg) for secondary prevention, the ICER for ezetimibe is £30,940.

The cost-effectiveness of ezetimibe for primary prevention of CV events was found to be improved in people with diabetes, with the ICERs for monotherapy and add-on estimated to be £20,294 and £31,352 respectively. The ICER for comparison with ezetimibe as an add-on to atorvastatin 20mg in people with CKD was also more favourable, at £30.939. Finally, whilst no specific subgroup analysis was conducted for people with heterozygous familial hypercholesterolaemia, results from sensitivity analysis suggest that the ICERs for ezetimibe will be more favourable in this group with high LDL-c at baseline.

The main uncertainties relate to whether or not further beneficial effects on non-CV deaths are assumed for ezetimibe versus statin alone, and also the approach used to estimate the effects of ezetimibe on CV events.

After making a series of stepped changes to the company's model - applying alternative utilities, removing the effect of ezetimibe on non-CV deaths, and including effects on TIA and stable angina - the ICERs for ezetimibe remained fairly consistent with the company's base case analysis. In the main primary prevention cohort the ICER for ezetimibe remained close to £30,000 per QALY gained for monotherapy, and substantially higher than £30,000 as an add-on to statin. In the secondary

prevention cohort, the ICER for ezetimibe remained below £20,000 for monotherapy, but rose to ~£36,000 as an add-on to statin. The cost-effectiveness of ezetimibe clearly improves as the baseline CV risk increases, and also as the baseline (pre-treatment) LDL-c level increases.

However, exploratory analysis conducted by the ERG suggests that the cost-effectiveness of ezetimibe as an add-on to statin (in those inadequately controlled on statin alone), may be sensitive to whether the estimated additive or multiplicative percentage reduction in LDL-c (compared to statin) is used to model the effects of ezetimibe. With the latter approach, the magnitude of the absolute further reduction in LDL-c achieved with ezetimibe (versus statin alone) is dependent on the LDL-c level achieved on statin. With the additive approach, only the baseline (pre-treatment) LDL-c level is used to the estimate the absolute further reduction in LDL-c. Based on further exploratory analysis conducted by the ERG (applying the multiplicative percentage reduction to varying levels of LDL-c achieved on statin, and keeping the baseline LDL-c level constant) the ICER for ezetimibe falls below £30,000 when the post statin LDL-c in the secondary prevention cohort is $\geq$ 3 mmol/L.

Finally, if directly estimated relative risks for the effect of ezetimibe (as an add-on to statin) on CV events are applied in the secondary prevention model (IMPROVE-IT trial), the ICER for ezetimibe as an add-on rises above £100,000 per QALY.

8.1 Implications for research

There remains a requirement for robust evidence from RCTs, especially with regard to ezetimibe monotherapy, despite this being a potentially common clinical scenario (many patients cannot tolerate statins).

Patients may experience rebound hypercholesterolaemia if statin is discontinued or poorly adhered to; it is possible that ezetimibe may reduce this risk. It would not be practical to investigate this with a RCT, but an extensive clinical practice audit would provide clinically relevant data.

Finally, there is an evident lack of RCT data comparing ezetimibe monotherapy or combination therapy with lipid lowering agents other than statins.

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APPENDICES

Appendix 1 Characteristics of included studies

Table 47 Study characteristics: ezetimibe monotherapy trials

Study ID	Country	Intervention & comparator(s)	Number randomised	Main inclusion criteria	Main exclusion criteria	Primary outcome
Ballantyne 2003[49]	NR (reported as USA in Ara 2008 and multination in CS)	Ezetimibe 10mg vs atorvastatin 10mg, 20mg, 40mg or 80mg vs ezetimibe 10mg + atorvastatin 10mg, 20mg, 40mg or 40mg vs placebo	628	• ≥18 years old • LDL-c 145 to 250 mg/dL, inclusive • Triglyceride ≤ 350mg/dL	• Heart disease • Unstable angina pectoris • Uncontrolled or newly diagnosed diabetes mellitus • Unstable endocrine or metabolic disease • Renal, hepatic or hepatobiliary disease • Known coagulopathy	% reduction in LDL-c for pooled ezetimibe + atorvastatin vs pooled atorvastatin treatment groups
Bays 2001[34] (Study A)	NR (reported as USA in Ara 2008) 25 centres	Ezetimibe 0.25mg vs ezetimibe 1mg vs ezetimibe 5mg vs ezetimibe 10mg vs placebo	243	• Adults with primary hypercholesterolaemia (LDL-c ≥130mg/dL & ≤250mg/dL and TG≤300mg/dL) • 18-75 years old • Baseline plasma liver enzyme values within laboratory ≤ 1.5 times	• Homozygous familial hypercholesterolaemia or non-type II hypercholesterolaemia • BMI>35 • Congestive heart failure • Blood pressure>160/95 • Heart disease	% reduction in LDL-c

Study ID	Country	Intervention & comparator(s)	Number randomised	Main inclusion criteria	Main exclusion criteria	Primary outcome
				upper limit of lab ref range	• Unstable or severe peripheral artery disease • Active, severe, unstable angina pectoris • Disorders of haematologic, digestive or central nervous system • Diabetes mellitus requiring medication • Renal, hepatic or hepatobiliary disease	
Bays 2004[59]	USA (61 sites) and 56 international sites in 24 countries	Ezetimibe 10mg vs ezetimibe 10mg + simvastatin 10, 20, 40 or 80mg vs simvastatin 10, 20, 40 or 80mg vs placebo	1528	• 18-80 years old • Primary hypercholesterolaemia (LDL-c ≥145mg/dL & ≤250mg/dL and TG ≤350mg/dL) • ALT & AST ≤1.5 times upper limit of normal (ULN) • No active liver disease • CK≤1.5 times ULN	• <50% ideal body weight • Hypersensitivity to statins • >14 drinks per week • Pregnancy or lactation •	Mean % change in LDL-c from baseline to study end point

Study ID	Country	Intervention & comparator(s)	Number randomised	Main inclusion criteria	Main exclusion criteria	Primary outcome
Clement 2014[42]	India (1 centre)	Ezetimibe 10mg vs simvastatin 20mg vs placebo	63	• Tamilnadu (India) males • ≥18 & ≤48 years • Dyslipidaemic (LDL-c129-2—mg/dL, TC 200-280md/dL, TG 150-350mg/dL, HDL 35-60mg/dL)	• Active liver disease • Abnormal haematology, blood chemistry, urine analysis and liver transaminases • Severe congestive cardiac failure • Unstable angina • Uncontrolled hypertension • Uncontrolled endocrine or metabolic disease • Impaired renal function	% change in LDL-c
Davidson 2002[40]	USA (61 centres)	Ezetimibe 10mg vs ezetimibe 10mg + simvastatin 10, 20, 40 or 80mg vs simvastatin 10, 20, 40 or 80mg vs placebo	668	• ≥18 years old • Primary hypercholesterolaemia (LDL-c ≥145mg/dL to ≤250mg/dL and TG≤350mg/dL)	• Congestive heart failure • Uncontrolled cardiac arrhythmias • Unstable or severe peripheral artery disease within 3mo of study entry • Unstable angina pectoris • Heart disease	% change in LDL-c

Study ID	Country	Intervention & comparator(s)	Number randomised	Main inclusion criteria	Main exclusion criteria	Primary outcome
					• Uncontrolled or newly diagnosed diabetes mellitus • Renal, hepatic or hepatobiliary disease • Known coagulopathy • Unstable endocrine disease	
Dujovne 2002[50]	USA (53 centres)	Ezetimibe 10mg vs placebo	892	• ≥18 years old • Primary hypercholesterolaemia (LDL-c 130-250mg/dL and TG≤350mg/dL)	• Pregnancy or lactation • Congestive heart failure • Uncontrolled cardiac arrhythmia • Heart disease • Unstable or severe peripheral artery disease within 3mo of study entry • Unstable angina pectoris • Disorders of the haematologic, digestive or central nervous system • Uncontrolled or newly diagnosed diabetes mellitus	% change in LDL-c from baseline to week 12

Study ID	Country	Intervention & comparator(s)	Number randomised	Main inclusion criteria	Main exclusion criteria	Primary outcome
					• Uncontrolled endocrine or metabolic disease • Renal, hepatic or hepatobiliary disease • HIV positive • Coagulopathy	
Farnier 2005[43]	International (centres NR)	Ezetimibe 10mg vs placebo	251	• 18-75 years old • Mixed hyperlipidaemia	• Coronary heart disease • CHD-equivalent disease • 10 year CHD risk > 20% • Homozygous familial hypercholesterolaemia • Type I or V hyperlipidaemia • LDL apheresis • Congestive heart failure • Uncontrolled cardiac arrhythmia • Unstable hypertension • Pancreatitis • Inadequately controlled diabetes • Gallbladder, renal or	% change in LDL-c

Study ID	Country	Intervention & comparator(s)	Number randomised	Main inclusion criteria	Main exclusion criteria	Primary outcome
					active liver disease • Uncontrolled endocrine or metabolic disease • Pregnancy or lactation • Contraindicated medication that cannot be discontinued	
Goldberg 2004[51]	USA (31 sites) and 40 sites in 22 countries	Ezetimibe 10mg vs ezetimibe 10mg + simvastatin 10, 20, 40 or 80 mg vs simvastatin 10, 20, 40 or 80 mg vs placebo	887	• ≥18 years old • Primary hypercholesterolaemia (LDL-c 145-250 mg/ dL and TG ≤350mg/dL) • ALT and AST no more than 2 times ULN • No active liver disease • Creatine kinase no more than 1.5 times ULN	• Congestive heart failure • Uncontrolled cardiac arrhythmia • Unstable or severe peripheral artery disease • Heart disease • Uncontrolled or newly diagnosed diabetes mellitus • Renal impairment • Coagulation abnormalities • Uncontrolled hypertension	% change in LDL-c
Knopp 2003[41]	USA (54 centres)	Ezetimibe 10mg vs placebo	827	• ≥18 years old • Primary hypercholesterolaemia	• Pregnancy or lactation • Congestive heart failure	% change in LDL-c

Study ID	Country	Intervention & comparator(s)	Number randomised	Main inclusion criteria	Main exclusion criteria	Primary outcome
				(LDL-c 130mg/dL to 250mg/dL and TG ≤ 350mg/dL	• Uncontrolled cardiac arrhythmia • Heart disease • Unstable or severe peripheral artery disease • Unstable angina pectoris • Disorders of the haematologic, digestive or central nervous system • Uncontrolled or newly diagnosed diabetes mellitus • Uncontrolled endocrine or metabolic disease • Renal, hepatic or hepatobiliary disease • HIV positive • Coagulopathy	
Krysiak 2011[52]	Poland (1 centre)	Ezetimibe 10mg vs simvastatin 40mg vs ezetimibe 10mg + simvastatin 40mg vs placebo	134	• 20 to 75 years old • Primary isolated hypercholesterolaemia (TC >200mg/dL, LDL-c >130 mg/dL, TG	• Isolated mixed hyperlipidaemia or hypertriglyceridaemia • Secondary hypercholesterolaemia	Change in monocyte cytokine release and systemic inflammation

Study ID	Country	Intervention & comparator(s)	Number randomised	Main inclusion criteria	Main exclusion criteria	Primary outcome
				<150mg/dL) • Medically stable	in the course of nephrotic syndrome, liver & biliary diseases, thyroid diseases, autoimmune disorders, chronic pancreatitis, or alcoholism • Diabetes mellitus • BMI > 40 • Any acute and inflammatory processes • Symptomatic congestive heart failure • Heart disease • Renal or hepatic impairment • Malignancy within last 5 years • Hypolipaemic treatment in last 3 months • Unsuitable concomitant medications	

Study ID	Country	Intervention & comparator(s)	Number randomised	Main inclusion criteria	Main exclusion criteria	Primary outcome
Krysiak 2012a[53]	Poland (1 centre)	Ezetimibe 10mg vs simvastatin 40mg vs ezetimibe 10mg + simvastatin 40mg vs placebo	104	• 20-75 years old • Primary isolated hypercholesterolaemia (TC>200mg/dL, LDL-c>130mg/dL, & TG < 150mg/dL	• As for Krysiak 2011 above	Change in coagulation and fibrinolysis markers
Krysiak 2012b[54]	Poland (1 Centre)	Ezetimibe 10mg vs simvastatin 40mg vs ezetimibe 10mg + simvastatin 40mg vs placebo	178	• 20-70 years old • Isolated hypercholesterolaemia (TC>200mg/dL, LDL-c>130mg/dL and TG<150mg/dL) • Previously untreated	• Elevated triglyceride levels (≥150 mg/dL) • Secondary hypercholesterolemia in the course of nephrotic syndrome, liver and biliary tract diseases, thyroid diseases, autoimmune disorders, chronic pancreatitis, or alcoholism • Diabetes mellitus • BMI>40 • Any acute and chronic inflammatory processes • Any form of coronary artery disease • Symptomatic congestive heart failure	Lymphocyte cytokine release and plasma levels of high-sensitivity C-reactive protein (hsCRP) and intercellular adhesion molecule 1 (ICAM-1)

Study ID	Country	Intervention & comparator(s)	Number randomised	Main inclusion criteria	Main exclusion criteria	Primary outcome
					• Moderate or severe arterial hypertension • Impaired renal or hepatic function • Treatment with other hypolipidaemic agents within 3 months prior to the study • Unsuitable concomitant medication • Pregnancy or lactation	
Melani 2003[56]	USA (52 centres)	Ezetimibe 10mg vs pravastatin 10, 20 or 40mg vs ezetimibe 10mg + pravastatin 10, 20 or 40mg vs placebo	538	• Adults with primary hypercholesterolaemia	• Congestive heart failure • Uncontrolled cardiac arrhythmias • Unstable or severe peripheral artery disease • Heart disease • Uncontrolled or newly diagnosed diabetes mellitus • Hepatic hepatobiliary disease • Renal impairment • Known coagulopathy	% change in LDL-c

Study ID	Country	Intervention & comparator(s)	Number randomised	Main inclusion criteria	Main exclusion criteria	Primary outcome
					• Unstable endocrine disease	

Note: In light of the company's response during the clarification process, the studies by Knopp and colleagues 2001 and Sager and colleagues 2003 have been excluded from this report and therefore not included in the table above.

Table 48 Study characteristics: ezetimibe/statin combination trials

Study ID	Country	Intervention & comparator(s)	Number randomised	Main inclusion criteria	Main exclusion criteria	Primary outcome
Atorvastatin studies (n=1)						
Ballantyne 2003[49]	NR (reported as USA in Ara 2008 and multination in CS)	Ezetimibe 10mg vs atorvastatin 10mg, 20mg, 40mg or 80mg vs ezetimibe 10mg + atorvastatin 10mg, 20mg, 40mg or 40mg vs placebo	628	See Table 46	See Table 46	% reduction in LDL-c for pooled ezetimibe + atorvastatin vs pooled atorvastatin treatment group
Fluvastatin studies (n=5)						
Alvarez-Sala 2008[48]	Spain (4 centres)	Ezetimibe 10mg + fluvastatin XL 80mg vs fluvastatin XL 80mg	89	• 18-75 years old • Primary hypercholesterolaemia (LDL-c≥130mg/dL and TG ≤400mg/dL)	• Congestive heart failure • Uncontrolled arrhythmia • Myocardial infarction • Unstable angina or severe or unstable peripheral artery disease in last 3mo • Uncontrolled endocrine or metabolic disease • Renal dysfunction	% change in LDL-c

Study ID	Country	Intervention & comparator(s)	Number randomised	Main inclusion criteria	Main exclusion criteria	Primary outcome
					• Active or chronic hepatic or hepatobiliary disease • Myopathic disorders • Coagulation disorders	
Habara 2014[44]	Japan (1 centre)	Ezetimibe 10mg + fluvastatin 30mg vs fluvastatin 30mg	63	• 30-80 years old • Clinically stable angina pectoris • Scheduled for percutaneous coronary intervention • Hypercholesterolaemia (TC>220mg/dL and LDL-c>140mg/dL, or previous statin therapy)	• Significant stenotic lesions in all coronary vessels • MI in last 4 weeks • OCT target vessel had lesions with angiographically detected thrombus • Contraindications to OCT • Other incompatible concomitant medical conditions • Pregnancy	Progression of coronary atherosclerotic plaque evaluated by OCT
Kinouchi 2013[45]	Japan (1 centre)	Ezetimibe 10mg + fluvastatin 20mg vs	54	• 20-70 years old • LDL-c>100mg/dL & TG<500mg/dL	• Kidney or liver dysfunction • Secondary or	% change in estimated glomerular filtration rate

Study ID	Country	Intervention & comparator(s)	Number randomised	Main inclusion criteria	Main exclusion criteria	Primary outcome
		fluvastatin 20mg			drug-induced dyslipidaemia • Unstable angina • Pregnancy or breast-feeding • Allergy to study medication	(eGFR)
Stein 2008[46]	Germany, Greece, Norway, Russia, Turkey and USA (27 centres)	Ezetimibe 10mg vs ezetimibe 10mg + fluvastatin XL 80mg vs fluvastatin XL 80mg	218	• ≥18 years old • Dyslipidaemia • Previous MRSEs leading to cessation of statin treatment or current statin treatment and QoL affected by MRSEs, requiring alternative treatment	• Homozygous familial hypercholesterolaemia • Fredrickson type I, IV & V dyslipoproteinaemia • Myopathy or similar asymptomatic creatine kinase increase • Sensitivity to study drugs • Renal impairment • Acute coronary syndrome, arterial revascularisation, CABG surgery or	% change in LDL-c

Study ID	Country	Intervention & comparator(s)	Number randomised	Main inclusion criteria	Main exclusion criteria	Primary outcome
					stroke in last 6 months	
Stojakovic 2010[36]	Austria (1 centre)	Ezetimibe 10mg + fluvastatin 80mg vs fluvastatin 80mg	84	• CHD or CHD risk equivalent with LDL-c 100-160 mg/d|L	• Lipid lowering drugs in last 3 months • Heart failure stage III-IV • >80 years old • Previous acute coronary syndrome or CABG in last 8 weeks	% change in lipoprotein subfractions
Pravastatin studies (n=1)						
Melani 2003[56]	USA (52 centres)	Ezetimibe 10mg vs pravastatin 10, 20 or 40mg vs ezetimibe 10mg + pravastatin 10, 20 or 40mg vs placebo	538	See Table 46	See Table 46	% change in LDL-c
Simvastatin studies (n=14)						
Bays 2004[59]	USA (61 sites) and 56 internationa l sites in 24	Ezetimibe 10mg vs ezetimibe 10mg + simvastatin 10, 20, 40 or 80mg vs	1528	See Table 46	See Table 46	Mean % change in LDL-c from baseline to study end point

Study ID	Country	Intervention & comparator(s)	Number randomised	Main inclusion criteria	Main exclusion criteria	Primary outcome
	countries	simvastatin 10, 20, 40 or 80mg vs placebo				
Davidson 2002[40]	USA (61 centres)	Ezetimibe 10mg vs ezetimibe 10mg + simvastatin 10, 20, 40 or 80mg vs simvastatin 10, 20, 40 or 80mg vs placebo	668	See Table 46	See Table 46	% change in LDL-c
Goldberg 2004[51]	USA (31 sites) and 40 sites in 22 countries	Ezetimibe 10mg vs ezetimibe 10mg + simvastatin 10, 20, 40 or 80 mg vs simvastatin 10, 20, 40 or 80 mg vs placebo	887	See Table 46	See Table 46	% change in LDL-c
IMPROVE-IT 2015[3]	39 countries (1158 centres)	Ezetimibe 10mg + simvastatin 40mg vs simvastatin 40mg + placebo	18144	• ≥50 years old • Hospitalised in last 10 days for an acute coronary syndrome • LDL-c ≥50mg/dL	• Planned CABG • Creatinine clearance <30ml/min • Active liver disease • Use of statin therapy with LDL-	Composite of death from CV disease, a major coronary event or non-fatal stroke

Study ID	Country	Intervention & comparator(s)	Number randomised	Main inclusion criteria	Main exclusion criteria	Primary outcome
					c lowering potency > simvastatin 40mg	
Kastelein 2008[4]	USA, Canada, South Africa, Spain, Denmark, Norway, Sweden, Netherlands (18 centres)	Ezetimibe 10mg + simvastatin 80mg vs simvastatin 80mg+ placebo	720	• 30-75 years old • Familial hypercholesterolaemia • Untreated LDL-c ≥210mg/dL	• High-grade stenosis or occlusion of the carotid artery • Carotid endarterectomy or carotid stenting • Homozygous familial hypercholesterolaemia • Congestive heart failure • Cardiac arrhythmia • Angina pectoris • Recent CV events	Change in ultrasonographic measurement of the mean carotid-artery intima-media thickness
Krysiak 2011[52]	Poland (1 centre)	Ezetimibe 10mg vs simvastatin 40mg vs ezetimibe 10mg + simvastatin 40mg vs placebo	134	See Table 46	See Table 46	Change in monocyte cytokine release and systemic inflammation

Study ID	Country	Intervention & comparator(s)	Number randomised	Main inclusion criteria	Main exclusion criteria	Primary outcome
Krysiak 2012a[53]	Poland (1 centre)	Ezetimibe 10mg vs simvastatin 40mg vs ezetimibe 10mg + simvastatin 40mg vs placebo	104	See Table 46	See Table 46	Change in coagulation and fibrinolysis markers
Krysiak 2012b[54]	Poland (1 Centre)	Ezetimibe 10mg vs simvastatin 40mg vs ezetimibe 10mg + simvastatin 40mg vs placebo	178	See Table 46	See Table 46	Lymphocyte cytokine release and plasma levels of high-sensitivity C-reactive protein (hsCRP) and intercellular adhesion molecule 1 (ICAM-1)
Krysiak 2014[55]	Poland (centres NR)	Ezetimibe 10mg + simvastatin 40mg vs simvastatin 40mg vs placebo	69 (pseudo-randomisation)	• Isolated hypercholesterolaemia (LDL-c>130mg/dL, TC>200mg/dL & TG<150mg/dL	• Any acute & chronic inflammatory processes • Coronary heart disease • Grade 2 or 3 hypertension • Symptomatic congestive heart failure • Thyroid disease	Change in low-grade systemic inflammation & plasma levels of selected adipokines

Study ID	Country	Intervention & comparator(s)	Number randomised	Main inclusion criteria	Main exclusion criteria	Primary outcome
					• Impaired renal or hepatic function • Nephrotic syndrome • Pancreatic, liver & biliary diseases • BMI>35 • Treatment with hypolipidaemic drugs in last 3 months	
Masana 2005[60]	NR	Ezetimibe 10mg + simvastatin 10, 20, 40 or 80mg vs simvastatin 10, 20, 40 or 80mg + placebo	433	• ≥18 years old • Stable daily dose of statin for at least 6 weeks • Primary hypercholesterolaemia • >80% compliant with therapy during base study • CK concentrations < 3 times ULN	• Heart failure • Uncontrolled cardiac arrhythmias • Heart disease • Unstable angina pectoris • Poorly controlled or newly diagnosed diabetes mellitus • Uncontrolled endocrine or metabolic disease • Renal impairment • Active or chronic	% change in LDL-c

Study ID	Country	Intervention & comparator(s)	Number randomised	Main inclusion criteria	Main exclusion criteria	Primary outcome
					hepatic or hepatobiliary disease	
Rodney 2006[57]	NR (reported as USA in CS)	Ezetimibe 10mg + simvastatin 20mg vs simvastatin 20mg	247	• African-American and black adults ≥18 years • Primary hypercholesterolaemia (LDL-c≥145 & ≤250mg/dL	• CV event in last 3 months • Congestive heart failure • Uncontrolled cardiac arrhythmias • Severe aortic stenosis • Obstructive cardiomyopathy • Uncontrolled hypertension • Active or chronic hepatobiliary disease • Renal impairment	% change in LDL-c
Shankar 2007[58]	India (centres NR)	Ezetimibe 10mg + simvastatin 10mg vs simvastatin 10mg	230	• ≥18 years old • Primary hypercholesterolaemia (LDL-c >135mg/dL for naïve participants and >120mg/dL and	• Unstable angina in last 3 months • Uncontrolled diabetes, hypertension, active hepatitis or	% change in LDL-c

Study ID	Country	Intervention & comparator(s)	Number randomised	Main inclusion criteria	Main exclusion criteria	Primary outcome
				TG<400mg/dL for participants already on lipid-lowering therapy	hepatic dysfunction, renal failure, hypothyroidism • Hypersensitive to statins • Pregnancy or lactation	
Zinellu 2012[37]	Italy (1 centre)	Ezetimibe 10mg + simvastatin 20 or 40mg vs simvastatin 40mg	30	• > 18 years old • LDL-c >100mg/dL • Presence of proteinuric chronic nephropathy • No evidence of UTI or overt heart failure	• Previous or concomitant treatment with steroids, anti-inflammatory & immunosuppressive agents, vitamin B6, B12, folate or statin • Renovascular disease, obstructive uropathy, type I diabetes, vasculitis	Change in oxidative stress and plasma taurine

Note: In light of the company's response during the clarification process, the study by Sager and colleagues 2003 has been excluded from this report and therefore not included in the table above.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia (review of TA132) [ID627]

You are asked to check the ERG report from Aberdeen HTA Group to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **12pm, Wednesday 2 August** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Search strategy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 29 of the ERG report it is stated: ***"Hypercholesterolaemia*** is not the correct MeSH or Emtree term. While Emtree automatically maps to the correct term ***Hypercholesterolemia***, MEDLINE and the Cochrane Library, return no hits because this term is invalid." We acknowledge that the wrong MeSH term was reported in our submission document, however, the correct term has been used in the search strategy. This was confirmed by cross-referencing the Excel workbooks that were used during the SLR process.	Please amend the sentence to reflect that: "***Hypercholesterolaemia*** has been incorrectly reported in the company's submission as the MeSH or Emtree term in the search strategy for MEDLINE and Cochrane Library but it was correctly used when the search was performed. "	Clarification provided.	The company recognises that *Hypercholesterolaemia* has been incorrectly reported in the company's submission. Not a factual error.
On page 30 of the report the ERG states that "One study[37] was not retrieved by this facet when replicated by the ERG." The facet being hypercholesterolemia. Line 2 of the search strategy would have picked up ***Hypercholesterolemia*** from the abstract of this study.	We request that the ERG checks again their search as we identified all the included studies using the search strategy documented in the submission.	Correct potential inaccuracy.	We have checked this: Zinellu A, Sotgia S, Pisanu E, Loriga G, Deiana L, Satta AE, et al. LDL S-homocysteinylation decrease in chronic kidney disease patients undergone lipid lowering therapy. Eur J Pharm Sci 2012;47:117-23. We are unable to find any word in the abstract that is retrieved by the term

			hypercholesterol$

Issue 2 Applicability of lovastatin to the appraisal

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 35 of the report the ERG it is stated: "The ERG identified the 12-week RCT by Kerzner and colleagues[47] which compared ezetimibe versus lovastatin versus ezetimibe plus lovastatin versus placebo in people with primary hypercholesterolaemia." Lovastatin is not marketed in the UK, so was not included as one of the comparators in the search strategy; therefore this study would not have been retrieved during searching.	Please remove this statement from the ERG report.	Studies including lovastatin would not have been retrieved in the SLR.	ERG is of the opinion that the arm comparing ezetimibe and placebo from this study would have been relevant to the SLR. Nevertheless, we agree that this study may not have been retrieved during literature searching as lovastatin was not included in the search strategy. Not a factual error.

Issue 3 Subgroup analyses

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 49 of the report it was stated: "Results of three subgroup analyses for three distinct patient subgroups are also presented, although, surprisingly, no meta-analyses have been performed." A meta-analysis for the three studies that reported data for	The text should be amended to reflect the analysis presented in the submission.	Factual inaccuracy	Please note that this sentence of the ERG report refers to the subgroup analyses on pages 71-72, which are presented prior to the section on meta-analysis. We agree that subgroup analyses by diabetes status have been presented on pages 77-78 of the submission.

patients with and without diabetes was presented in Figure 10, page 75 of the submission. For the other two subgroups presented, i.e. people with CKD and people with HeFH, only one study was identified for each population, so a meta-analysis could not be performed.			No changes required.

Issue 4 Heterogeneity

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On pages 4, 11 and 53 of the report it was stated: "Despite the high levels of statistical heterogeneity between the trials, the company has made no attempt to investigate reasons for the variable effects of the studies." We acknowledge variation between studies in terms of treatment effects; we did an investigation into the reasons for the heterogeneity by exploring inclusion/exclusion criteria and baseline patient characteristics across studies and did not identify any obvious pattern that could explain the heterogeneity from a clinical perspective. As such we did not perform a meta-regression. We feel that trying to	The text should be amended to: "High levels of statistical heterogeneity between the trials have been reported in the company's submission but the company has not presented results from their investigation of heterogeneity for the variable effects of the studies."	Factual inaccuracy	We accept the company's explanation but the ERG's comment is not inaccurate based on the content of the submission.

explore further the variables less likely to be deemed as relevant a priori is not recommended as it constitutes a post-hoc analysis. We acknowledge that we did not include this data in the submission, nor had the opportunity to provide comments during clarification questions.			

Issue 5 Trials with 100% Japanese and Indian patients

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 3 of the report the ERG states: "Trials with 100% Japanese and Indian participants were excluded from the primary analyses, but the company did not provide a clear rationale for their exclusion." Also on page 54 the ERG report states: "The ERG was concerned … and the rationale for excluding these patient populations was not backed up with appropriate references." On page 73 of the MSD's submission we stated that: " These populations metabolise a number of drugs differently."	Please reflect that a rationale for exclusion of these patients has been provided.	To provide a full and accurate representation of the submission	The ERG is not convinced that this statement constitutes a strong enough rationale for excluding these studies. The ERG would have expected a clearer explanation of how ethnicity is related to drug metabolism (why only Japanese/Indian people and not East/South Asian people?) with adequate references provided.

Whilst we acknowledge that we have not provided reference substantiating the argument, the lower recommended statin doses in these populations and studies in the literature support this.[1] For this reason, trials that included 100% patients from Asia were removed as they do not represent the demographic characteristics of the UK patients treated with statins. [1] Liao JK. Safety and Efficacy of Statins in Asians. *The American journal of cardiology*. 2007;99(3):410-414. doi:10.1016/j.amjcard.2006.08.051.			

Issue 6 Eligibility criteria in the SLR

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On numerous pages the definition of primary hypercholesterolaemia with regard to the SLR eligibility criteria has been discussed. MSD would like to re-emphasise and clarify our comments during clarification questions. Whilst the license for ezetimibe from 2003 is for primary hypercholesterolaemia, in today's clinical practice clinicians treat a patients CV risk and lowering LDL-c	No amendment required	Further clarification	No changes required.

is a major contributor to managing CV risk. Traditional values of an LDL-c greater than 3 mmol/L, which the ERG states on page 13 of their report, are defined as hypercholesterolaemic, however recent scientific literature has discussed that the LDL-c level that provides benefit to a person's CV risk is a lot lower. As clinician thinking around what is an appropriate level that an individual's LDL-c level should be decreased to, MSD has tried to reflect this in the submission and hence the SLR.			

Issue 7 Application of non-CV treatment effect for ezetimibe, CG181

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 113 of the ERG Report, there is a description of the relative treatment effects regarding non-CV applied in the manufacturer's approach and in previous NICE-related guidance and guidelines, TA132 and CG181, respectively. "Since the results of the CTTC meta-analysis show a non-significant effect for LDL-c	With respect to the second sentence, the statement referring that applying a RR = 1 was applied in CG181 should be corrected to reflect that non-CV benefits were modelled: "Since the results of the CTTC meta-analysis show a non-significant effect for LDL-c lowering on non-CV deaths (RR 0.97 (95% CI: 0.91-1.03), the ERG assessed the impact of setting this to one in the model. This is consistent with the modelling for TA132 **but not** the modelling conducted for CG181."	Inaccuracy in reflecting the approach adopted as part of the de novo cost-effectiveness analyses conducted for NICE CG181, 2014	The ERG has amended the text accordingly in the erratum document. Note, adding further non-CV mortality reductions with ezetimibe (as an add-on) over statin alone, does not appear to be consistent with the assumptions of CG181. In CG181, it was assumed that further reductions in LDC-C over those achieved with low-intensity statins, inferred no

lowering on non-CV deaths (RR 0.97 (95% CI: 0.91-1.03), the ERG assessed the impact of setting this to one in the model. This is consistent with the modelling for TA132 and the modelling conducted for CG181"			additional benefits on this outcome.

Issue 8 Comment regarding over adjustment for non CV deaths

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 8, 106-107 and 119 the ERG states: "Some of the model output appeared to lack face validity, particularly the modelled survival for the primary prevention (20% CV risk) cohort, where this exceeded the expectation for the age/sex matched general population. This appeared to be due to over-adjustment of background mortality for modelled CV deaths. Any bias associated with this may also depend on whether the inclusion of non-significant effects for lipid lowering on non-CV deaths is considered appropriate or not." We are unclear as to how the ERG has produced Figure 4 (page 107). However, when we have compared with age/sex matched general population mortality, the modelled survival, in fact, does not exceed the expectation for the age/sex matched population within the model submitted by MSD for any of the populations. We would like to clarify that non-CV deaths were included for statins and ezetimibe as the evidence for these was felt sufficient for them to be included within the NICE clinical guideline CG181 (see Table 80).	Update Figure 4 and remove reference to the statement regarding face validity versus general population mortality. Update text to provide the rationale behind inclusion of an effect on non-CV death & also that this impact is explored through probabilistic analysis.	It is unclear how the ERG has calculated the modelled survival in Figure 4, however, this does not reflect the survival within the model submitted by MSD. We have also made a request to NICE for a copy of the amended model to investigate this further.	We acknowledge that we made an error when deriving Figure 4. We have now amended the figure, which shows the modelled probability of survival over 40 cycles of the company's model, versus modelled probabilities of survival using the age/sex matched probabilities of all-cause mortality for the general population (see erratum document). We have removed all statements suggesting a higher overall rate of mortality compared to the the age/sex matched general population (pages 8, 11 and 105).

Issue 9 Cost-effectiveness model

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG has commented that it is possible to estimate more up-to-date stroke costs as follows: "It is possible that a more up to date estimate of stroke costs could have been calculated using reported data on resources use (such as length of stay) coupled with up to date reference costs covering the acute admission, excess bed days, and rehabilitation period."	MSD believes this statement should be removed.	In the NHS, the management of patients that have experienced stroke encompasses both primary and secondary care. The health state for stroke that has been included in the model needs to reflect the holistic care pathway for stroke immediately after the event as well as the long-term costs The approach suggested by the ERG would only capture the acute cost of care and would therefore not be consistent with the management of stroke in clinical practice.	We maintain that this suggestion could have been explored as for our statement. Not a factual inaccuracy
The following statement on page 11 of the ERG report should be updated to include a statement to reflect the impact on the ICER: "A number of apparent 'bugs' were identified throughout the model"	MSD requests that text is updated with the following text: "A number of apparent 'bugs' were identified throughout the model, although once corrected, the ICERs for ezetimibe improved"	To be consistent with the statement on page 8 and 119 of the ERG report, which concluded that the impact was minimal	The clarification has been added to the erratum document.

Issue 10 Minor corrections

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The following paragraph on page 8 of the ERG report, should be amended to state that angina	MSD requests that the health state excluded is updated from stroke to stable angina:	The current statement is factually incorrect. TIA and stable angina were not included as health states	The identified typo has been corrected in the erratum document. We have also

rather than stroke was excluded from the base case model: "Conversely, the effects of statin and ezetimibe on TIA and **stroke** were excluded from the base case model, rather than being assumed consistent with those observed for MI and stroke."	"Conversely, the effects of statin and ezetimibe on TIA and **stable angina** were excluded from the base case model, rather than being assumed consistent with those observed for MI and stroke."	in the base case. Stroke was included as a health state in the base case	corrected the same typo on page 119.
Spelling mistake, page 72 (1st line) "Whist this appears generally appropriate …"	To correct the spelling mistake from "Whist" to "Whilst"	Spelling mistake	Typographical error. Not a factual error.
We believe the title for Table 45 should refer to secondary prevention and Table 46 we think should refer to scenario B	Amend titles	To increase clarity	Amended in the erratum
The following sentence on page 105 of the ERG report, should be amended to reference the correct figure: "These results indicate greater overall survival in the modelled cohort compared with the age/sex matched general population **(Figure 3)**."	MSD requests that text is updated with the following text: "These results indicate greater overall survival in the modelled cohort compared with the age/sex matched general population **(Figure 4)**."	To increase clarity	This has now been amended in the erratum document.

Aberdeen HTA Group

Ezetimibe for treating primary (heterozygous-familial and non-familial) hypercholesterolaemia

Erratum

Completed 7 September 2015

This report was commissioned by
the NIHR HTA Programme as
project number 12/61/01.

Does not contain CIC/AIC

This document is intended to replace pages 8, 11, 105, 106, 107, 113, 117, 118 and 119 of the original ERG assessment report for *Ezetimibe for treating primary (heterozygous-familial and non-familial) hypercholesterolaemia*, which contained a few inaccuracies. The main issue related to an error in the ERG's calculations behind Figure 4 (page 107 of the ERG submitted report). This shows the modelled probability of survival over 40 cycles of the company's model (primary prevention cohort, age 60, 20% cardiovascular risk) versus modelled probabilities of survival using the age/sex matched probabilities of all-cause mortality for the general population. This had implications for text on pages 8, 11 and 105-106 of the report. In addition, we amended a number of further minor inaccuracies identified in the report. The amended pages follow in order of page number below.

were not designed to retrieve evidence from the literature for all relevant events in the model (stroke, MI, angina, TIA) as was the case for the quality of life searches. Thus information relevant for health state costs may have been missed.

The economic model was generally appropriately structured and consistent with previous modelling work used to inform NICE guidance in the area of hypercholesterolemia and lipid modification. The ERG identified a number of issues as follows:

- A number of apparent bugs were identified throughout the model, but, once corrected, the ICERs for ezetimibe actually improved.
- It was noted that rate of increase in the annual mortality rate did not keep pace that expected in the age and sex matched general population. This appeared to be due to over-adjustment of the background mortality rate for modelled CV deaths. Any bias associated with this may also depend on whether the inclusion of non-significant effects for lipid lowering on non-CV deaths is considered appropriate or not.
- Inconsistent with the modelling previously carried out for TA132, the new model included a non-significant effect for ezetimibe on non-CV deaths, with the point estimate favouring ezetimibe versus no treatment and statin alone. Whilst the effect is small, the point estimates of the ICERs are moderately sensitive to this assumption.
- Conversely, the effects of statin and ezetimibe on TIA and stable angina were excluded from the base case model, rather than being assumed consistent with those observed for MI and stroke. The latter was assumed in the modelling for TA132 and CG181.
- The approach used to combine background utility values with CV event utilities did not appear to follow the NICE DSU recommendation to use age adjusted multipliers. In addition, some more up to date utility estimates were identified from a single UK source. However, implementation of these new utilities with age adjustment had little impact on the ICERs

    - Lack of clarity on how and why studies were excluded on the basis of participant ethnicity.
- High levels of statistical heterogeneity (I^2>99%) in all main meta-analyses for LDL-c and TC outcomes with no attempt to investigate reasons for inconsistency between trials.
- A number of apparent data errors, although individually these were of minor concern.
- No attempt to perform a systematic review and meta-analyses of clinical outcomes.
- The company has excluded TIA and stable angina health states from the base case analysis, which is problematic for the model face validity.
- There are some deficiencies in the approach used to search for cost data pertaining to the health states.
- The estimated uncertainty surrounding the ICERs is likely to be underestimated due to misspecification of some distributions in the model.
- A number of apparent 'bugs' were identified throughout the model but, once corrected, the ICERs for ezetimibe actually improved.
- Some of the model output appeared to lack face validity. In particular, there was over adjustment of the background (non-CV) mortality rate for modelled CV deaths.
- In contrast with previous modelling approach used in TA132, the company's model includes a non-significant effect for ezetimibe on non-CV deaths which has significant impact on the estimated ICERs.
- The approach used to combine background utility values with CV events utilities did not appear to follow the NICE DSU recommendations on the use of age-adjusted multipliers.
- Up-to-date utility estimates for patients with a clinical history of CV events, derived from a patient population in the UK, were not taken into consideration by the company.
- There was limited exploration regarding the importance of full compliance and adherence assumptions in the sensitivity analyses.

Table 27 Comparison of events in IMPROVE-IT and the cost-effectiveness model

Events	Mean number of events per patient			
	Cost-effectiveness model		IMPROVE IT trial	
	Ezetimibe + simvastatin 40mg	simvastatin 40mg monotherapy	Ezetimibe + simvastatin 40mg	simvastatin 40mg monotherapy
MI	0.098	0.113	0.104	0.119
Stroke	0.012	0.015	0.027	0.034
CV death	0.071	0.072	0.059	0.059
Non CV death	0.046	0.046	0.056	0.055

The ERG carried out a number of checks to assess the face validity of the model output. Comparing the modelled survival of the 60 year-old primary prevention cohort (20% CV risk) to that expected using the age/sex weighted probabilities of all-cause mortality, it was noted that the rate of increase in mortality slowed with age relative to the rate of increase in the general population over time (Figure 4). It was also noted that the ratio of CV to non-CV deaths (by annual cycle) decreased over time in the model. This appears inconsistent with UK mortality data, which suggests that the proportion of deaths attributable to vascular causes keeps increasing with age, whilst the annual proportion of deaths from ischaemic heart disease and cerebrovascular disease remains fairly constant from age 60 upwards. This suggests that the age related rate of increase in CV events (and CV deaths) may not be increasing sharply enough in the model.

The above anomalies may also be partly related to the way in which vascular deaths have been adjusted out of the background (non-CV) mortality in the model. To estimate background mortality, UK life tables 1980-82 to 2011–2013 (Office of National Statistics (ONS)[98] were used to obtain age and sex- specific probabilities of death. The life table data were adjusted by excluding the proportion of deaths (by age and sex) attributable to all diseases of the circulatory system (ICD-10 codes I00-I99); the rationale behind this being that CV deaths are explicitly modelled through the CV event risks. However, the CV deaths that are modelled explicitly only include deaths attributable to ischaemic coronary heart disease and cerebrovascular disease. The impact of this is that the overall mortality for the cohort in question may be underestimated in the model, with all circulatory deaths taken out of the

background mortality, and only deaths from ischaemic heart disease and stoke put back in. This, in turn, may lead to overestimation of estimated LYs and QALYs in the model.

It is difficult to predict what impact the above inconsistencies might have on the modelled cost-effectiveness results. If the increase in CV risk associated with aging in the primary prevention model is progressing too slowly, this might act against ezetimibe. This is because the effects of lipid lowering therapy are not applied to the component of CV risk attributable to ageing. Conversely and somewhat counterintuitively, increasing other cause mortality could act in favour of ezetimibe, since a small additional effect on other cause mortality is modelled for ezetimibe through is further lowering of LDL-c.

A reproduction of the Markov trace is provided in Figure 5, which shows the proportion of the 60 year old primary prevention cohort under no treatment in the different states of the model over a 40-year time horizon. Note, this figure was modified to include the proportion of the cohort in the well state, which was not included in the original primary prevention traces provided in company's submission.

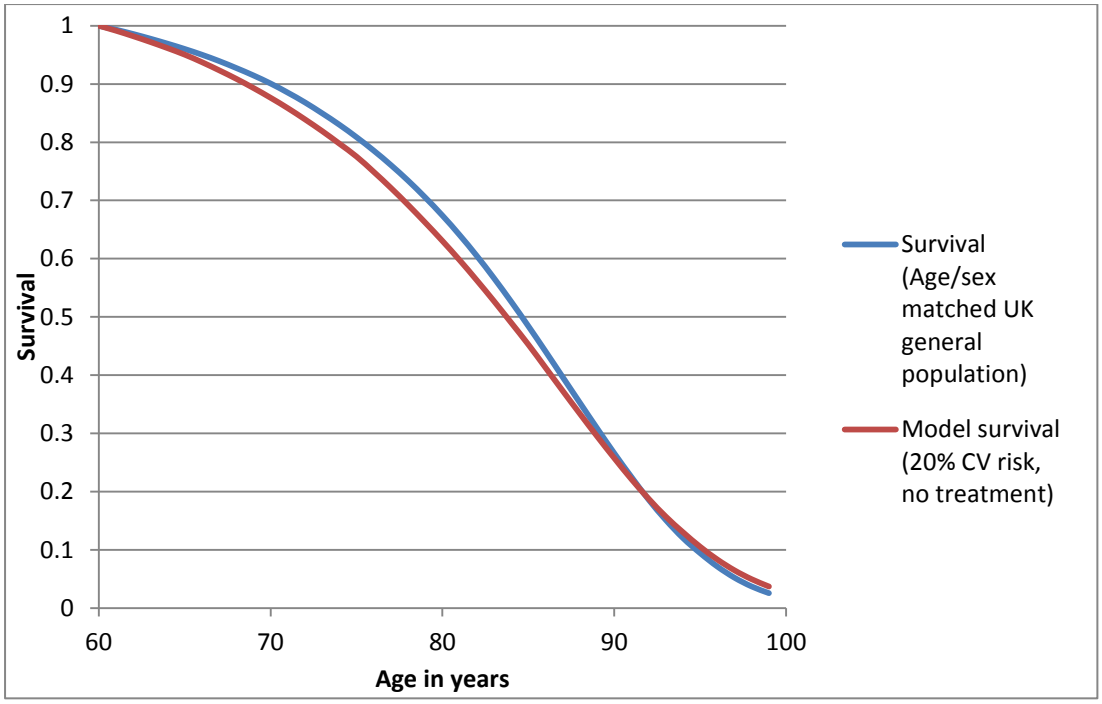

Figure 4 ERGs estimates of overall survival in the primary prevention cohort (age 60, 20% CV risk) compared with the age/sex matched UK general population

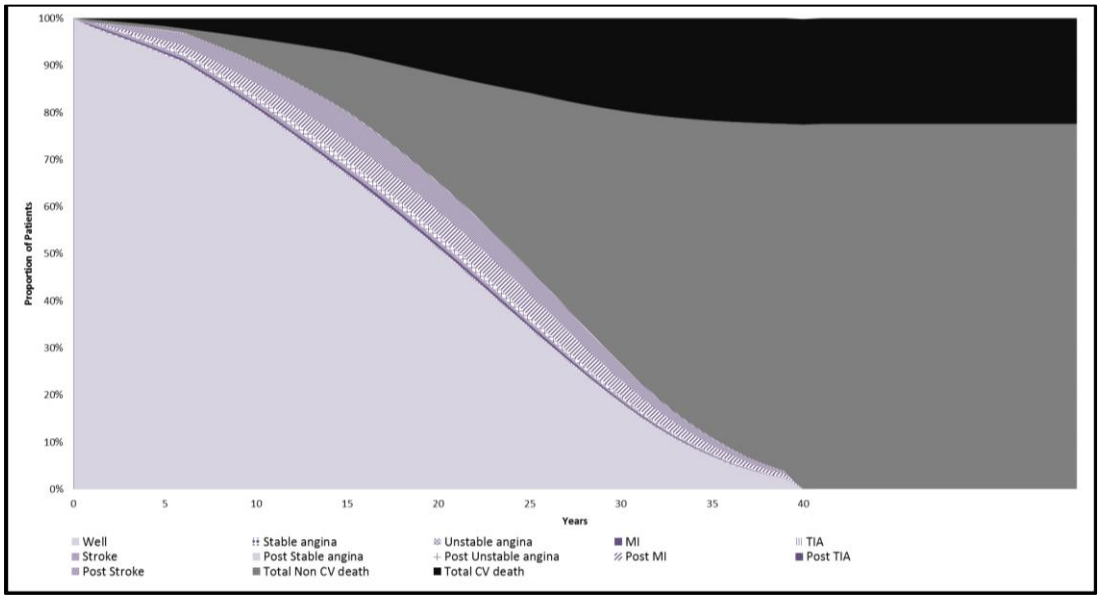

Figure 5 Markov trace: primary prevention, no treatment for 60 year-old cohort with 20% CV risk

Table 37 Results with alternative age adjusted health state utility values, on top of changes made in steps 1 and 2 above: primary prevention, add on to statin

	Total Costs	Total QALYs	Total LYs	Incremental Costs	Incremental QALYs	ICER
Atorvastatin (20mg)	£7,313	11.93	24.06			
Ezetimibe + Atorvastatin (20mg)	£12,493	12.04	24.38	£5,181	0.110	£47,045

Table 38 Results with alternative age adjusted health state utility values, on top of changes made in steps 1 and 2 above: secondary prevention, monotherapy

	Total Costs	Total QALYs	Total LYs	Incremental Costs	Incremental QALYs	ICER
No Treatment	£18,870	6.27	13.65			
Ezetimibe	£22,511	6.51	14.27	£3,640	0.243	£14,988

Table 39 Results with alternative age adjusted health state utility values, on top of changes made in steps 1 and 2 above: secondary prevention, add on to statin

	Total Costs	Total QALYs	Total LYs	Incremental Costs	Incremental QALYs	ICER
Atorvastatin (40mg)	£19,027	6.80	15.00			
Ezetimibe + Atorvastatin (40mg)	£22,963	6.94	15.37	£3,936	0.141	£27,937

Step 4: Assigning no effect of further LDL-c reductions on non-CV deaths (RR=1) but applying relative treatment effects for TIA and stable angina

Since the results of the CTTC meta-analysis show a non-significant effect for LDL-c lowering on non-CV deaths (RR 0.97 (95% CI: 0.91-1.03), the ERG assessed the impact of setting this to one in the model. This is consistent with the modelling for TA132.[5] Furthermore, in the review for CG181, more intensive statin doses (which result in further reductions in LDL-c) were not found to be associated further significant reductions in non-CV deaths compared with less intensive doses. However, the previous modelling for TA132 and CG181 did assume treatment effects of lipid lowering on TIA and stable angina, and these were assumed to be the same as those observed for stroke and MI respectively. Thus, in this exploratory analysis, treatment effects for TIA and stable angina are included for

Table 45 Results incorporating changes in step 1-4 above, and multiplicative effect of ezetimibe on post-statin LDL-c levels: secondary prevention, add on to statin

Post statin LDL-c attainment	Alternatives	Total Costs	Total QALYs	Total LYs	Incremental Costs	Incremental QALYs	ICER
2	Atorvastatin (40mg)	£18,669	6.75	14.84	-	-	-
	Ezetimibe (10mg) + Atorvastatin (40mg)	£22,471	6.82	15.02	£3,801	0.073	£51,975
2.5	Atorvastatin (40mg)	£18,727	6.66	14.62	-	-	-
	Ezetimibe (10mg) + Atorvastatin (40mg)	£22,477	6.76	14.87	£3,751	0.099	£37,755
3	Atorvastatin (40mg)	£18,792	6.56	14.38	-	-	-
	Ezetimibe (10mg) + Atorvastatin (40mg)	£22,485	6.69	14.71	£3,693	0.130	£28,496
3.5	Atorvastatin (40mg)	£18,865	6.46	14.12	-	-	-
	Ezetimibe (10mg) + Atorvastatin (40mg)	£22,493	6.62	14.53	£3,629	0.165	£22,056

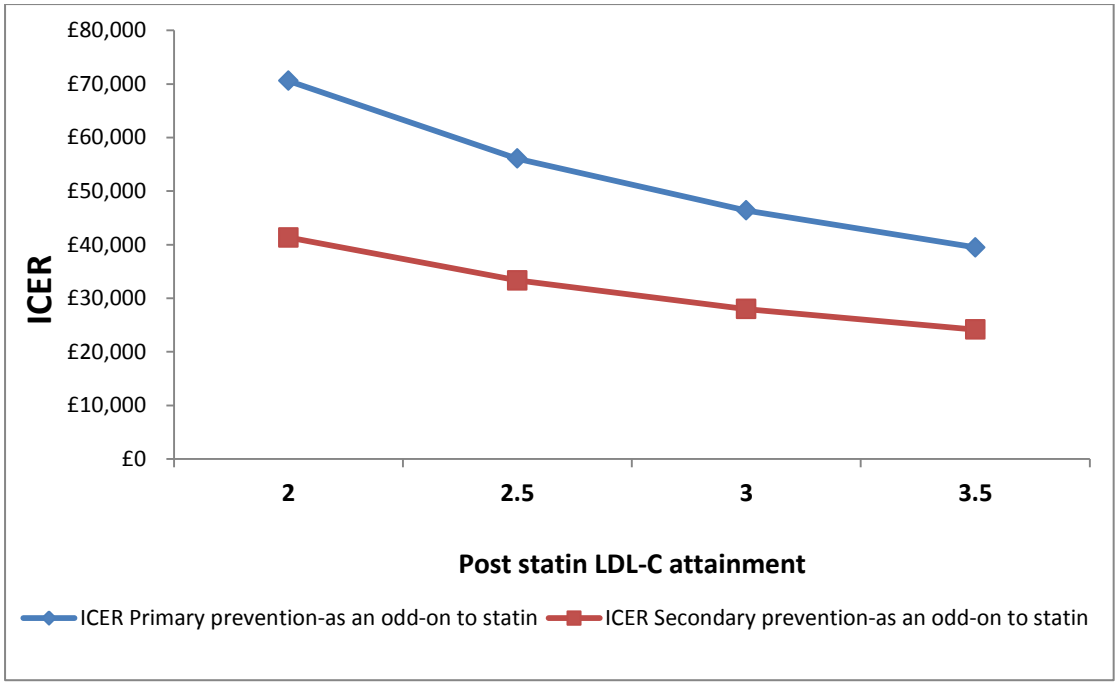

Figure 7 Incremental cost-effectiveness ratios for ezetimibe as an add-on to statin, using the multiplicative effect of ezetimibe on post-statin LDL-c levels

Scenario B: Using the results from the IMPROVE-IT trial for the secondary prevention, add-on to statin analysis

Using the updated model from step 4 above, the ERG finally investigated the effect of applying the directly estimated relative risks for ezetimibe from the IMPROVE-IT trial. This was done only for secondary prevention as an add-on to statin, using Simvastatin (40mg) as the comparator (the comparator in IMPROVE-IT). The results are provided in Table 46.

Table 46 Results from scenario B: secondary prevention, add on to Simvastatin (40mg)

	Total Costs	Total QALYs	Total LYs	Incremental Costs	Incremental QALYs	ICER
Simvastatin (40mg)	£18,496	6.60	14.44			
Ezetimibe + Simvastatin (40mg)	£21,831	6.62	14.49	£3,335	0.029	£115,354

5.4 Conclusions of the cost effectiveness section

The company conducted literature reviews of the cost effectiveness and quality of life literature in the area of hypercholesterolemia. In identifying economic evaluations, sensitivity of the searches may have been enhanced by the inclusion of additional terms, both for the clinical conditions and economic data relevant to the assessment.

The economic model is generally appropriately structured and consistent with previous modelling work used to inform NICE guidance in the area hypercholesterolemia and lipid modification. The ERG identified a number of issues as follows:

- A number of apparent bugs were found throughout the model, but once corrected the ICERs for ezetimibe actually improved.
- It was noted that rate of increase in the annual mortality rate did not keep pace that expected in the age and sex matched general population. This appeared to be due to over-adjustment of the background mortality rate for modelled CV deaths. Any bias associated with this may also depend on whether the inclusion of non-significant effects for lipid lowering on non-CV deaths is considered appropriate or not.
- The approach used to combine background utility values with CV event utilities did not appear to follow NICE DSU recommendations to use age adjusted multipliers, and some more up to date utility estimates were identified from a single UK source. However, implementing these new utilities with age adjustment had little impact on the ICERs.
- Inconsistent with the modelling previously carried out for TA132, the new model included a non-significant effect for ezetimibe on non-CV death, with the point estimate favouring ezetimibe versus no treatment and statin alone. Whilst the effect is small, the ICERs are moderately sensitive to this assumption.
- Conversely, effects of statin and ezetimibe on TIA and stable angina were excluded from the base case model, rather than being assumed consistent with those observed for MI and stroke. The latter was assumed in the modelling for TA132 and CG181.