National Institute for Health and Care Excellence

Consultation

Cardiovascular disease: risk assessment and reduction, including lipid modification

Cost-utility analysis: Lipid therapy escalation for secondary prevention

NICE guideline CG181

Economic analysis report

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Draft for Consultation

This analysis was developed by the National Guideline Centre, NICE

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1 Introduction

Currently, secondary prevention for people who have developed cardiovascular disease (CVD) is described by the Accelerated Access Collaborative[10] guidance and it is informed by various guidance including NICE CG181[35] and five NICE technology appraisals (TA) of lipid-lowering drugs[32, 34, 37-39]. The pathway requires people to be initially prescribed with the highest tolerated dose of statin (ideally atorvastatin 80 mg). If the statin fails to reduce “bad” or non high-density cholesterol (non-HDL cholesterol) by 40% compared to its pre-treatment value, an additional oral medicine called ezetimibe is added to the therapy. If ezetimibe and statin do not lower a different measurement of “bad” cholesterol called low density lipid cholesterol (LDL cholesterol) below certain thresholds identified in NICE TA733[39], 393[32], 394[37], people can receive an injectable therapy, that is either inclisiran or one of the two PCSK9 inhibitors available, evolocumab and alirocumab. For people who cannot tolerate a statin, a fourth oral drug is available – bempedoic acid[34].

This pathway has attracted criticisms for being hard to implement and a source of confusion. Firstly, baseline non-HDL cholesterol values are not consistently recorded prior to initiating a statin therapy, making it challenging for a general practitioner (GP) to evaluate whether the patient has achieved the desired 40% reduction. Secondly, the sequence includes both LDL and non-HDL cholesterol targets, which are two distinct measures of cholesterol often not reported together in a lipid profile test. Therefore, there is a clear need for a pragmatic and evidence-based target that could be understood and implemented in primary care.

An update to NICE CG181 was commissioned to explore the most cost-effective target for treatment escalation in secondary prevention. A health economic model was developed using real-world data to estimate baseline cholesterol levels and cardiovascular risk in people with CVD in England. Additionally, a comprehensive systematic review and a network meta-analysis were conducted to estimate the treatment effects that were input into the model.

2 Methods

2.1 Model overview

A cost-utility analysis was undertaken where lifetime quality-adjusted life years (QALYs) and costs from a current UK NHS and personal social services perspective were considered. The analysis followed the standard assumptions of the NICE reference case for interventions with health outcomes in an NHS setting including discounting at 3.5% for costs and health effects[36]. An incremental analysis was undertaken.

2.1.1 Comparators

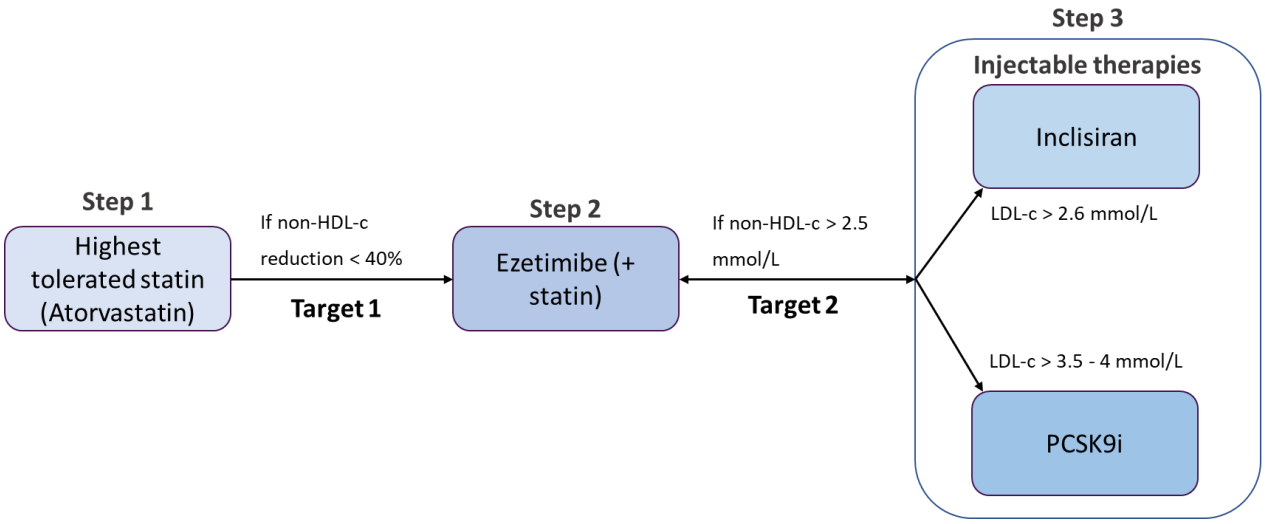
The pathway defined by the Accelerated Access Collaborative (AAC) Guidance[10] for people who can tolerate a statin is illustrated in the figure below (Figure 1) and includes the following steps:

Step 1. Highest tolerated intensity of statin

Step 2. Ezetimibe + statin

Step 3. Injectable therapy (inclisiran or PCSK9 inhibitors)

Figure 1: Accelerated Access Collaborative pathways



Source: Accelerated Access Collaborative (AAC)[10]

A sensitivity analysis including people who are intolerant to statin and who follow a different treatment pathway was conducted and it is described in section 2.5.1.

The committee agreed that a pragmatic, clear and cost-effective target for escalation should be identified. This should be an absolute value to allow for people without a baseline record to be assessed.

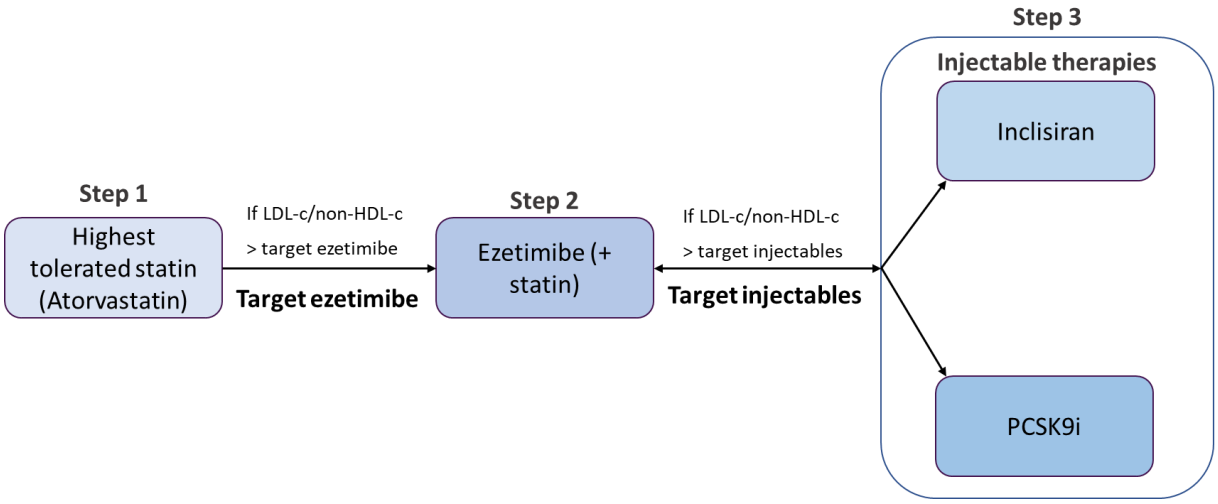
This model uses two different approaches to identify the target:

1. Treatment-specific targets approach
2. Single target approach

With the first approach, two distinct targets are identified specific to one of the treatments available in the sequence: ezetimibe and injectable therapies (Figure 2). These are considered and reported as 2 separate threshold analyses. The first as a target for adding

Ezetimibe to a statin (and not adding an Injectable). The second as a target for adding an Injectable to statin+ezetimibe. A larger group would be prescribed the more affordable ezetimibe, whereas a smaller group with elevated cholesterol levels and higher risk would be recommended the more effective but expensive injectable therapies. This approach aligns with the NICE TAs[32, 37] on injectable therapies, which identified specific LDL cholesterol threshold for PCSK9i (3.5 – 4 mmol/litre) and Inclisiran (2.6 mmol/litre) considering their effectiveness and price.

Figure 2: Treatment-specific targets

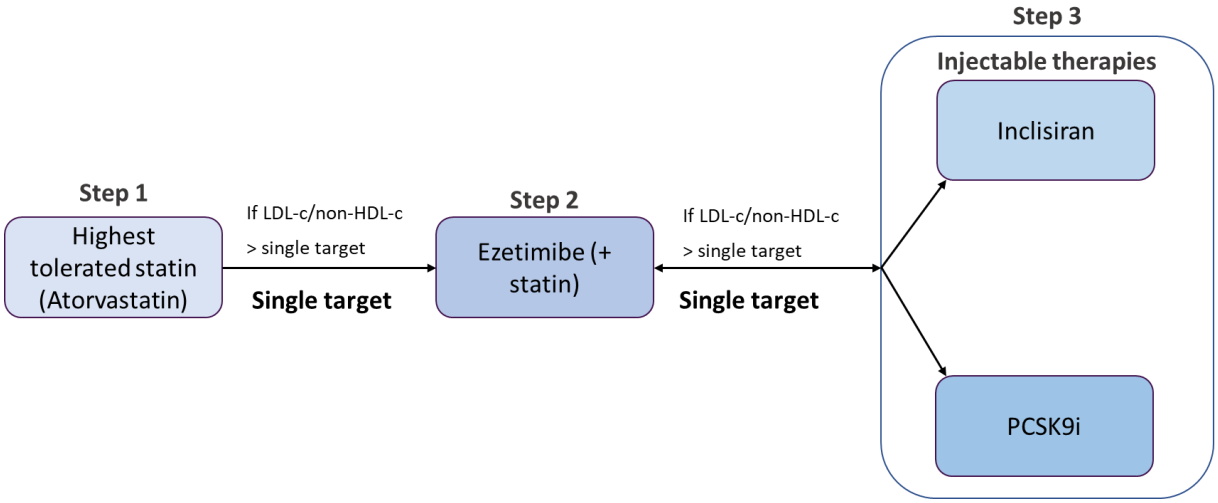


The second approach does not differentiate between treatment-specific thresholds and instead identifies a single target above which people would receive the next treatment available in the sequence if they are still above the target (Figure 3). This strategy was included as it is common in international guidelines to recommend treating patients to a specific target value, although there are significant variations in targets for LDL-c in secondary prevention. For instance, the European Society of Cardiology (ESC)[29] identified a LDL-c target of 1.4 mmol/litre whereas the American Heart Association(AHA)/American College of Cardiology(ACC)/Multisociety and the Canadian Cardiovascular Society (CCS) guidelines identified a LDL-c target of 1.8mmol/L[3].

Moreover, this approach follows the rationale of Quality Outcomes Framework (QOF), which provides indicators representing a specific level of performance that general practices are expected to achieve, independent of the treatment. With a QOF target, general practitioners are incentivized to offer additional treatments only to those who fall short of meeting the target in order to align with the indicator.

In both approaches the therapy is continued over the patient's lifetime. This is because stopping the treatment would let lipid levels return to their baseline level and the risk of cardiovascular events including death would rise again.

Figure 3: Single target



The model was built to identify the most cost-effective target or targets defined in both approaches. The drugs within the sequence for escalation as well as their order was not altered in any of the analysis as modifying the escalation sequence was outside the scope of this guideline update. Hence, people always receive Ezetimibe first before being escalated to an injectable. As the NICE Technology Appraisal for inclisiran (TA733) does not require that ezetimibe is offered first, a sensitivity analysis was conducted to explore the case where people receive injectable therapies without receiving ezetimibe first.

In the base case analysis, the injectable therapy people receive is inclisiran as its less frequent administration and similar efficacy means that it is more cost effective than the two PCSK9 inhibitors[39]. The committee noted that inclisiran is typically prescribed in primary care and could be the most promptly available treatment for people with a cholesterol above the target. Sensitivity analyses were added to look at scenarios where people receive PCSK9 inhibitors instead of inclisiran or where some receive inclisiran while other receive PCSK9 inhibitors (see section 2.5). This was because a) PCSK9 inhibitors might be better tolerated by some patients and b) if the current discount available for inclisiran were to cease then inclisiran might be no more cost effective than the PCSK9 inhibitors.

A range of targets were compared with each other to identify the most cost-effective target or targets using both approaches.

While LDL cholesterol is the most reported cholesterol measure in clinical trials, the committee agreed that non-HDL cholesterol is more commonly reported in primary care in England. Therefore, it was agreed to conduct both an LDL cholesterol and a non-HDL cholesterol analysis and present respective cholesterol targets.

A range of targets were compared with each other to identify the most cost-effective target or targets using both approaches:

- From 0.5 to 4.0 mmol/litre LDL cholesterol
- From 1.0 to 4.5 mmol/litre non-HDL cholesterol.

2.1.2 Population

The population of the analysis was adults who have established CVD and who are on lipid modification treatment with the highest tolerated intensity statin. The CVD diagnoses used to identify the population were:

1. Ischaemic stroke,
2. Transient ischaemic attack,
3. Peripheral artery disease (including non-coronary revascularisation),
4. Myocardial infarction,

5. Angina pectoris,
6. Coronary revascularisation

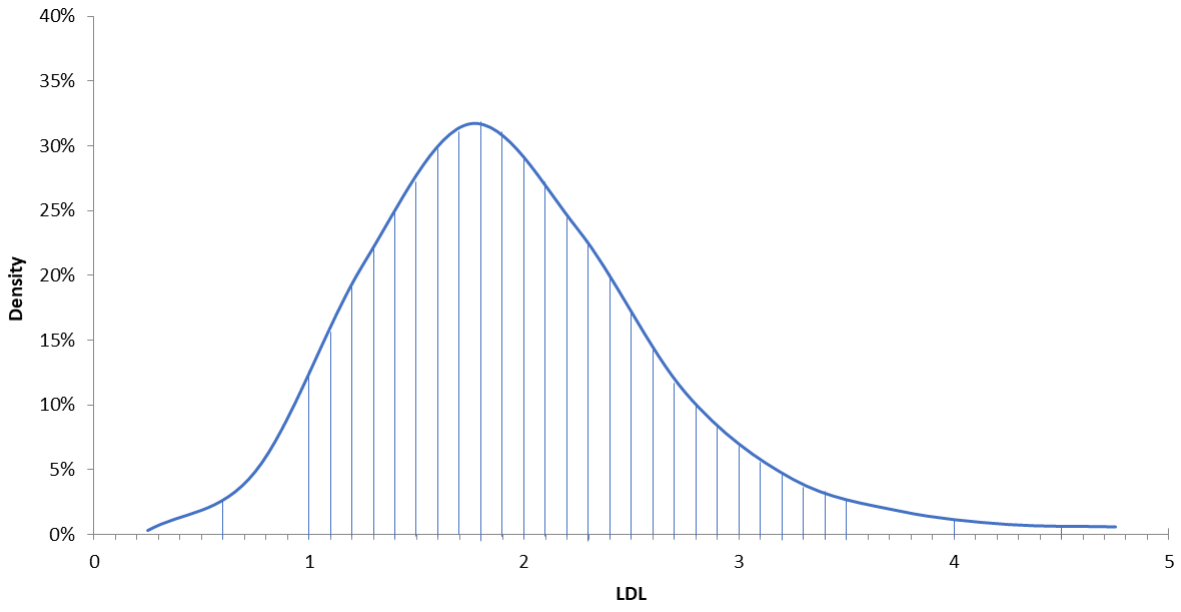
In the base case, people who are on any statin was included to reflect the heterogeneity of statin prescription in current practice. However, CG181 already recommends Atorvastatin 80mg for people with CVD[33]. Therefore, a sensitivity analysis including only people on Atorvastatin 80mg was conducted. Another sensitivity analysis was conducted on people who are intolerant to statin and receive different medications.

2.2 Approach to modelling

People entering the model were divided into subgroups based on their gender and baseline cholesterol measurement. Each subgroup corresponds to a particular cholesterol range (Figure 4) and is used to determine the cardiovascular disease (CVD) event risk across the entire distribution. To effectively account for the diversity of risk and treatment effectiveness in our target population, the densely populated region of the distribution (LDL cholesterol: 1 – 3.5; non-HDL cholesterol: 1.5 – 4) was divided into subgroups with a narrow range of 0.1 mmol/litre. For the distribution's extremes, wider subgroups with a cholesterol range of 0.5 were employed. Overall, 30 subgroups per gender (60 in total) were identified. This approach allows incorporate heterogeneity of risk and treatment outcomes into the model.

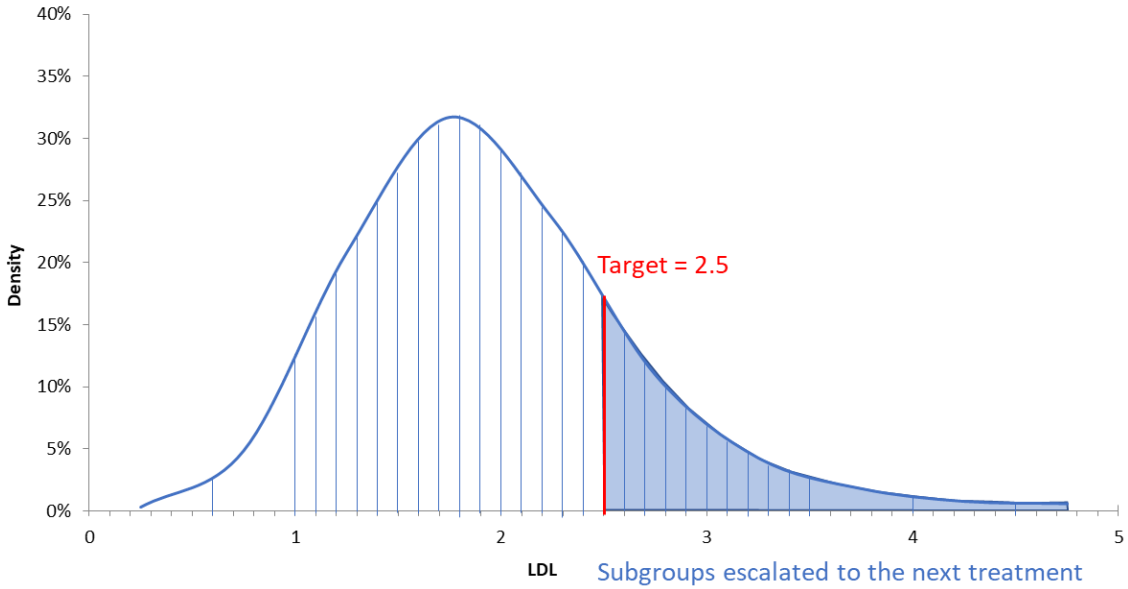
Cholesterol values within the model are dynamic and subject to change as they are influence by treatment but also gradually increase over time.

Figure 4: Subgroups by LDL cholesterol



When a subgroup lies above a target (see Figure 5), they receive the next line of treatment. Due to the observed rise in cholesterol levels in individuals over time, subgroups that are slightly below the target are not escalated immediately, but do so at a later stage, when their cholesterol values reach the target.

Figure 5: Subgroups by LDL cholesterol with a 2.5 mmol/litre target

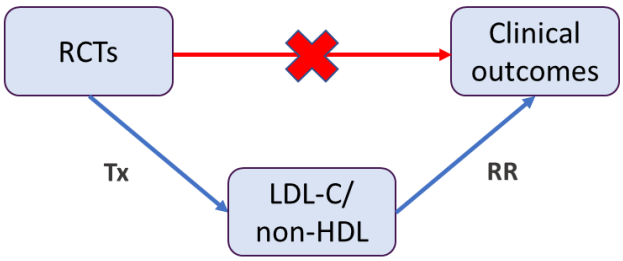


The risk of subsequent CVD events and mortality at each cycle is dynamic and affected by age, cholesterol level and gender. The relationship between cholesterol level and risk is explained in 2.3.4.

The treatment effect of each treatment is incorporated as a relative reduction in cholesterol (see 2.3.5). This is an indirect approach to estimate clinical outcomes as, instead of using MACE (Major adverse cardiovascular events) reduction from clinical trials, it involves estimating cholesterol reduction first, that is in turn used to estimate CVD event risk reduction (see Figure 6). This was a necessary approach, as the model must estimate the effectiveness of treatment effects for very narrowly defined cholesterol subgroups. . Moreover, it aligns with common practice in the health economic literature where either:

- randomised trial MACE outcomes were not available for novel treatments, or
- the limited duration of the trials made it challenging to estimate treatment effects for relatively infrequent events such as deaths.

Figure 6: Indirect approach to estimate clinical outcomes

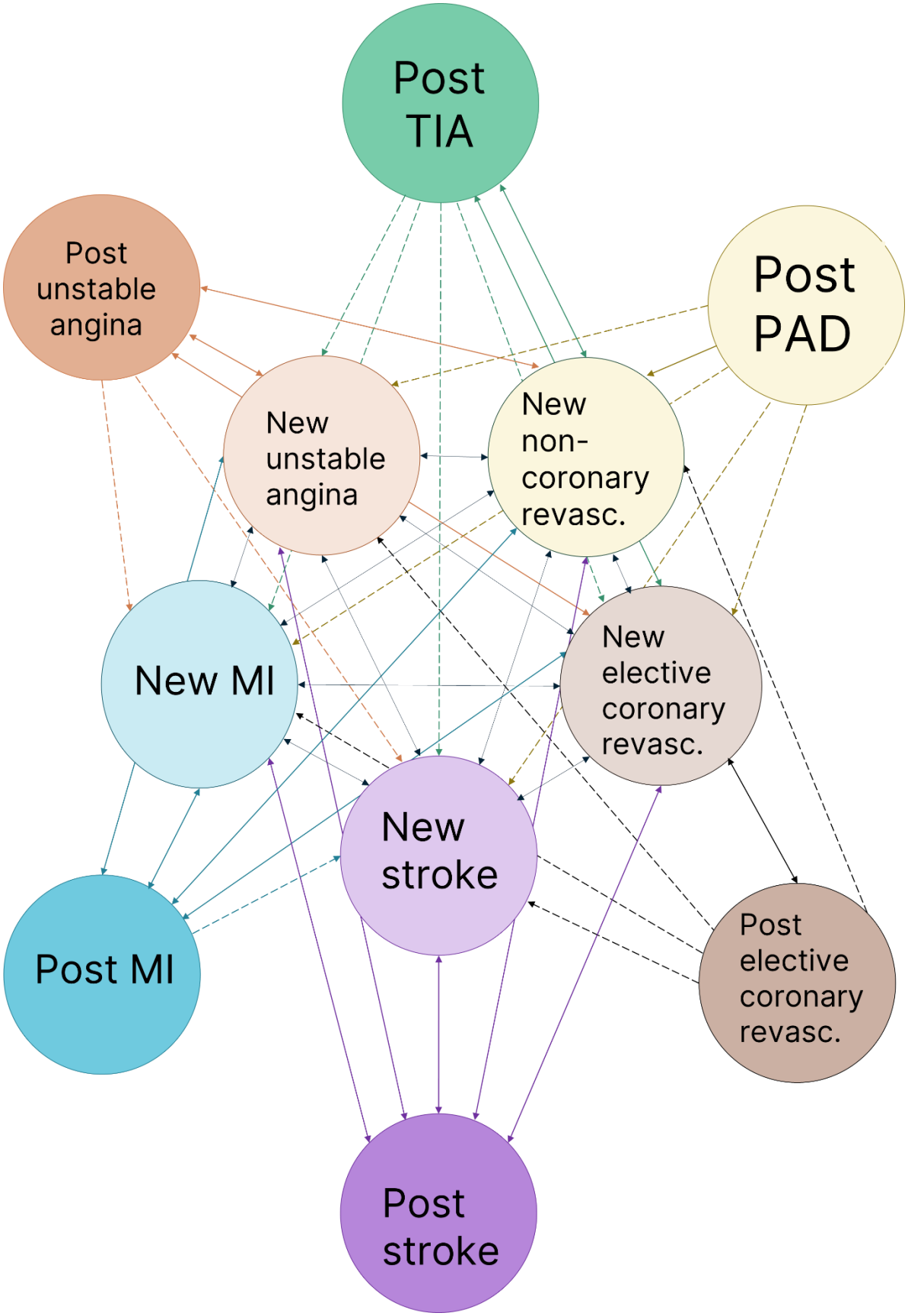


Abbreviations: Tx = treatment effect; RR = relative risk

A Markov model was used to estimate the incidence of subsequent CVD events (hospitalisations) and mortality. Each subgroup was simulated separately using a different Markov trace as each had its own sex, baseline age and baseline cholesterol level. The structure of the model is presented in Figure 7, where people start in the post CVD states in the outer part of the figure, with the starting proportion in each defined by the initial CVD prevalence. Dotted lines in the diagram indicate one-way transitions, where transitioning in the opposite direction is not permitted. So, for instance, a person who move from the “post-angina” state to the “new stroke” state cannot return to the previous but can transit only to the “post stroke” state. Solid lines represent “round-trip” transitions, where the person would

return to the original state in the next cycle. For instance, if a person moves from the “post stroke” state to the “new MI” state, they will return to the “post stroke” state in the following cycle. This is so that people who are in a more severe post-state do not have their long-term quality of life improved after experiencing a new (less severe) event.

Figure 7: Structure of the Markov model



Note: dotted line: one-way transitions; solid lines: transitions can occur in both directions.

Although not shown in the diagram, all states can transition to the 'Dead' state; the probability of dying due to 'modifiable CVD cause' or 'non-modifiable cause' is specific to the state (and to the mean age and sex of the subgroup in that cycle).

With Markov models generally, there is a trade-off between having a short cycle and more precise results or a longer cycle length and faster model runtime. For this model a cycle length of 1 year was chosen, partly because that was a pragmatically suitable length but also because it meant that input parameters, such as the unit costs of events did not need to be transformed. The model was built such that escalation could take place once or even twice within a single cycle and mean cholesterol levels and cardiovascular risk could be calculated accordingly.

At each cycle, people are at risk of a new CVD admission (see 2.3.3.1) or death (2.3.3.2). The risk of re-admission is based on their age, gender, and cholesterol level. The risk of death is based on their age, gender, cholesterol level, whether they have had a CVD event in the last 12 months and if so, which one.

Cholesterol is assumed to be measured annually as part of routine monitoring as well as three months after initiating a new treatment. At the beginning of each cycle, people whose cholesterol is above the target receive the next step of the escalation, which reduces their cholesterol and consequently their risk of a subsequent CVD event and mortality. It is possible for individuals to escalate once or twice in a single cycle if their cholesterol remains above the target after the first escalation. Once they reach the last step of the escalation (inclisiran or PCSK9 inhibitors), no further escalation is allowed even if the cholesterol level remains above the target.

Upon entry to a new CVD admission state, people incur a cost and a loss of quality of life. They will also experience increased mortality for the duration of the year (see 2.3.3.2). From the new CVD admission event, people transit to the post-CVD event where they incur a lower cost and loss of utility until they experience a new CVD event or they die. Mortality in the post-CVD state is lower than in the acute state.

The following outcomes were assumed to be cholesterol-dependent and were included as model outcomes:

1. Ischaemic stroke admissions,
2. Transient ischaemic attack (TIA) (included only as cost, not as a health state, since the impact on quality of life is brief)
3. Non-coronary revascularisation admissions,
4. Myocardial infarction admissions,
5. Unstable angina admissions,
6. Elective coronary revascularisation admissions
7. All-cause mortality (either CVD-related as the underlying cause or non-CVD)

Heart failure was not included as it might have multiple causes and there is no strong evidence of a causal association with cholesterol level.

TIA was included in the base case but only as a cost, not as a state, since the utility multiplier associated with the acute TIA state was potentially higher than the utility multiplier in some of the post-state utilities (see 2.3.7). Furthermore, there were some concerns that TIA could be over-recorded. Likewise, only admissions for unstable angina were included as the committee were concerned that admission episodes for angina (and stable angina in particular) could capture undifferentiated chest pain that would not be affected by a lipid-modification therapy. Both events were removed in scenario analyses (see section 2.5).

Post-CVD states were ranked from one to 5 according to their severity: stroke, MI, unstable angina, TIA, elective coronary revascularisation and PAD. The model was designed to prevent individuals from transitioning from a more severe post state to a less severe post state via a less severe new cardiovascular event. This restriction aims to prevent individuals from potentially improving their quality of life if they experience a less severe new event. Including composite CVD event states, e.g. “stroke and unstable angina”, was initially

considered but deemed unfeasible due to the lack of data and the structural limitation of a Markov model (see 4.2.5).

The model was run for 50 one-year cycles to capture the entire lifetime of the population. A range of treatment-specific and single targets were compared and costs and QALYs collected. The comparison between costs and QALYs across all target scenarios allowed the most cost-effective target or targets to be identified.

2.3 Model inputs

2.3.1 Summary table of model inputs

Model inputs were based on clinical evidence identified in the systematic review undertaken for the guideline, supplemented by additional data sources as required. Model inputs were validated with clinical members of the guideline committee. A summary of the model inputs used in the base-case (primary) analysis is provided in Table 1 below. More details about sources, calculations and rationale for selection can be found in the sections following this summary table.

Table 1: Overview of parameters and parameter distributions used in the base case analysis

Input	Data	Source	Probability distribution
Comparators	Targets ranging from: • 0.5 to 4.0 mmol/L LDL-C • 1.0 to 4.5 mmol/L Non-HDL-c.		n/a
Population	Adults with CVD and on a statin		n/a
Perspective	UK NHS & PSS	NICE reference case[36]	n/a
Time horizon	Lifetime (50 yearly cycles)		n/a
Discount rate	Costs: 3.5% Outcomes: 3.5%	NICE reference case[36]	n/a
Cohort characteristics			
Distribution of 30 cholesterol / gender subgroups	See Table 3 and Table 4	Bespoke analysis of CPRD-HES-ONS	Dirichlet
Mean age	Varies by subgroup (See Table 3 and Table 4)	Bespoke analysis of CPRD-HES-ONS	n/a
Mean LDL-c	Varies by subgroup (See Table 3)	Bespoke analysis of CPRD-HES-ONS	n/a
Mean non-HDL-c	Varies by subgroup (See Table 4)	Bespoke analysis of CPRD-HES-ONS	n/a
Baseline annual hazard rates			
Ischaemic stroke	Varies by age in 5-year bands and sex (see Table 6)	Bespoke analysis of CPRD-HES-ONS	Gamma
MI			
Unstable angina			
Non-coronary revascularisation			

Input	Data	Source	Probability distribution
Elective Coronary revascularisation			
Death ('modifiable CVD' underling cause)	Varies by age in 5-year bands, sex and event in last year (see Table 7)	Bespoke analysis of CPRD-HES-ONS	Gamma
Death (not 'modifiable CVD' underling cause)	Varies by age in 5-year bands, sex and event in last year (see Table 8)		
TIA (as a relative to ischaemic stroke)	54.5 TIAs for every 100 strokes	Oxford Vascular study [49]	n/a
Mortality hazard ratio 95-100 vs 90-95	Male: 1.502 Female: 1.533	ONS Life tables 2017-2019[1]	n/a
Mortality hazard ratio 100+ vs 90-95	Male: 2.009 Female: 2.112	ONS Life tables 2017-2019[1]	n/a
Treatment effects - cholesterol			
Ezetimibe on LDL-c	-17.8%	Network Meta-analysis	Simulated samples from the joint posterior distribution of the NMA
Inclisiran on LDL-c	-51.3%	Network Meta-analysis	Simulated samples from the joint posterior distribution of the NMA
PCSK9 inhibitors on LDL-c	-55.0%	Network Meta-analysis	Simulated samples from the joint posterior distribution of the NMA
Ezetimibe on non-HDL-c	-15.7%	Network Meta-analysis adjusted to be consistent with LDL-c (see 2.3.5)	Simulated samples from the joint posterior distribution of the NMA
Inclisiran on non-HDL-c	-45.1%	Network Meta-analysis	Simulated samples from the joint posterior distribution of the NMA
PCSK9 inhibitors on non-HDL-c	-47.0%	Network Meta-analysis	Simulated samples from the joint posterior distribution of the NMA
Treatment effects – cardiovascular events per 1 mmol/L reduction in cholesterol			
Unstable angina or non-coronary revascularisation RR – LDL-c	0.78	CTT Collaboration 2010[8]	Lognormal $\mu = -0.25$ $\sigma = 0.01$
Coronary revascularisation RR – LDL-c	0.74	Weighted average from CTT collaboration 2010[8]	Lognormal $\mu = -0.30$ $\sigma = 0.03$
Ischaemic stroke RR – LDL-c	0.78	Weighted average from CTT collaboration 2010[8]	Lognormal $\mu = -0.25$ $\sigma = 0.07$
Myocardial infarction RR – LDL-c	0.73	Weighted average from CTT collaboration 2010[8]	Lognormal $\mu = -0.31$ $\sigma = 0.04$

Input	Data	Source	Probability distribution
All-cause mortality RR – LDL-c	0.90	CTT Collaboration 2012[9]	Lognormal μ = -0.11 σ = 0.02
Unstable angina or non-coronary revascularisation RR – non-HDL-c	0.81	Derived using the non-HDL-c effect for MI and stroke combined with ratio of relevant LDL-c effects[9, 12]	Lognormal
Any coronary revascularisation RR – non-HDL-c	0.78	Derived using the non-HDL-c effect for MI and stroke combined with ratio of relevant LDL-c effects[9, 12]	Lognormal
Ischaemic stroke RR – non-HDL-c	0.81	Derived using the non-HDL-c effect for MI and stroke combined with ratio of relevant LDL-c effects[9, 12]	Lognormal
Myocardial infarction RR – non-HDL-c	0.77	Derived using the non-HDL-c effect for MI and stroke combined with ratio of relevant LDL-c effects[9, 12]	Lognormal
All-cause mortality RR – non-HDL-c	0.91	Derived using the non-HDL-c effect for MI and stroke combined with ratio of relevant LDL-c effects[9, 12]	Lognormal
Health-related quality of life - utility multipliers			
Post stroke	0.816	Bespoke analysis of Health Survey for England 2017[20]	Lognormal μ = -0.20 σ = 0.02
Acute stroke	0.756	Bespoke analysis of Health Survey for England 2017[20]	Gamma (post – acute) α = 0.8 β = 0.07
Post unstable angina	0.878	Bespoke analysis of Health Survey for England 2017[20]	Lognormal μ = -0.13 σ = 0.01
Acute unstable angina	0.682	Bespoke analysis of Health Survey for England 2017[20]	Gamma (post – acute) α = 69.8 β = 0.003
Post PAD/non-coronary revascularisation	0.927	Health Survey for England 2017[20]	Lognormal μ = -0.08 σ = 0.02
Acute non-coronary revascularisation	0.88	[20]Assumed to be the same as coronary revascularisation	n/a
Post myocardial infarction	0.847	Bespoke analysis of Health Survey for England 2017[20]	Lognormal μ = -0.17 σ = 0.01
Acute myocardial infarction	0.839	Bespoke analysis of Health Survey for England 2017[20]	Gamma (post – acute) α = 0.02 β = 0.38

Input	Data	Source	Probability distribution
Post elective coronary revascularisation	0.889	Bespoke analysis of Health Survey for England 2017[20]	Lognormal μ = -0.12 σ = 0.03
Acute elective coronary revascularisation	0.881	Indirectly calculated from post state using ratio of acute MI to post-MI=0.889x0.839/0.847 [20]	n/a
Post TIA	0.90	NICE CG181[35]	Lognormal μ = -0.11 σ = 0.03
Costs			
Statin (Atorvastatin)	£1.40 for 28 tablets	BNF[5] and Drug Tariff[42]	n/a
Ezetimibe	£1.47 per 28 tablets	BNF[5] and Drug Tariff[42]	n/a
Inclisiran	[redacted]	Novartis (CIC)	n/a
Alirocumab	[redacted]	Sanofi (CIC)	n/a
Evolocumab	[redacted]	Amgen (CIC)	n/a
Lipid test including phlebotomy	£6	NHS Reference Costs 2019/2020[43]	n/a
Nurse visit (including qualification cost)	£11	PSSRU 2020/2021[21]	n/a
GP appointment (including qualification cost)	£38	PSSRU2020/2021[21]	n/a
Outpatient visit	£138	NHS Reference Costs 2019/2020[43] - WF01A	n/a
Ischaemic stroke admissions	Acute cost varying by age in 5-year band and sex (Table 16); Post-event cost: £3,245	Zhou et al. 2023[59]	Gamma α = 25 β =130
Myocardial infarction admissions	Acute cost varying by age in 5-year band and sex (Table 16); Post-event cost: £368	Zhou et al. 2023[59]	Gamma α = 25 β =15
Elective coronary revascularisation admissions	Acute cost varying by age in 5-year band and sex (Table 16); Post-event cost: £148	Zhou et al. 2023[59]	Gamma α = 25 β =6
TIA episodes	Acute cost: £2,620 Post-event cost: £341	Danese et al. 2016[11]	Gamma α = 64, 23 β =41, 15

Input	Data	Source	Probability distribution
Unstable angina pectoris admissions	Acute cost: £3,196 Post-event cost: £327	Danese et al. 2016[11]	Gamma α = 195, 6 β =16, 56
Non-coronary revascularisation admissions	Acute cost: £8,835 Post-event cost: £428	Acute cost: NHS Reference cost 2019/20[43] Post-event cost: Walker et al. 2016[56]	Acute: n/a Post-event: Gamma α = 597 β =1
Vascular deaths	£2,720	Zhou et al. 2023[59]	Gamma α = 147 β =19

Abbreviations: BNF = British national formulary; CAA = Commercial Access Agreement CIC = commercial in confidence; CPRD = clinical practice research datalink; CVD = cardiovascular disease; HES = hospital episode statistics; MI = myocardial infarction; ONS = office of national statistics; PAD = peripheral artery disease; PAS = Patient Access Scheme; RR = relative risk; TIA = transient ischemic attack

2.3.2 Cohort characteristics

For the model baseline, bespoke data analysis was conducted on a large database of general practice medical records – Clinical Practice Research Datalink (CPRD). CPRD data was linked to both Hospital Episode Statistics (HES) and Office for National Statistics (ONS) death registrations.

The population was people with CVD who were on a statin, either:

- the prevalent population on 1st January 2013 (that is, 10 years ago at the time of analysis); or
- the incident population between 1st January 2013 and 28th February 2020 (that is, censoring at the beginning of the Covid-19 pandemic)

Follow-up was also censored when the patient:

- was escalated to other lipid lowering therapy,
- discontinued statin therapy,
- left the general practice, or
- died.

The CPRD dataset provided:

- LDL cholesterol and non-HDL distribution
- CVD events rate
- CVD and non-CVD mortality rates
- Demographic characteristics of people
- Statin types and doses.

In total there were 590,917 people with CVD and on a statin, of whom 226,210 (38.3%) were women. Table 2 shows the diagnosis at baseline. For the incident population this was their first CVD event/diagnosis. For the prevalent population it was their most recent CVD event/diagnosis.

Table 2: Diagnosis at baseline

	Ischaemic stroke	Angina pectoris	Peripheral arterial disease (PAD)	Myocardial infarction (MI)	Elective coronary revascularisation	Transient ischaemic attack (TIA)
Male	14%	26%	6%	30%	11%	12%
Female	20%	30%	5%	21%	5%	19%
All	16%	28%	6%	27%	9%	15%

2.3.2.1 Cholesterol distribution

LDL cholesterol levels and non-HDL cholesterol distributions were estimated using the CPRD dataset. The specific analysis plan is in Appendix B: Cholesterol measurements were from fasting and non-fasting samples. For the baseline cholesterol distribution, the baseline was the first measurement of cholesterol during the study period that was at least 3 months after the initiation of the statin to allow time for the statin to take effect. In total there were baseline LDL cholesterol measurements for 233,900 people (40% of CPRD cohort). The baseline distribution of LDL cholesterol is shown in Table 3. Similarly, the baseline distribution of non-HDL cholesterol is shown in Table 4 for 302,783 people (52% of CPRD cohort). The mean age and sex for both the LDL cholesterol and non-HDL cholesterol populations at baseline were almost identical in these different but overlapping samples:

- LDL cholesterol population: 72.3 years, 37% female, mean LDL cholesterol =1.93 mmol/litre
- Non-HDL cholesterol population: 72.5 years, 37% female, mean non-HDL cholesterol =2.59 mmol/litre

In Figure 8 and Figure 9 it can be seen that those people on the most effective statin (80mg atorvastatin) had a lower mean lipid level than the broader population on any statin.

As described in 2.2 above, for the model the population was sub-divided into 30 LDL cholesterol subgroups stratified by gender, so 60 subgroups in total. The weighting (relative sample size), mean LDL cholesterol, mean age of each subgroup is shown in Table 3. Note that in both tables the mean age is inversely correlated with the mean cholesterol. This must be because, the people with higher cholesterol levels are less likely to live to very old age. At each lipid level, the mean age for women was higher than the mean age for men.

The change in cholesterol between baseline and the last observation within the study time frame was calculated and from that an annual change per person. Although the change over time varied greatly between individuals, a trend over time was identified – Table 5. There was a modest increase in both LDL cholesterol and non-HDL cholesterol over time that was higher in women than in men. This mean change over time was built into the model, such that some subgroups might be below the target in the first cycle of the model but rise above it at a later time and subsequently have their lipid therapy escalated at that time. An alternative cholesterol change model was specified which includes coefficients for baseline cholesterol, age and interaction terms. This allows regression to the mean to be captured and it was tested in a sensitivity analysis (see 2.4.9).

Figure 8: LDL cholesterol distribution for people with CVD and on a statin

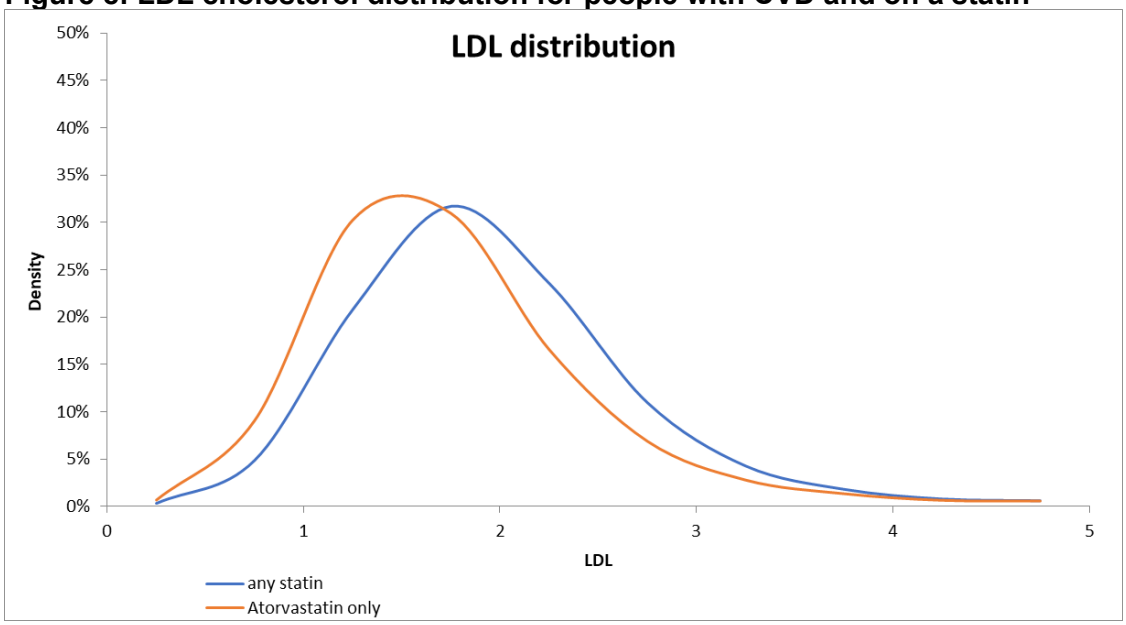


Figure 9: Non-HDL cholesterol distribution for people with CVD and on a statin

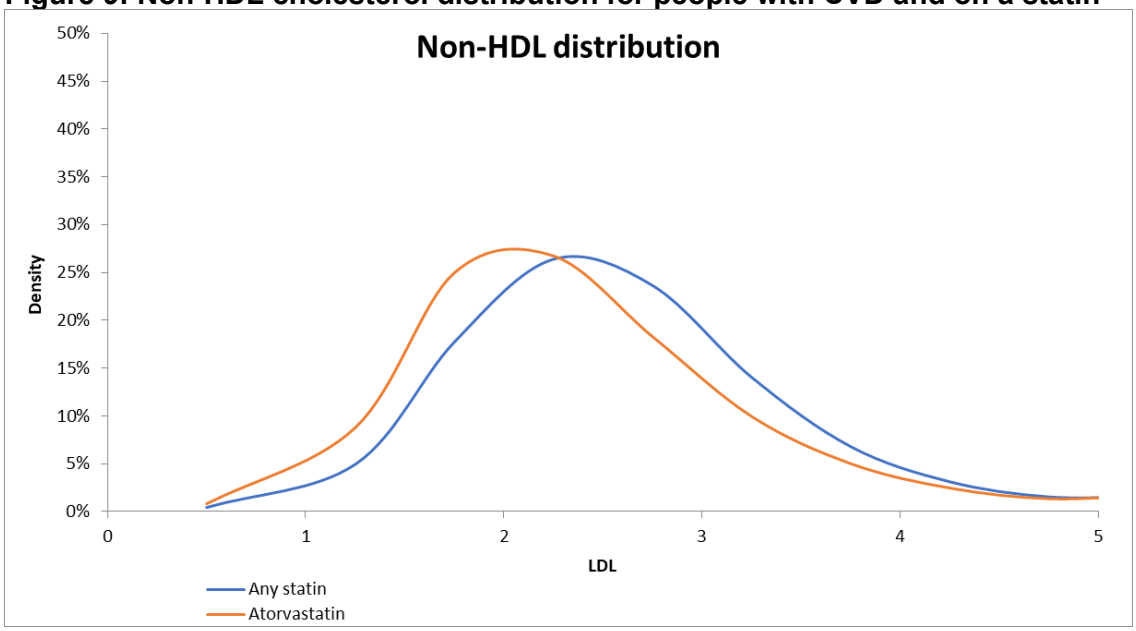


Table 3 LDL cholesterol / gender subgroups

		LDL-c - Male			LDL-c - Female		
Index	LDL-c subgroup	Mean LDL	Mean age	Proportion of LDL-c population	Mean LDL	Mean age	Proportion of LDL-c population
1	0-0.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	0.5-1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	1.0-1.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	1.1-1.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	1.2-1.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	1.3-1.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	1.4-1.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	1.5-1.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	1.6-1.7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	1.7-1.8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	1.8-1.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	1.9-2.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	2.0-2.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	2.1-2.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	2.2-2.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	2.3-2.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
17	2.4-2.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	2.5-2.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
19	2.6-2.7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	2.7-2.8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21	2.8-2.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
22	2.9-3.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
23	3.0-3.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	3.1-3.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
25	3.2-3.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
26	3.3-3.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
27	3.4-3.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28	3.5-4.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
29	4.0-4.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	4.5+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
				63.0%			37.0%

Note: This information has been redacted so that the commercial in confidential drug prices used in the model cannot be back-calculated from the optimal target.

Table 4: Non-HDL cholesterol / gender subgroups

	Non-HDL-c - Male			Non-HDL-C - Female		
Non-HDL-c subgroup	Mean LDL	Mean age	Proportion of Non HDL-c population	Mean LDL	Mean age	Proportion of Non HDL-c population
0-1.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.0-1.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.5-1.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.6-1.7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.7-1.8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.8-1.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.9-2.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.0-2.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.1-2.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.2-2.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.3-2.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.4-2.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.5-2.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.6-2.7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.7-2.8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.8-2.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.9-3.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3.0-3.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3.1-3.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3.2-3.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3.3-3.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3.4-3.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3.5-3.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3.6-3.7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3.7-3.8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3.8-3.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3.9-4.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4.0-4.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4.5-5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			62.9%			37.1%

Note: This information has been redacted so that the commercial in confidential drug prices used in the model cannot be back-calculated from the optimal target.

Table 5: Change in cholesterol over time

	Average annual change (arithmetic difference between measurements on the same patient, mmol/l)	Lower 95% CI	Upper 95% CI
LDL-C - Male	0.006	0.004	0.008
LDL-C - Female	0.015	0.012	0.019
Non-HDL-C - Male	0.010	0.008	0.012
Non-HDL-C - Female	0.022	0.019	0.025

2.3.2.2 Background statin therapy

Dose	Total Prescriptions	Dose %	Drug%
Atorvastatin calcium trihydrate			48.5%
10mg	162,130	6.9%	
20mg	303,522	13.0%	
40mg	439,533	18.8%	
80mg	230,517	9.8%	
Fluvastatin sodium			0.3%
20mg	1,981	0.1%	
40mg	2,841	0.1%	
80mg	1,555	0.1%	
Pravastatin sodium			4.8%
10mg	17,229	0.7%	
20mg	29,251	1.2%	
40mg	66,267	2.8%	
Rosuvastatin calcium			3.5%
5mg	20,178	0.9%	
10mg	34,926	1.5%	
20mg	21,733	0.9%	
40mg	4,097	0.2%	
Simvastatin			43.0%
10mg	49,815	2.1%	
20mg	320,938	13.7%	
40mg	619,367	26.4%	
80mg	15,954	0.7%	
	2,341,834	100.0%	100.0%

2.3.3 Baseline rates

Baseline event rates for CVD hospitalisation, CVD mortality and non-CVD mortality in a secondary prevention population were estimated by age group and gender using CPRD-HES-ONS.

2.3.3.1 Cardiovascular events

Admission rates, by age group and sex were estimated from the study cohort of people with CVD and on a statin, calculated as the total number of events divided by the total patient-

years of observation (Table 6). Full details including events, sample size and confidence intervals can be found in Appendix D: MI and stroke rates increased with age; elective revascularisation rates declined with age, as you would expect, given that comorbidity could contraindicate intervention. Curiously unstable angina admissions also declined with age.

Table 6: Admission rates

Age	Myocardial infarction	Ischaemic stroke	Unstable angina	Non-coronary revascularisation	Elective coronary revascularisation
Male	**Admission rates**				
50-54	0.012	0.005	0.009	0.007	0.026
55-59	0.012	0.005	0.007	0.008	0.024
60-64	0.011	0.006	0.007	0.009	0.021
65-69	0.010	0.006	0.006	0.010	0.016
70-74	0.012	0.008	0.005	0.009	0.014
75-79	0.014	0.012	0.005	0.009	0.011
80-84	0.017	0.015	0.005	0.007	0.007
85-90	0.021	0.018	0.005	0.006	0.004
>90	0.029	0.024	0.005	0.004	0.001
Female	**Admission rates**				
50-54	0.009	0.006	0.009	0.007	0.012
55-59	0.007	0.006	0.008	0.007	0.012
60-64	0.008	0.007	0.006	0.007	0.011
65-69	0.008	0.007	0.005	0.006	0.009
70-74	0.008	0.010	0.005	0.006	0.008
75-79	0.011	0.014	0.005	0.007	0.006
80-84	0.014	0.018	0.005	0.005	0.004
85-90	0.017	0.024	0.004	0.004	0.002
>90	0.020	0.030	0.004	0.003	0.000

Initially all angina episodes were included. However, the committee were concerned that this would include undifferentiated chest pain that would not be preventable with lipid lowering therapy. It was decided to include only coronary revascularisations and not admissions for angina. Therefore, we have made an adjustment to the angina admissions, so that they relate to unstable angina rather than all angina pectoris admissions. This was done using the proportion of 35% (15,148/42,756) from national HES Admitted Patient Care data for 2021-2022.

TIAs are not normally treated as admissions and so could not be sourced from HES. Although, they were picked up in HES, the episodes were so frequent, far outweighing the other CVD events, such that it was clear that individual episodes were being picked up multiple times. An alternative source was used for TIAs. The OxVasc study had prospectively collected data on CVD events and found that there were 55 TIAs for every 100 strokes [49]. This ratio was used to calculate the TIA rates for each age/sex group in the model.

2.3.3.2 Mortality

Mortality rates, by age group, sex and admission type in last 12 months were estimated from the study cohort of people with CVD and on a statin, calculated as the number of deaths divided by the total patient-years of observation (Table 7 and Table 8). Mortality was divided

into those deaths that were deemed most likely to be preventable using lipid lowering therapy and those which were less likely to be modifiable. The committee defined modifiable cardiovascular mortality as those where the underlying cause recorded by the ONS was:

- ischaemic (or unspecified) stroke,
- coronary heart disease (including myocardial infarction),
- other cardiac disease (including cardiac arrest, sudden cardiac death, and heart failure),
- other vascular disease (including atherosclerosis and aortic aneurysm), or
- sudden death of unknown cause.

Event numbers, sample size and confidence intervals can be found in Appendix D:

Table 7: Rates of mortality - underlying cause was modifiable cardiovascular

Age	None	Myocardial infarction	Ischaemic stroke	Unstable angina	Non-coronary revascularisation	Elective coronary revascularisation
Male	**CVD mortality rates**					
50-54	0.002	0.016	0.020	0.004	0.013	0.002
55-59	0.002	0.010	0.058	0.004	0.017	0.003
60-64	0.003	0.014	0.044	0.004	0.010	0.004
65-69	0.005	0.024	0.077	0.005	0.020	0.006
70-74	0.006	0.039	0.072	0.015	0.031	0.006
75-79	0.010	0.060	0.118	0.021	0.041	0.020
80-84	0.015	0.086	0.207	0.032	0.051	0.016
85-90	0.026	0.150	0.334	0.060	0.077	0.012
90-95	0.046	0.200	0.497	0.083	0.078	0.000
Female	**CVD mortality rates**					
50-54	0.001	0.009	0.019	0.000	0.000	0.000
55-59	0.001	0.004	0.015	0.006	0.006	0.007
60-64	0.002	0.028	0.038	0.007	0.024	0.008
65-69	0.003	0.024	0.084	0.007	0.007	0.004
70-74	0.004	0.031	0.101	0.006	0.011	0.007
75-79	0.006	0.062	0.145	0.013	0.021	0.007
80-84	0.012	0.068	0.216	0.026	0.050	0.015
85-90	0.019	0.100	0.320	0.035	0.026	0.048
90-95	0.038	0.145	0.628	0.065	0.062	0.000

Table 8: Rates of mortality - underlying cause was not modifiable

Age	None	Myocardial infarction	Ischaemic stroke	Unstable angina	Non-coronary revascularisation	Elective coronary revascularisation
Male	**Non-CVD mortality rates**					
50-54	0.006	0.019	0.036	0.004	0.030	0.003
55-59	0.008	0.026	0.027	0.014	0.020	0.002
60-64	0.012	0.054	0.044	0.018	0.030	0.003
65-69	0.016	0.090	0.084	0.022	0.064	0.008
70-74	0.025	0.144	0.093	0.037	0.095	0.019

Age	None	Myocardial infarction	Ischaemic stroke	Unstable angina	Non-coronary revascularisation	Elective coronary revascularisation
75-79	0.038	0.204	0.138	0.058	0.122	0.028
80-84	0.059	0.291	0.186	0.090	0.150	0.052
85-90	0.098	0.424	0.244	0.140	0.302	0.081
90-95	0.171	0.676	0.368	0.223	0.355	0.172
Female	**Non-CVD mortality rates**					
50-54	0.008	0.041	0.025	0.003	0.011	0.010
55-59	0.009	0.061	0.040	0.008	0.049	0.007
60-64	0.014	0.076	0.077	0.003	0.039	0.028
65-69	0.018	0.119	0.117	0.023	0.094	0.009
70-74	0.024	0.137	0.106	0.030	0.076	0.021
75-79	0.035	0.172	0.136	0.046	0.121	0.025
80-84	0.052	0.308	0.186	0.072	0.134	0.012
85-90	0.085	0.364	0.251	0.097	0.205	0.016
90-95	0.159	0.577	0.423	0.170	0.318	0.038

The mortality rate among individuals undergoing elective coronary revascularisation is remarkably low, even lower than the mortality rate of people with no acute event or of the general population. This can be attributed to the fact that individuals must possess a certain level of physical fitness to qualify for such a significant elective procedure. The model applies the mortality rate associated with no acute event (general population) to people who undergo elective revascularisation. This is to avoid treatments reducing revascularisations but conversely increasing in mortality rates.

Due to the limited representation of individuals older than 95 in the sample, accurate estimation of mortality for this population was challenging. Therefore, an adjustment was implemented by applying hazard ratios obtained from ONS life tables 2017-2019[1] by comparing people older than 95 with people between 90-94 (see Table 9). These hazard ratios were applied to the mortality observed in the oldest group of our sample (90-95) to obtain a more reliable mortality estimation for those older than 95.

Table 9: Mortality hazard ratios

Age groups	Male	Female
95 – 99 vs 90-94	1.67	1.71
100 vs 90-94	2.24	2.36

Source: Office of National Statistics 2023[1] Years 2017-2019. Hazard ratios were calculated using the midpoint age mortality for each age range group.

2.3.4 Adjusting rates by cholesterol level

To calculate costs and health outcomes associated with a particular cholesterol target, different levels of cholesterol were transformed into CVD risks and mortality. A well-recognized way of estimating change in CVD risks associated with changes in LDL cholesterol is recommended in a consensus statement by the European Atherosclerosis Society (EAS)[14] and it is based on the Cholesterol Treatment Trialists' (CTT) Collaboration. This approach was undertaken by different analyses on lipid-modification treatment including NICE TA733[39] and several studies on lipid-lowering theapies[17, 18, 23-28, 45, 50, 52, 54, 55, 57]. The CTT Collaboration has conducted various meta-analyses of statin trials; it has shown that lowering LDL cholesterol by 1 mmol/litre is associated with a reduction in the rate of major

CVD events by 22%[8]. CVD event-specific relative risk reductions (RR) were also estimated (see Table 10).

Table 10: Relative effect on vascular events and mortality per 1 mmol/litre reduction in LDL cholesterol

Event	Application in model base case	Relative risk reduction (95% confidence interval)	Source
Major cardiovascular event	Non-coronary revascularisation	0.78 (0.76 – 0.80)	CTT Collaboration 2010[8]
Any coronary revascularisation	Any coronary revascularisation	0.74 (0.71 – 0.79)	Weighted average from CTT collaboration 2010[8]
Ischaemic stroke	Ischaemic stroke	0.78 (0.69 – 0.80)	Weighted average from CTT collaboration 2010[8]
Myocardial infarction	Myocardial infarction	0.73 (0.67 – 0.80)	Weighted average from CTT collaboration 2010[8]
Coronary heart disease death	CVD death (sensitivity analysis only)	0.80 (0.74 – 0.87)	CTT Collaboration 2010[8]
All-cause mortality	All deaths	0.90 (0.87 – 0.93)	CTT Collaboration 2012[9]

The European Atherosclerosis Society (EAS)[14] proposed the following equation to calculate the relative risk reduction of CVD events:

(1) $$Risk\ reduction = 1 - RR^{LDL*Tx}$$

where RR is the relative risk reduction, like those in Table 10, LDL is baseline LDL and Tx is the treatment effect expressed as a percentage reduction in mmol/litre. Based on the above equation we defined the following equation:

(2) $$CVD_x = R_0 \times RR^{LDL_x}$$

where CVD_x is the cardiovascular risk of subgroup x, R_0 is the hypothetical cardiovascular risk the subgroup would incur if their LDL cholesterol was reduced to 0, RR is the relative risk reduction from CTT collaboration study and LDL_x is the actual LDL level of subgroup x. Equation 2 follows the same approach as equation 1 but allows estimation of LDL-specific risk across the whole distribution of LDL cholesterol. This equation was used to calculate both the baseline risk in various subgroups prior to any treatment and the risk after individuals in the subgroup are escalated to the next treatment level.

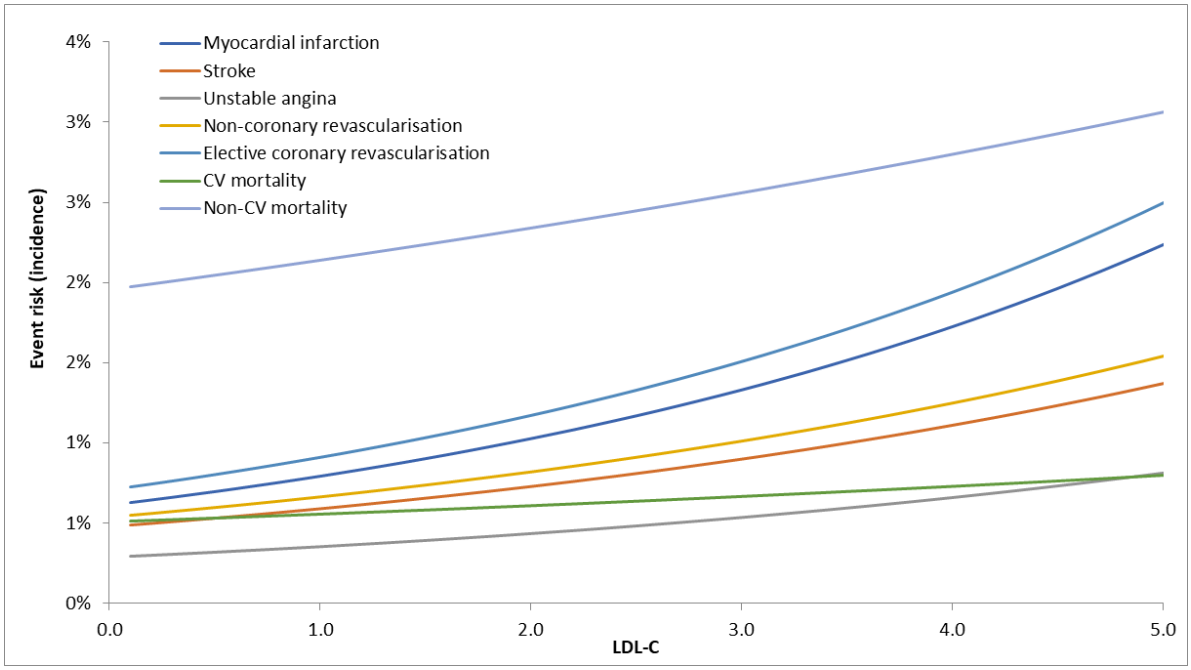
In the base case scenario, the model uses event-specific relative risk reductions. Since the CTT study did not report non-coronary revascularization or peripheral artery disease (PAD) as a specific outcome, the major CVD event risk reduction value (0.78) was used instead for these outcomes. The mortality risk reduction was not applied during the acute state of any disease to avoid the over-estimation of life-years saved resulting from the simultaneous application of two types of relative risk reduction: one for the admissions and mortality. Furthermore, the all-cause mortality risk reduction was calibrated so that the average mortality reduction per mmol/L resulting from the model was exactly the same as the CTTC estimate.

The committee raised concerns about the difficulties in defining cardiovascular deaths that are preventable through lipid lowering therapy. Consequently, there was a possibility that the

model could underestimate the treatment's impact on mortality if the RR for CVD mortality from Table 10 is applied to a baseline CVD mortality that it is too low. Instead, the effect on all-cause mortality was used in the base case scenario. It is important to note that this approach does not assume that the treatment affects CVD and non-CVD mortality in the same way. Rather, it serves to capture the overall mortality effect, considering the potential under-recording of CVD mortality data (see also 4.2.2).

Equation 2 was used to estimate the risk of an event (CVD or death) across the entire cholesterol distribution. Figure 10 illustrates an example featuring a 70-year-old man. Events that are less influenced by cholesterol, such as non-CVD mortality, exhibit a slower growth as LDL cholesterol level increase. Conversely, events strongly associated with cholesterol, such as MI or coronary revascularisation, shown a significantly steeper growth rate with increasing LDL cholesterol level. This approach was used in the model to dynamically estimate how event risks vary as cholesterol changes.

Figure 10: Relationship between LDL cholesterol and modelled events (70 year old males)



The only CTT collaboration estimate of relative risk reduction in non-HDL cholesterol was for MI and CHD death, which was 0.79, or a 21% reduction per 1 mmol/litre reduction[12]. The corresponding figure for LDL cholesterol in the same CTT publication was 26% reduction. The non-HDL reduction specifically for MI was estimated as the 21% multiplied by the LDL cholesterol reduction for MI divided by the LDL cholesterol reduction for MI and stroke (= 21% X (27%/26%). The other non-HDL treatment effects were approximated in the same manner (see Table 11).

Table 11: Relative effect on vascular events and mortality per 1 mmol/litre reduction in non-HDL cholesterol

Event	Application in model base case	Relative risk reduction	Source
Major CVD event	Non-coronary revascularisation	0.81	Derived using the non-HDL-c effect for MI and stroke combined with ratio of relevant LDL-c effects[8, 12]
Any coronary revascularisation	Any coronary revascularisation	0.78	Derived using the non-HDL-c effect for MI and stroke combined with ratio of relevant LDL-c effects[8, 12]
Ischaemic stroke	Ischaemic stroke	0.81	Derived using the non-HDL-c effect for MI and stroke combined with ratio of relevant LDL-c effects[8, 12]
Myocardial infarction	Myocardial infarction	0.77	Derived using the non-HDL-c effect for MI and stroke combined with ratio of relevant LDL-c effects[8, 12]
CHD death	CVD death (sensitivity analysis only)	0.83	Derived using the non-HDL-c effect for MI and stroke combined with ratio of relevant LDL-c effects[8, 12]
All-cause mortality	All deaths	0.91	Derived using the non-HDL-c effect for MI and stroke combined with ratio of relevant LDL-c effects[9, 12]

2.3.5 Treatment effects – cholesterol

The treatment effect of any medicine included in the pathway is expressed in terms of LDL cholesterol or non-HDL cholesterol reduction. A comprehensive systematic review was conducted, focusing on randomized controlled trials that examined the treatment efficacy of ezetimibe, inclisiran, alirocumab, evolocumab, or their combination. Additionally, a network meta-analysis (NMA) was performed to estimate the treatment effect of any of these interventions compared to placebo (see also evidence review A and the NMA results appendix).

In total 4 networks were identified relative to the following outcomes:

- Relative reduction in LDL cholesterol (18 RCTs)
- Absolute reduction in LDL cholesterol (32 RCTs)
- Relative reduction in non-HDL cholesterol (13 RCTs)
- Absolute reduction in non-HDL cholesterol (8 RCTs)

Although there was more data available for the absolute change analysis, the committee decided to use the relative change effect for the model because there was higher between-study heterogeneity observed in the absolute change analysis. Moreover, a meta regression analysis showed that greater reductions were achieved at higher baseline cholesterol levels, which is consistent with a relative reduction effect. Additionally, this approach aligns with published economic models[17, 18, 23-28, 39, 45, 50, 52, 54, 55, 57] on lipid-modification treatment, which have assumed a relative treatment effect. The results of the NMA on the relative reduction in LDL cholesterol and non-HDL cholesterol of each medicine compared to placebo are presented in Table 12. A random effects meta-analysis was conducted to account for heterogeneity in the results.

Table 12: Difference in relative reduction in cholesterol – Network meta-analysis (random effects)

	LDL-c (95% credible interval)	Non-HDL-c (95% credible interval)
Ezetimibe vs placebo	-17.8% (-23.7%, -11.9%)	-20.0%[(a)] (-33.0%, -6.9%)
Inclisiran vs placebo	-51.3% (-61.9%, -40.5%)	-45.1% (-58.6%, -31.0%)
PCSK9 inhibitors vs placebo	-55.0% (-60.3%, -49.4%)	-47.0% (-54.3%, -39.4%)

(a) Adjusted to -15.7%=17.8%x45.1/51.3% in the base case analysis due to lack of data for non-HDL-c and inconsistency of result

When examining the treatment effects, it is noteworthy that non-HDL cholesterol estimates tend to be lower for injectable therapies (ranging from 45.1% to 47.0%) compared to LDL cholesterol estimates (ranging from 51.3% to 55.0%). However, the opposite trend is observed for ezetimibe, where the non-HDL cholesterol estimate is larger (20.0% compared to 17.8%). This discrepancy can be attributed to the fact that there was only one small study involving 40 participants that estimated the relative change in non-HDL cholesterol directly for ezetimibe versus placebo. This study could have been an outlier but (due to its small sample size) its weight in the analysis was far less than the indirect evidence for this comparison in the network. In comparison the LDL cholesterol analysis had 6 trials comparing ezetimibe with placebo. For this reason, a decision was made by the committee to estimate the non-HDL cholesterol ezetimibe treatment effect by adjusting the LDL cholesterol ezetimibe effect using the ratio between the inclisiran treatment effects, which gave 15.7%.

2.3.6 Treatment-related adverse events

The guideline's systematic review of clinical trials found no evidence of significant treatment-related adverse events. Therefore, none were included in the model. There were some injection site-related adverse events, but these were minor and transient and so would not impact on cost or quality of life, although could have a small impact on continuation of treatment.

2.3.7 Utilities

Age- and sex-specific quality of life scores ('utilities') were used in the model. They were derived from Health Survey for England data (see below) as reported in a publication by the NICE Decision Support Unit[19].

When a patient experienced a cardiovascular event, their age- and sex-specific baseline quality of life was adjusted using a utility multiplier associated with the respective acute cardiovascular event in the year the event was experienced in, and by the respective post-cardiovascular event multiplier in the years following.

The impact on quality of life associated with the CVD events was estimated through an original analysis of the Health Survey for England (HSE)[20]. The HSE is a survey conducted on a random sample of residents in England, encompassing various aspects such as socio-economic factors, demographics, and health indicators. Each publication of the survey centres on a different theme, and the 2017 survey focused on cardiovascular diseases providing valuable information such as history of CVD, recent CV episodes, and any surgeries people underwent. Noticeably, the survey provides information on most of the diseases included in this analysis, including angina, stroke, MI, peripheral artery disease and revascularisation.

HSE 2017 included responses to the EQ-5D-5L questionnaire. NICE does not currently endorse the use of EQ-5D-5L for directly calculating utility values[13] but, instead, recommends using EQ-5D-3L values in the reference case, which can be mapped from 5L values using the function developed by Van Hout 2012[53]. Hence, EQ-5D-3L utility scores were estimated

using the Van Hout 2012 mapping functions. To obtain utility multipliers that could be applied to the values of the general population, the mean EQ-5D utility score of people who had experienced a specific CVD event was divided by the mean EQ-5D utility score of the whole sample, adjusted for age and gender. The analysis was done using Stata v13[51]. Table 15 shows the multipliers calculated from the HSE 2017.

Table 13: Utility multipliers

Cardiovascular event	Acute state	Post state
Stroke	0.756 (0.064)	0.816 (0.013)
Unstable angina	0.682 (0.021)	0.878 (0.011)
Myocardial infarction (MI)	0.839 (0.054)	0.847 (0.010)
Peripheral artery disease	-	0.927 (0.016)
Elective revascularisation	-	0.889 (0.028)

Source: HSE 2017[20]. Mean multipliers with standard errors in parentheses.

It was not possible to derive utility multipliers for the non-coronary revascularisation and elective coronary revascularisation acute states. The first was not reported in the HSE questionnaire and the latter was too rare for estimating meaningful values (only 6 observations). Consequently, multipliers in these two states were indirectly derived by applying the ratio between the acute MI and post MI multipliers to the multiplier of post coronary revascularisation. Likewise, TIA was not reported in the HSE so the value used in the NICE statin model (0.90) was used instead.

To ensure that the probabilistic analysis maintains the expected relationship between the acute and post states, probabilistic values in the acute states were calculated as a difference between the post and acute states and modelled through a gamma distribution. This distribution cannot assume a value lower than 0 and, consequently, it ensures that, in all simulations, the utility score in the acute state of a disease will always be lower than the utility score in corresponding post state.

2.3.8 Resource use and costs

2.3.8.1 Medicines

The medication dosages were obtained from the British National Formula (BNF)[5], and the NHS Drug Tariff[42] was used for drug prices when publicly available. However, the contract prices for the two PSCK9 inhibitors and inclisiran are much lower than currently listed prices due to a Commercial Access Agreement (CAA) or a Patient Access Scheme (PAS) between the pharmaceutical companies and NHS England. For this analysis, the companies were contacted and the prices were obtained but are commercial-in-confidence (CIC).

For inclisiran, two prices were obtained: the current invoice price NHS is currently charged for each dose; a discounted price based on a population health agreement discount that would be applied if a specific volume of patients is achieved over several years. The base case analysis uses the invoice price whereas the population health agreement price was tested in a scenario analysis (see section 2.5).

Inclisiran is intended for healthcare professional administration and is not licensed for self-administration, thus the cost of a nurse appointment was added to each administration. Conversely, PCSK9 inhibitors are delivered to the patient's home and are licensed for self-administration, but the cost of a nurse visit is included for the first administration as people require instruction on safely injecting the medication. Table 14 shows prices and doses used in the model.

Table 14: Drug prices, dose and administration methods

Drug	Price	Dose and administration	Source
Statin (Atorvastatin)	£1.40 for 28 tablets	80mg daily administered orally	BNF[5] and Drug Tariff[42]
Ezetimibe	£1.47 per 28 tablets	10mg daily administered orally	BNF[5] and Drug Tariff[42]
Inclisiran	[redacted]	284mg 1 dose followed by a second after 3 months. Then 1 dose every 6 months. Administered by a nurse.	Novartis (CIC)
Alirocumab	[redacted]	150 mg every 2 weeks self-administered	Sanofi (CIC)
Evolocumab	[redacted]	140 mg every 2 weeks self-administered	Amgen (CIC)

Abbreviations: BNF = British national Formulary; CIC = Commercial in confidence; CAA = Commercial Access Agreement; PAS = Patient Access scheme

2.3.8.2 Tests and escalation

The model assumes that people undergo an annual lipid test at the start of each cycle for routine monitoring. When someone's cholesterol level exceeds the target, an escalation takes place. If a person is escalated to ezetimibe or inclisiran, a prescription can be obtained through a GP appointment alone. However, for the two PCSK9 inhibitors, outpatient secondary care is assumed to be necessary. After being initiated to a new therapy, the model assumes that another lipid test is offered approximately three months later to evaluate adherence and effectiveness. If the subsequent lipid test still indicates elevated cholesterol levels, a new escalation occurs, and the individual receives the next treatment in the sequence. As a result, people in a specific subgroup may experience two escalations within the same cycle. Table 15 illustrates all the unit costs associated with testing and escalation.

Table 15: Costs associated with monitoring and escalation to new treatments

Resource	Unit cost	Source
Lipid test including phlebotomy	£6	NHS Reference Costs 2019/2020[43]
Nurse visit (including qualification costs)	£11	PSSRU 2020/2021[21]
GP appointment (including qualification costs)	£38	PSSRU2020/2021[21]
Outpatient visit	£138	NHS Reference Costs 2019/2020[43] - WF01A

Abbreviations: PSSRU = Personal Social Service Research Unit

2.3.8.3 Health states

The annual healthcare costs associated with different CVD events were obtained from peer-reviewed literature and were stratified into the year of the event (event year) and following years (post-event years) (see Table 1).

Costs for ischaemic stroke admissions, myocardial infarction admissions, elective coronary revascularisation admissions and cardiovascular deaths were obtained from a recently published study that used the UK Biobank dataset, including 57,271 adults aged 40-69 with established CVD, to estimate the impact of incident CVD events on primary care (including

primary care consultation, diagnostic and monitoring tests and prescription medicines) and hospital care costs over a ten-year period from 2006 to 2016 [59].

Three cost figures were reported for each CVD event: the annual cost in the event year, in year one and year two after the event. To reduce the chance of including the re-admission costs in subsequent years, the post-event costs used in our analysis were based on year two costs. As outpatient hospital care use was not recorded in the UK Biobank dataset, following committee's suggestions, one outpatient visit per person per year following admission in the event year was added in our cost calculation (NHS reference cost[43]: Consultant-led Non-Admitted Face-to-Face Attendance, Cardiology).

The acute costs (costs incurred in the event year) of co-occurring events (myocardial infarction admissions interacted with vascular death, stroke interacted with vascular death, myocardial infarction admissions interacted with elective coronary revascularisation admissions) were considered by applying the coefficients of relevant interaction terms to the expected costs of the events in the same year (calculated as multiplying the likelihood of incurring cost of the event by the average cost of the event if incurred) including coefficients for age and gender (more details presented in section 2.4.7).

Apart from healthcare cost, we also included social care costs (e.g. costs of care home, home help, meals on wheels, and social service day centre visits) for stroke patients and assumed that 50% of it was covered by out-of-pocket payments from patients, in line with the assumptions made in previous NICE guideline CG181[58]. Table 16 shows the estimated costs of stroke, MI and elective coronary revascularisation for each gender and age group.

Table 16: Acute cost (in the event year) of stroke, myocardial infarction admissions and elective coronary revascularisation admissions by age and gender

	Stroke (including cost of social care)		Myocardial infarction admissions		Elective coronary revascularisation admissions	
Age	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
50-54	£11,610	£11,799	£7,706	£8,067	£7,667	£7,854
55-59	£11,636	£12,076	£7,869	£8,314	£7,780	£7,955
60-64	£11,952	£12,438	£8,150	£8,474	£7,902	£8,079
65-69	£12,325	£12,774	£8,464	£8,854	£8,027	£8,204
70-74	£12,545	£12,830	£8,856	£9,053	£8,174	£8,340
75-79	£12,913	£13,109	£9,244	£9,308	£8,409	£8,509
80-84	£13,234	£13,467	£9,740	£10,123	£8,619	£8,738
85-90	£13,573	£13,873	£10,321	£10,447	£8,928	£9,064
>90	£14,216	£14,632	£11,278	£11,378	£9,392	£9,676

Costs calculated using the coefficients obtained from Zhou 2023[59]

Costs for TIA episodes and unstable angina pectoris admissions were based on a cohort study using Clinical Practice Research Datalink records from 2006 to 2012 linked with Hospital Episode Statistics data for people among patients ≥18 years who had a CVD event and received at least 2 lipid-modifying therapy prescriptions[11]. As costs were reported for months 1-6 and months 7-36 separately, we assumed a uniform distribution of costs during months 7-36 to obtain the annual healthcare costs.

The annual cost for non-coronary revascularisation admissions in the event year were estimated using the NHS Reference Costs[43]: based on Healthcare Resource Groups (HRGs), the standard grouping of clinically similar treatments, while post-event costs were taken from Walker et al. 2016 [56]. To exclude costs associated with further admissions or events, coronary-disease related costs were subtracted from overall CVD costs to ensure

that only costs associated with a non-coronary disease are captured. All costs were inflated to year 2022 using the NHS cost inflation index[22], where necessary.

2.4 Computations

2.4.1 Markov model

The model was constructed in Microsoft® Excel® for Microsoft 365 MSO (Version 2304) and was evaluated by cohort simulation. Time dependency was built in by using, for each subgroup, the age at each cycle as a risk factor for mortality. Utility was also time dependent and conditional on subgroup age.

Patients start in cycle 0 in an alive health state. Patients moved to the dead health state at the end of each cycle as defined by the mortality transition probabilities and dependent on exactly which CVD state they are in.

People can transition from any alive state to any new CVD event acute state. This is because people are always at risk of experiencing a new cardiovascular event throughout their lifetime. However, the model prohibits people from moving from a worse post state to a better post state when they experience a new CVD event (see also Figure 7 in section 2.2). This was achieved by assigning a severity rank (from 1 to 5) to the diseases based on the burden of the state per cycle measured in QALYs lost:

$$Burden = (1 - Utility_x) + \frac{Cost_x}{20{,}000}$$

where $Utility_x$ is the utility multiplier of disease x and $Cost_x$is the cost associated with disease x.

During each cycle, the model calculates the proportion of people who transition from each post state to a new CVD acute state. When these people move back to the post state in the next cycle, the model ensures that the same proportion of people who transitioned from the most severe disease (stroke) would return to its corresponding post state, taking into account those who died. This is applied to all disease states although movement from a less severe post state to a more severe state is allowed. This approach guarantees that people's disease burden does not improve after experiencing a new cardiovascular event, which would be illogical.

Number of people in PostMI state in cycle t: $N(PostMI)^t =$ $N(PostMI)^{t-1}.(1-P(Death)^t - P(newEvent)^t)$ $+N(NewMI)^{t-1}.(1-P(Death)^t - P(newEvent)^t)$ $.(N(NewBetter)^{t-2} + N(PostBetter)^{t-2}) / N(Alive)^{t-2}$ $+N(NewBetter)^{t-1}.(1-P(Death)^t - P(NewEvent)^t)$ $.(N(NewMI)^{t-2} + N(PostMI)^{t-2}) / N(Alive)^{t-2}$	Where: $P(Death)^t$ =Probability of death in cycle t $P(NewEvent)^t$ =Probability of new cardiovascular event in cycle t $N(Alive)^{t-2}$ =Number of people alive in cycle t-2 $N(NewBetter)^{t-2}$ =Number of people in a new event better than or equal to MI in cycle t-2 $N(PostBetter)^{t-2}$ =Number of people in a post-event state better than or equal to MI in cycle t-2 Etc.

2.4.2 Lipid measurement

In the cohort of patients from CPRD, some patients had a cholesterol measurement but non-HDL cholesterol or LDL cholesterol were not recorded. For these observations, non-HDL cholesterol or LDL cholesterol (in mmol/litre) were imputed using the following formulae:

Non-HDL-c = TC - HDL-c	Where: *TC*=total cholesterol

LDL-c = TC – HDL-c – trig/2.2	Where: *TC*=total cholesterol *trig*=triglycerides

The latter formula from Friedewald[16] is not applicable at high levels of triglycerides[30] and so, where triglycerides were greater than 4.5, the observation was recorded as missing.

2.4.3 Event rates – Cardiovascular events

Annual mortality rates were calculated for each specific CVD event as the number of events (fatal or non-fatal) divided by the number of person-years of observation. This was stratified by age (in 5-year bands) and sex.

These event rates were then adjusted for cholesterol level using the following formulae:

$Cholesterol\ specific\ event\ rate$ $q1 = q0.(1/RR)^{c1}$	Where: *q1*=event rate for age-sex cohort that are in cholesterol subgroup 1 *q0*=event rate in age-sex cohort if cholesterol level=0 *RR*=risk reduction per 1 unit reduction in mmol/L *c1*=cholesterol level in mmol/L in in cholesterol subgroup 1 of age-sex cohort
$q0 = q(all)/(p1.RR^{c1} + p2.RR^{c2} \ldots p16.RR^{c16})$	Where: *q0*=event rate if cholesterol level=0 *q(all)* =overall event rate for age-sex subgroup *RR*=risk reduction per 1 unit reduction in mmol/L *p1*=proportion of age-sex cohort that are in cholesterol subgroup 1 *c1*=mean cholesterol in cholesterol subgroup 1 of age-sex cohort

These calculations were conducted separately for both LDL cholesterol and non-HDL cholesterol. In the base case analysis, the risk reductions were different for each type of CVD event.

2.4.4 Event rates – Mortality

Annual mortality rates were calculated as the number of deaths divided by the number of person-years of observation. This was stratified by:

- age (in 5-year bands),
- sex,
- type of CVD event in the last 12 months (if any), and
- CVD versus non-CVD related underlying cause of death.

All-cause mortality rates were adjusted for cholesterol level in the same manner as CVD event rates – see above. However, this was not done in the first 12 months after a CVD event as this was assumed to be more dependent on the event than on the treatment.

2.4.5 Transition probabilities – Mortality

Annual mortality rates were converted into transition probabilities for the respective cycle length (1 year) before inputting into the Markov model.

The CVD-related mortality and non-CVD related mortality rates were added to give an all-cause mortality rate. The probability of death was then calculated using the following formulae:

$Probability\ of\ death\ (Pd) = 1 - e^{-mt}$	Where: *m*=annual all-cause mortality rate *t*=cycle length (1 year) e=exponential

The respective transition probabilities were then calculated as

$TP(CVD\ mortality) = Pd\ \frac{m(CVD)}{m(CVD) + m(nonCVD)}$ $TP(nonCVD\ mortality) = Pd\ \frac{m(nonCVD)}{m(CVD) + m(nonCVD)}$	Where: *m(CVD)=annual CVD-related mortality rate* *m(nonCVD)=annual non-CVD related mortality rate*

2.4.6 Transition probabilities – Cardiovascular events

Annual event rates were converted into transition probabilities for the respective cycle length (1 year) before inputting into the Markov model using the following formulae:

$Probability\ (P) = q * t$	Where: q=annual event rate *t*=exposure time during cycle
$Cycle\ exposure\ time\ (t) = Pd/m$	Where: *Pd=probability of death (all-cause)* *m=mortality rate (all-cause)*

The former formula is different to that of mortality because a person can have multiple events but it still has to account for censoring due to death.

The latter formula is derived by taking definition of the mortality rate and then dividing numerator and denominator by the sample size and then rearranging:

$m = \frac{deaths}{Personyears} = \frac{Pd}{t} =$	Where: *m=mortality rate* *Pd=probability of death* *t=exposure time per person*

2.4.7 Acute costs calculation

Acute costs associated with CVD events were estimated using the formula provided by Zhou 2023[59]. Two different models were specified for primary care and hospital care costs.

Primary care costs were analysed and predicted using one-part generalised linear models (GLMs) (see the equation below).

$Primary\ care\ costs = \sum(Coefficient\ \times value)$	Where: $Coefficient$ is the cost associated with any particular characteristic (e.g. gender) $Value$ is the binary representation of the characteristic, taking the value of 1 when the characteristic is present and 0 when it is absent.

Hospital care costs were analysed using a two-part model, with the first part predicting the probability of incurring in any positive costs using a logistic regression, and the second part predicting costs conditional on experiencing any positive costs using GLMs. When a person

receives a coronary revascularisation (either eligible or within an MI admission), costs become certain during that particular year.

$Hospital\ care\ costs = \frac{Odds_{P1}}{1 + Odds_{P1}} \times Costs_{P2}$	Where: $Odds_{P1}$ = the odds of incurring any positive costs (part 1) – logistic regression model $Costs_{P2}$ = expected cost conditional on experiencing any positive cost (part 2) – Generalised Linear Model

2.4.8 QALYs and costs

Life years for the cohort were computed each cycle. To calculate QALYs for each cycle, the time spent in each alive state of the model was weighted by a utility value that is dependent on the mean age of the patient subgroup in that cycle and then combined with a utility multiplier associated with the health state.

A half-cycle correction was applied. QALYs were then discounted to reflect time preference (discount rate 3.5%). The total discounted QALYs were the sum of the discounted QALYs per cycle.

To calculate NHS costs for each cycle, the number of people in each alive state of the model was weighted by a unit cost associated with the health state. A half-cycle correction was conducted for the post-event states but not for the acute states where the costs were assumed to be incurred at the beginning of the cycle. Costs, were discounted to reflect time preference (discount rate 3.5%) in the same way as QALYs using the following formula:

Discounting formula:

$\text{Discounted total} = \frac{\text{Total}}{(1+r)^n}$	Where: *r*=discount rate per annum *n*=time (years)

In the deterministic and probabilistic analyses, the total number of QALYs and resource costs accrued by each subgroup was recorded. These subtotals were summed across all subgroups to ascertain the total number of patients in the population and the total QALYs and resource costs accrued for the population. The total cost and QALYs accrued by the cohort was divided by the number of patients in the population to calculate a cost per patient and QALYs per patient.

2.4.9 Uncertainty

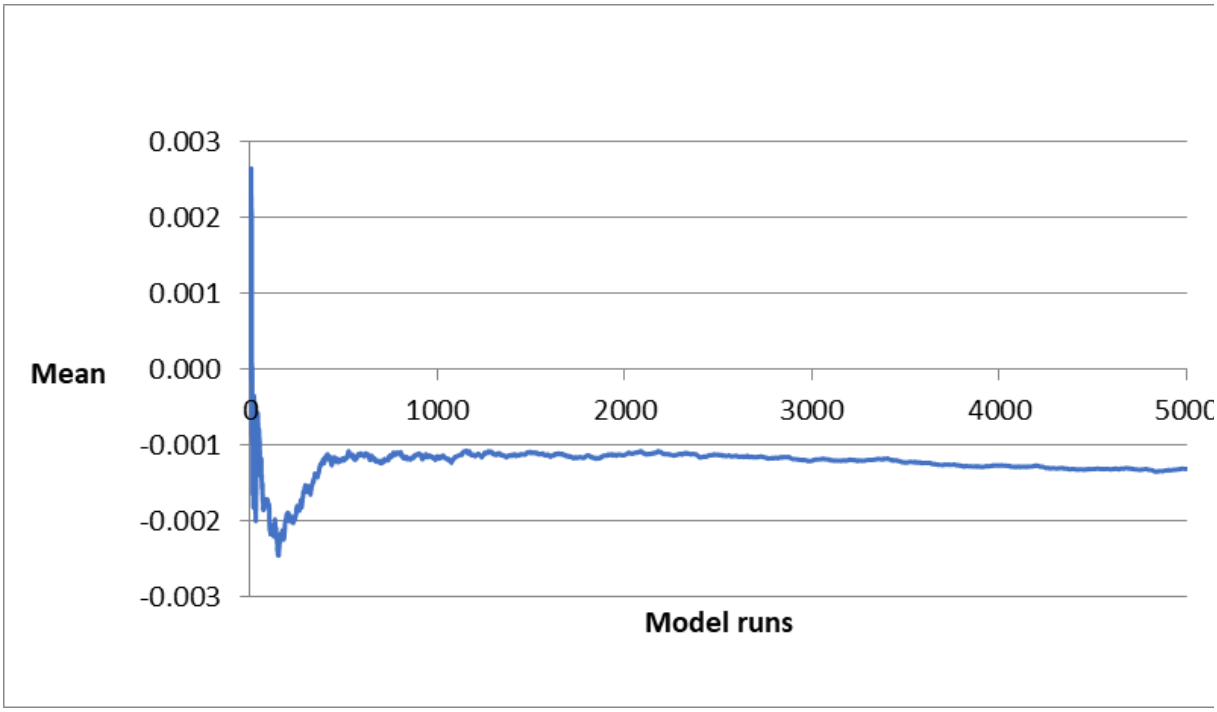
The base case LDL cholesterol analyses were run probabilistically to take account of the uncertainty around input parameter point estimates. A probability distribution was defined for most model input parameters. When the model was run, a value for each input was randomly selected simultaneously from its respective probability distribution; mean costs and mean QALYs were calculated using these values. The model was run repeatedly – 10,000 times. The following scenarios were explored probabilistically:

1. LDL cholesterol target for ezetimibe
2. Non-HDL cholesterol target for ezetimibe
3. LDL cholesterol target for injectable therapies
4. Non-HDL cholesterol target for injectable therapies
5. LDL cholesterol single target
6. Non-HDL cholesterol single target

When running the probabilistic analysis, multiple runs are required to take into account random variation in sampling. To ensure the number of model runs were sufficient in the

probabilistic analysis we checked for convergence in incremental costs, QALYs and net health benefit at a threshold of £20,000 per QALY gained for a single LDL cholesterol target of 2.0 mmol/litre versus 1.8 LDL cholesterol mmol/litre. This was done by plotting the number of runs against the mean outcome at that point (see example in Figure 11) for the base-case analysis. Convergence was assessed visually, and all had stabilised before 5000 runs.

Figure 11: Checking for convergence: Single target LDL cholesterol 2.0 mmol/litre vs 1.2 mmol/litre



Abbreviations:

The way in which distributions are defined reflects the nature of the data, so for example event rates were given a gamma distribution, which is bounded at 0, reflecting that the rate of an event could not be lower than 0. The variables that were probabilistic in the model and their distributional parameters are summarised in Table 17. Probability distributions in the analysis were parameterised using error estimates from data sources.

Table 17: Description of the type and properties of distributions used in the probabilistic sensitivity analysis

Parameter	Type of distribution	Properties of distribution
Proportion of people in each subgroup	Dirichlet	Fitted to multinomial data. Represents a series of conditional distributions, bounded on 0–1 interval. Derived by the number of patients in the sample and the number of patients in a particular subgroup.
Cardiovascular risk reduction Utility multipliers	Lognormal	The parameters for the log-normal (m and s) are the mean and standard error on the log-scale, which can be calculated from observed mean and confidence interval as follows: • $m = \ln(\text{mean}) - s^2/2$ • $s = [\ln(\text{upper 95\% CI}) - \ln(\text{lower 95\% CI})]/(1.96\times2)$ This formula includes an adjustment to ensure the mean generated in the probabilistic analysis is the same as the reported mean.

Parameter	Type of distribution	Properties of distribution
Treatment-related cholesterol reduction	Bespoke	The network meta-analysis used simulation methods, which yielded 24,000 individual estimates of each treatment's percentage cholesterol reduction. These estimates represent the joint posterior distribution of the percentage cholesterol reduction.
Hospitalisation rate Mortality rate Cholesterol trend per year Mean Costs	Gamma	Bounded at 0, positively skewed. Derived from mean and its standard error. Alpha and beta values were calculated as follows: • Alpha = $(mean/SE)^2$ • Beta = $SE^2/Mean$

Abbreviations: 95% CI = 95% confidence interval; SE = standard error; SMR = standardised mortality ratio.

The following variables were left deterministic (that is, they were not varied in the probabilistic analysis):

- The cost-effectiveness threshold, which is £20,000 per QALY gained based on the NICE reference case (see 2.8)
- Unit costs
- Adherence to the medicine, which is assumed to be 100% in the base case scenario.

In addition, various deterministic sensitivity analyses were undertaken to test the robustness of model assumptions. In these, one or more inputs were changed, and the analysis rerun to evaluate the impact on results and whether conclusions on which intervention should be recommended would change. Details of the sensitivity analyses undertaken can be found in the next section.

2.5 Sensitivity analyses

Various scenario analyses were conducted to test the robustness of the results of the model. Table 18 describes the different scenario analyses where green colour indicates the scenarios adopted in the base case scenario.

Table 18: Scenario analyses

Feature	Scenario	Description
Relative risk reduction	Event-specific relative reduction*	Use a different event-specific treatment effect for each outcome
	Single major cardiovascular events (Mace) relative reduction	Use MACE treatment effect for all CVD outcomes
Effect of cholesterol on mortality	Cholesterol affects all-cause mortality*	The corresponding relative risk from CTT is applied to all-cause mortality
	Cholesterol affects CVD mortality only	The corresponding relative risk from CTT is applied to CVD mortality only
PCSK9 inhibitors	Inclisiran only*	Nobody is escalated to PCSK9 inhibitors. People above the target who are taking ezetimibe receive Inclisiran
	PCSK9 inhibitors only	Nobody is escalated to inclisiran. People above the target after taking ezetimibe receive a PCSK9 inhibitor
	PCSK9 inhibitors at 3.5 mmol/L	People are escalated to PCSK9 inhibitors if their LDL cholesterol is above 3.5
Population	People on any statin*	Analysis on people on any statin

Feature	Scenario	Description
	People on atorvastatin 80mg	Analysis uses the age/sex/cholesterol distribution for the subgroup of people on atorvastatin 80 mg
	People on any statin and people who are statin intolerant	The base case population is run through the model then the statin intolerant population is run through the model using an alternative treatment sequence. Both populations are treated to the same target and weighted average results are calculated.
Angina	Include unstable angina*	Include unstable angina admissions
	Exclude unstable angina	Exclude angina from the model
TIA	Include TIA	Include TIAs (costs only)
	Exclude TIA	Exclude TIA costs from the analysis
Quality of life weights	Health survey for England 2017*	Use the quality-of-life multipliers calculated from the HSE 2017
	Old version of Statins model	Use the quality-of-life multipliers used in the 2014 version of Statins model NG181
	Inclisiran TA	Use the quality-of-life multipliers used in the Inclisiran TA
Adherence to ezetimibe	100% adherence*	Assume a 100% adherence to ezetimibe
	80% adherence	Assume an 80% adherence to ezetimibe (that is for 20% of patients there is no cost of ezetimibe and no benefit either)
	50% adherence	Assume a 50% adherence to ezetimibe (that is for 50% of patients there is no cost of ezetimibe and no benefit either)
Adherence to injectable therapies	100% adherence*	Assume a 100% adherence to injectable therapies
	80% adherence	Assume an 80% adherence to injectable therapies (that is for 20% of patients there is no cost and no benefit either)
	50% adherence	Assume a 50% adherence to injectable therapies (that is for 50% of patients there is no cost of ezetimibe and no benefit either)
Inclisiran price	Invoice price*	Use the invoice price of inclisiran that the NHS is currently charged for
	Volume discounted price	Use volume discounted price which will be applicable once specific patient volumes are achieved
Escalation to inclisiran	1 GP attendance*	Assume that one GP atenndance is sufficient to be prescribed inclisirasn
	2 GP attendances and 1 nurse attendance	Add an extra GP attendance and a nurse-led attendance
Ezetimibe prescription fee	No prescription fee*	The cost of ezetimibe does not include the prescription fee paid to the pharmacist

Feature	Scenario	Description
	Including prescription fee	The cost of ezetimibe includes the prescription fee paid to the pharmacist
Cholesterol change over time	Lifetime change adjusted for gender*	Cholesterol changes over time using a gender-specific rate
	3-cycles change adjusted for gender and baseline cholesterol	Cholesterol change for 3 cycles using a gender-, age- and baseline cholesterol-adjusted model

** Base case assumption*

In the base case scenario, event-specific RRs were applied to all outcomes although the single MACE RR from CTT 2010[8] was tested in another scenario.

As discussed in section 2.3.4, due to the committee being concerned about the potential definition of CVD mortality in the CPRD analysis, the all-cause mortality risk reduction was used in the base case while in a scenario analysis the CVD mortality risk reduction was used.

Inclisiran can be prescribed in primary care and is a more affordable alternative than PCSK9 inhibitors. Moreover, in an eligible secondary prevention population, inclisiran was found to be cost-effective[39]. Hence, in the base case scenario analysis, it is assumed that all individuals escalated to injectable therapy will receive Inclisiran. However, in current practice, clinicians may opt for prescribing one of the PCSK9 inhibitors if a patient's cholesterol level is above the threshold indicated in NICE TA393/394[32, 37]. This was explored in the scenario analysis where PCSK9 inhibitors were prescribed at 3.5 LDL cholesterol. Additionally, a separate scenario assumed that individuals escalated to injectable therapies would exclusively receive a PCSK9 inhibitor. This was tested because the current contract price for inclisiran is due to expire in 2024. If the discount is discontinued, then inclisiran might no longer have a significant cost effectiveness advantage over the PCSK9 inhibitors.

The study population was defined as people who had a CVD event and are currently on a statin (see 2.1.2 for details). This population encompasses the individuals who could potentially be escalated to receive ezetimibe or injectable therapies in current practice. However, it does not align with the best clinical practice, which is Atorvastatin 80 mg as recommended by NICE CG181[35], before considering other therapeutic options. To explore this, a scenario analysis using the age/sex/cholesterol distribution for the sub-population from CPRD who are being prescribed Atorvastatin 80 mg, was included.

Another scenario was developed for a broader population incorporating people with statin intolerance. In this scenario first the base case population is run through the model then the statin intolerant population is run through the model using an alternative treatment sequence. Both populations are treated to the same target and weighted average (9.1% intolerant, 90.9% tolerant) results are calculated. The assumptions for this analysis can be found in 2.5.1. There were some limitations to this analysis, hence why this pathway was not captured in the base case model: a) a fully systematic review was not conducted for the effectiveness and side effects of bempedoic acid; b) many of the parameters for the intolerant population (including cholesterol distribution and demographics) were not known and so were derived from the tolerant population; c) statin intolerance is difficult to define and measure.

In the base case scenario, both unstable angina and transient ischemic attack (TIA) were included as outcomes. However, in response to concerns raised by the committee that these are not well-defined in practice and so might not be preventable with lipid-lowering therapy, these outcomes were excluded in the scenario analysis.

Regarding the utility multipliers, the base case scenario applied the ones that were extracted from the HSE 2017. However, due to uncertainty surrounding the appropriate values, two alternative sets of values were also tested.

Not everyone who is eligible for a lipid-lowering therapy will accept the treatment, some might not tolerate it, and some might be contraindicated. To explore this possibility, two scenarios were assessed, wherein ezetimibe adherence (take-up) was reduced to 80% and to 50% respectively. This means more people moving on to the 3rd line of therapy. Similarly, two scenarios were assessed where adherence to injectable therapies was reduced to 80% and 50% respectively.

Although we used the current invoice price for inclisiran in the base case, there was a a scenario analysis that used a lower price, that would be applicable if specific patient volumes are achieved.

In the base case analysis, it was assumed that a single GP appointment is sufficient to be prescribed inclisiran. However, it is possible that more than a GP appointment is needed, especially if the new therapy needs to be discussed and to allow informed and shared decision-making. Also, people may need to visit a nurse during the first months after initiating inclisiran if they experience adverse events. For this reason, a scenario analysis was included which increases the cost of escalation to inclisiran by adding an extra GP and an extra nurse appointment.

In the base case scenario, the professional dispensing fee paid to the pharmacist was not included for ezetimibe. However, as the target is expected to be sensitive to any assumptions on drug prices, the fee was added in a scenario analysis.

Cholesterol was allowed to gradually increase every cycle in the base case, using gender-specific rates that were estimated using CPRD data. However, there can be error in measuring cholesterol and it is subject to regression to the mean.[15] This would mean that the benefits of escalation are potentially over-estimated for subgroups with a high baseline cholesterol level but under-estimated for people at a high baseline cholesterol level. Therefore, a further statistical model was specified that calculated change in cholesterol from the same CPRD dataset using covariates for initial cholesterol, age, gender, and interactions between those terms. The mean follow-up time was 3.2 years per person. This was used in a scenario analysis where the cholesterol was allowed to vary over the first 3 cycles separately for each cholesterol / gender subgroup – increasing in subgroups with lower baseline cholesterol but decreasing in those with higher baseline cholesterol levels.

2.5.1 Statin intolerant population

To model the intolerant population an approach laid out in Table 19 was taken.

Table 19: Parameters for statin intolerant population

Component	Specification
Sequence	1. Ezetimibe for all 2. Bempedoic acid 3. Inclisiran
Effectiveness of bempedoic acid vs placebo	20.3% reduction based on CLEAR Outcomes trial[44]. The population were ‘unable or unwilling to take statins owing to unacceptable adverse effects’, but 22.7% were receiving a very low dose statin (an average daily dose of rosuvastatin <5 mg, atorvastatin <10 mg, simvastatin <10 mg, lovastatin <20 mg, pravastatin <40 mg, fluvastatin <40 mg, or pitavastatin <2 mg). 70% had CVD (N = 13,970).
Effectiveness of ezetimibe vs placebo	Same as for base case population
Effectiveness of inclisiran vs placebo	Same as for base case population

Component	Specification
Demographics	Same age/sex distribution as base case population
LDL-c distribution	The LDL-c distribution was taken from the base case population but then the LDL-c level was increased for each subgroup by reversing the treatment effect of statins
Effectiveness of statins	41% reduction in LDL-c, estimated by a weighted average of the different statins in the CPRD data and using the summary effect sizes from the guideline's statins review – see Table 20.
Admission rates and mortality rates, by age, sex, and LDL-c level	Same as for base case population
Unit cost of bempedoic acid	Patient Access Scheme discounted price: [redacted] for 28 tablets, taken once a day.
Other unit costs	Same as for base case population
Utility scores	Same as for base case population
Prevalence of statin intolerance	9.1% from recent systematic review[6]

1

2

3 **Table 20: Statin treatment effect**

Dose	Frequency*		LDL reduction**
Atorvastatin calcium trihydrate			
10mg	162,130	6.9%	37%
20mg	303,522	13.0%	43%
40mg	439,533	18.8%	49%
80mg	230,517	9.8%	55%
Fluvastatin sodium			
20mg	1,981	0.1%	21%
40mg	2,841	0.1%	27%
80mg	1,555	0.1%	33%
Pravastatin sodium			
10mg	17,229	0.7%	20%
20mg	29,251	1.2%	24%
40mg	66,267	2.8%	29%
Rosuvastatin calcium			
5mg	20,178	0.9%	38%
10mg	34,926	1.5%	43%
20mg	21,733	0.9%	48%
40mg	4,097	0.2%	53%
Simvastatin			
10mg	49,815	2.1%	27%
20mg	320,938	13.7%	32%
40mg	619,367	26.4%	37%
80mg	15,954	0.7%	42%
All	2,341,834	100.0%	40.6%***

** Frequencies are from CPRD analysis – see 2.3.2.*
***LDL reduction from guideline statin review[35]*
**** Weighted average*

2.6 Model validation

The model was developed in consultation with the committee; model structure, inputs and results were presented to and discussed with the committee for clinical validation and interpretation.

The model was systematically checked by the health economist undertaking the analysis; this included inputting null and extreme values and checking that results were plausible given inputs. The model was peer reviewed by a second experienced health economist from NICE; this included systematic checking of many of the model calculations. Formal peer-review was also conducted by an experienced NICE health economist, who weas not involved with development, and by Joe Carroll, Ayman Sadek, and Nicky Welton from the NICE Guidelines Technical Support Unit, based at the University of Bristol University.

2.7 Estimation of cost effectiveness

The widely used cost-effectiveness metric is the incremental cost-effectiveness ratio (ICER). This is calculated by dividing the difference in costs associated with 2 alternatives by the difference in QALYs. The decision rule then applied is that if the ICER falls below a given cost per QALY threshold then the result is considered to be cost effective. If both costs are lower and QALYs are higher the option is said to dominate and an ICER is not calculated.

$$ICER = \frac{Costs(B) - Costs(A)}{QALYs(B) - QALYs(A)}$$

Where: Costs(A) = total costs for option A; QALYs(A) = total QALYs for option A

Cost effective if:
- ICER < Threshold

When there are more than 2 comparators, as in this analysis, options must be ranked in order of increasing cost then options ruled out by dominance or extended dominance before calculating ICERs excluding these options. An option is said to be dominated, and ruled out, if another intervention is less costly and more effective. An option is said to be extendedly dominated if a combination of 2 other options would prove to be less costly and more effective.

It is also possible, for a particular cost-effectiveness threshold, to re-express cost-effectiveness results in term of net health benefit (NHB). This is calculated by dividing the total cost for a comparator by the threshold cost per QALY value (for example, £20,000) and then subtracting this from the total QALYs (formula below). The decision rule then applied is that the comparator with the highest NHB is the cost-effective option at the specified threshold. That is the option that provides the highest number of QALYs at an acceptable cost.

$$Net\ Health\ Benefit(X) = \left(QALYs(X)\right) - Costs(X)/\lambda$$

Where: λ = threshold (£20,000 per QALY gained)

Cost effective if:
- Highest net benefit

Both methods of determining cost effectiveness will identify exactly the same optimal strategy. For ease of computation NHB is used in this analysis to identify the optimal strategy.

The probability that a specific target was cost effective was defined as the proportion of Monte Carlo simulations where that target had the highest NHB. The 2.5th and 97.5th

centiles of the Monte Carlo simulations for the cost per QALY gained are presented for those comparisons where none of the interventions were dominated in any of the simulations.

2.8 Interpreting results

NICE sets out the principles that committees should consider when judging whether an intervention offers good value for money.[36, 40, 41] In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- The intervention costs less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy.

As many different cholesterol targets are being compared, the NHB was used to rank the strategies based on their relative cost effectiveness. The highest NHB identifies the most cost-effective target at a willingness to pay of £20,000 per QALY gained.

3 Results

3.1 Cost effectiveness of ezetimibe and inclisiran

Table 21 shows the impact if every patient in the cohort was escalated. Adding ezetimibe reduced cardiovascular events and so increased QALYs. It also reduced NHS costs overall. Adding inclisiran reduced events further and the QALY gain was more than twice as great as that achieved by adding ezetimibe, but the cost per QALY was considerably higher than £30,000.

Table 21: Model results for treatment strategies

	1. Statin only	2. Statin + ezetimibe	3. Statin + ezetimibe + inclisiran	2 vs 1	3 vs 2
Mean age at start	72.3	72.3	72.3		
% Female at start	37%	37%	37%		
Mean LDL at 1 year	1.94	1.59	0.78	-0.35	-0.81
Admissions over lifetime per 1000 patients					
Stroke	179	168	145	-11	-24
Myocardial infarctions	184	169	138	-15	-31
Unstable angina	61	57	48	-4	-9
Elective revascularisation	91	82	65	-8	-17
Non coronary revascularisation	84	78	65	-6	-13
TIA	98	92	79	-6	-13
Survival					
Mean survival	11.55	11.77	12.31	0.22	0.54
Mean QALYs	7.58	7.72	8.07	0.14	0.35
Mean QALYs (discounted)	5.95	6.04	6.26	0.09	0.22
Mean cost (discounted)	13,125	13,094	[redacted]	-31	[redacted]
Cost per QALY gained (discounted)				Ezetimibe dominant	[redacted]

3.2 Ezetimibe treatment threshold analysis

With the first approach, two distinct targets are identified. These are considered and reported as two separate threshold analyses. The first as a target for adding Ezetimibe to a statin (and not adding an Injectable). The second as a target for adding an Injectable to statin+ezetimibe. Table 22 shows the cost and QALYs at a wide range of different LDL cholesterol thresholds. As the treatment threshold falls, the proportion of the population on ezetimibe increases and the mean LDL cholesterol falls and mean QALYs increase. Initially the cost falls indicating that ezetimibe is cost saving at higher LDL cholesterol levels. Below a threshold of 1.8 mmol/litre, there is an incremental cost per QALY gained but it is below £20,000 per QALY at every cholesterol level, indicating that it is cost effective for the whole cohort. Table 23 shows that this remains the case for all sensitivity analyses and Table 24

showed that the lowest cholesterol levels were the most cost-effective treatment thresholds in 100% of iterations.

Table 22: LDL cholesterol treatment threshold analysis for ezetimibe – full incremental analysis

LDL mmol/L	Mean cost	Mean QALYs	% of people on ezetimibe	Mean LDL-c at 1 year	Cost per QALY gained vs row above	Net health benefit (£20k per QALY)
1.8	£13,060	6.014	50.6%	1.72	-	5.361
1.6	£13,063	6.025	67.8%	1.66	£245	5.372
1.5	£13,068	6.029	73.9%	1.65	£1,112	5.376
1.4	£13,073	6.033	81.3%	1.63	£1,326	5.380
1.2	£13,080	6.037	88.7%	1.61	£1,849	5.383
1.1	£13,084	6.039	92.1%	1.60	£2,175	5.385
1.0	£13,087	6.040	94.8%	1.60	£2,711	5.386
0.9	£13,065	6.197	94.7%	1.59	£3,879	5.543
0.8	£13,094	6.042	99.6%	1.59	£4,022	5.387
0.3	£13,094	6.042	100.0%	1.59	£15,476	5.387

Note: Targets that were subject to dominance were removed from the table to to allow for a correct estimation of cost per QALY

Table 23: Ezetimibe treatment thresholds – sensitivity analyses

	Optimal target	Cost	QALYs	Net health benefit (£20k per QALY)	% Ezetim.
LDL-c					
Base case	0.3	£13,094	6.042	5.387	100.0%
£30k per QALY threshold	0.3	£13,094	6.042	5.387	100.0%
CVD mortality RR	0.5	£13,024	6.014	5.363	99.6%
Atorvastatin cholesterol distribution	0.3	£15,332	7.771	7.004	100.0%
Exclude unstable angina	0.3	£13,017	6.054	5.404	100.0%
Exclude TIA	0.3	£12,921	6.042	5.396	100.0%
Previous statin model Utilities	0.3	£13,094	5.796	5.141	100.0%
Inclisiran TA Utilities	0.3	£13,094	6.300	5.645	100.0%
Different CVD event costs	0.3	£18,692	6.042	5.107	100.0%
Pharmacist fee with ezetimibe	0.5	£13,245	6.042	5.380	99.6%
3-cycles LDL-c change adjusted for gender and baseline LDL-c	0.4	£13,045	6.057	5.405	100.0%
Non-HDL					
Base case	0.8	£13,087	5.998	5.343	100.0%
£30k per QALY threshold	0.8	£13,087	5.998	5.343	100.0%
CVD mortality RR	0.8	£13,042	5.977	5.325	100.0%
Atorvastatin cholesterol distribution	0.8	£15,332	7.685	6.918	100.0%
Exclude unstable angina	0.8	£13,009	6.010	5.360	100.0%

	Optimal target	Cost	QALYs	Net health benefit (£20k per QALY)	% Ezetim.
Exclude TIA	0.8	£12,912	5.998	5.352	100.0%
Previous statin model Utilities	0.8	£13,087	5.753	5.099	100.0%
Inclisiran TA Utilities	0.8	£13,087	6.254	5.599	100.0%
Different CVD event costs	0.8	£13,087	5.998	5.343	100.0%
Pharmacist fee with ezetimibe	0.8	£13,238	5.998	5.336	100.0%

Table 24: Probabilistic analysis of selected treatment thresholds for ezetimibe

		Ezetimibe LDL-C treatment threshold		
		0.3	**0.8**	**1.2**
	Mean costs	£13,256	£13,255	£13,241
	Mean QALYs	6.044	6.044	6.039
	Probability cost-effective at £20k per QALY gained	76%%	24%	0%
		Mean	**2.5th centile**	**97.5th centile**
Cost per QALY gained 0.8 vs 1.2		£3,329	£1,766	£6,467
Cost per QALY gained 0.3 vs 0.8		£15,819	£10,608	£31,738

3.3 Inclisiran treatment threshold analysis

With the first approach, two distinct targets are identified. These are considered and reported as two separate threshold analyses. In this section the second target is reported, for adding an Injectable to statin+ezetimibe.

Table 25 shows the cost and QALYs at a wide range of different LDL cholesterol thresholds. As the treatment threshold falls, the proportion of the population on inclisiran increases and the mean LDL cholesterol falls and mean QALYs increase. There is a trend for the incremental cost per QALY gained to increase as the baseline LDL cholesterol decreases. It increases above £20,000 per QALY for LDL cholesterol below 3.1 mmol/litre

Table 26 shows this was sensitive to the choice of utility scores and the cost effectiveness threshold, where it went down to 2.7 and 2.1 respectively. Alternatively, this went up to 4.0 when the CVD mortality effect was applied instead of all-cause mortality or if PCSK9 inhibitors were used instead of inclisiran.

Table 25: LDL cholesterol treatment threshold analysis for inclisiran – full incremental analysis

LDL mmol/L	Mean cost	Mean QALYs	% of people on incl	Mean LDL at 1 year	Cost per QALY gained vs row above	Net health benefit (£20k per QALY)
4.0	[redacted]	6.046	0.7%	1.58	-	[redacted]
3.5	[redacted]	6.047	0.7%	1.58	[redacted]	[redacted]
3.4	[redacted]	6.050	1.5%	1.56	[redacted]	[redacted]

LDL mmol/L	Mean cost	Mean QALYs	% of people on incl	Mean LDL at 1 year	Cost per QALY gained vs row above	Net health benefit (£20k per QALY)
3.2	[redacted]	6.050	1.5%	1.56	[redacted]	[redacted]
3.1	[redacted]	6.052	1.5%	1.56	[redacted]	[redacted]
2.9	[redacted]	6.058	3.4%	1.53	[redacted]	[redacted]
2.8	[redacted]	6.061	3.7%	1.53	[redacted]	[redacted]
2.7	[redacted]	6.063	4.2%	1.52	[redacted]	[redacted]
2.6	[redacted]	6.068	5.6%	1.50	[redacted]	[redacted]
2.5	[redacted]	6.074	6.7%	1.49	[redacted]	[redacted]
2.4	[redacted]	6.079	7.8%	1.47	[redacted]	[redacted]
2.3	[redacted]	6.084	9.8%	1.45	[redacted]	[redacted]
2.2	[redacted]	6.094	13.2%	1.41	[redacted]	[redacted]
2.1	[redacted]	6.104	14.0%	1.40	[redacted]	[redacted]
2.0	[redacted]	6.114	18.8%	1.35	[redacted]	[redacted]
1.9	[redacted]	6.125	23.7%	1.30	[redacted]	[redacted]
1.8	[redacted]	6.143	31.2%	1.23	[redacted]	[redacted]
1.7	[redacted]	6.157	32.9%	1.21	[redacted]	[redacted]
1.6	[redacted]	6.175	44.3%	1.12	[redacted]	[redacted]
1.5	[redacted]	6.186	50.6%	1.07	[redacted]	[redacted]

Note: Targets that were subject to dominance were removed from the table to to allow for a correct estimation of cost per QALY

Table 26: Inclisiran treatment thresholds - sensitivity analyses

	Optimal target	Cost	QALYs	Net health benefit (£20k per QALY)	% Incl
LDL-c					
Base case	3.1	[redacted]	6.052	[redacted]	1.5%
£30k per QALY threshold	2.2	[redacted]	6.094	[redacted]	13.2%
CVD mortality RR	4.0	[redacted]	6.017	[redacted]	0.7%
Only PCSK9i	4.0	[redacted]	6.046	[redacted]	0.7%
PCSK9i at >3.5 mmol/L	3.1	[redacted]	6.052	[redacted]	1.5%
Atorvastatin cholesterol distribution	3.5	[redacted]	7.776	[redacted]	0.6%
Exclude unstable angina	3.1	[redacted]	6.064	[redacted]	1.5%
Exclude TIA	3.1	[redacted]	6.052	[redacted]	1.5%
Previous statin model Utilities	3.4	[redacted]	5.804	[redacted]	1.5%
Inclisiran TA Utilities	3.1	[redacted]	6.311	[redacted]	1.5%
Ezetimibe 80% adherence	3.2	[redacted]	6.034	[redacted]	1.5%
Ezetimibe 50% adherence	3.1	[redacted]	6.018	[redacted]	4.0%
Ezetimibe 0% adherence	3.1	[redacted]	5.985	[redacted]	5.9%
Different CVD costs	3.4	[redacted]	6.050	[redacted]	1.5%
Volume discounted inclisiran price	2.9	[redacted]	6.058	[redacted]	3.4%

	Optimal target	Cost	QALYs	Net health benefit (£20k per QALY)	% Incl
Higher inclisiran escalation cost	3.1	[redacted]	6.052	[redacted]	1.5%
3-cycles LDL-c change adjusted for gender and baseline LDL-c	3.8	[redacted]	6.061	[redacted]	0.7%
Non-HDL-c					
Base case	4.0	[redacted]	6.010	[redacted]	1.6%
£30k per QALY threshold	3.1	[redacted]	6.041	[redacted]	9.6%
CVD mortality RR	4.5	[redacted]	5.983	[redacted]	1.6%
Atorvastatin cholesterol distribution	4.2	[redacted]	7.694	[redacted]	1.7%
Exclude unstable angina	4.1	[redacted]	6.020	[redacted]	1.6%
Exclude TIA	4.1	[redacted]	6.007	[redacted]	1.6%
Previous statin model Utilities	4.5	[redacted]	5.761	[redacted]	1.6%
Inclisiran TA Utilities	4.0	[redacted]	6.267	[redacted]	1.6%
Ezetimibe 80% adherence	4.2	[redacted]	5.989	[redacted]	1.6%
Ezetimibe 50% adherence	4.4	[redacted]	5.962	[redacted]	1.6%
Ezetimibe 0% adherence	4.3	[redacted]	5.928	[redacted]	3.2%
Different CVD costs	4.5	[redacted]	6.006	[redacted]	1.6%
Volume discounted inclisiran price	4.0	[redacted]	6.010	[redacted]	1.6%
Higher inclisiran escalation cost	4.1	[redacted]	6.007	[redacted]	1.6%

1 Table 27 shows the probabilistic results for the inclisiran thresholds (ezetimibe for everyone)
2 for selected cholesterol treatment thresholds.

3 **Table 27: Probabilistic analysis of selected treatment thresholds for inclisiran**

		Inclisiran LDL-C treatment thresreshold		
		2.8	3.1	3.3
	Mean costs	[redacted]	[redacted]	[redacted]
	Mean QALYs	6.062	6.054	6.051
	Probability cost-effective at £20k per QALY gained	26%	25%	49%
		Mean	2.5th centile	97.5th centile
Cost per QALY gained 3.1 vs 3.3		[redacted]	[redacted]	[redacted]
Cost per QALY gained 2.8 vs 3.1		[redacted]	[redacted]	[redacted]

4

3.4 Single target analysis

Table 28 shows that, if treating to a single target, then the most cost-effective LDL cholesterol target was of 2.2 mmol/litre. Table 29 shows that this was sensitive to the choice of utility scores and the cost effectiveness threshold, where it went down to 1.7 and 2.0 respectively. Alternatively, this went up to 2.7 when the CVD mortality effect was applied instead of all-cause mortality effect and 3.2 if the PCSK9 inhibitors were used instead of inclisiran.

Table 28: LDL cholesterol treatment threshold analysis for a single target – full incremental analysis

LDL mmol/L	Mean cost	Mean QALYs	% of people on eze at 1 year	% of people incl at 1 year	Mean LDL at 1 year	Cost per QALY gained vs row above	Net health benefit (£20k per QALY)
4.0	[redacted]	5.959	1.5%	0.7%	1.91	-	[redacted]
3.4	[redacted]	5.968	4.0%	1.5%	1.88	[redacted]	[redacted]
3.1	[redacted]	5.973	5.9%	1.5%	1.87	[redacted]	[redacted]
2.7	[redacted]	5.994	13.2%	4.2%	1.79	[redacted]	[redacted]
2.4	[redacted]	6.021	22.4%	7.8%	1.70	[redacted]	[redacted]
2.2	[redacted]	6.046	31.2%	13.2%	1.60	[redacted]	[redacted]
2.0	[redacted]	6.078	42.3%	18.8%	1.50	[redacted]	[redacted]
1.9	[redacted]	6.095	50.6%	23.7%	1.42	[redacted]	[redacted]
1.7	[redacted]	6.136	61.3%	32.9%	1.30	[redacted]	[redacted]
1.6	[redacted]	6.158	67.8%	44.3%	1.19	[redacted]	[redacted]
1.5	[redacted]	6.174	73.9%	50.6%	1.12	[redacted]	[redacted]
1.4	[redacted]	6.196	81.3%	61.3%	1.02	[redacted]	[redacted]
1.3	[redacted]	6.210	81.3%	67.8%	0.98	[redacted]	[redacted]
1.2	[redacted]	6.225	88.7%	74.6%	0.92	[redacted]	[redacted]
1.1	[redacted]	6.234	92.1%	81.3%	0.87	[redacted]	[redacted]
1.0	[redacted]	6.245	94.8%	88.7%	0.83	[redacted]	[redacted]
0.8	[redacted]	6.253	99.6%	94.8%	0.79	[redacted]	[redacted]

Note: Targets that were subject to dominance were removed from the table to to allow for a correct estimation of cost per QALY

Table 29: Single target - sensitivity analyses

	Optimal target	Cost	QALYs	Net health benefit (£20k per QALY)	% ezetim.	% inclis.
LDL-c						
Base case	2.2	[redacted]	6.046	[redacted]	31.2%	13.2%
£30k per QALY threshold	1.7	[redacted]	6.136	[redacted]	61.3%	32.9%
CVD mortality RR	2.7	[redacted]	5.986	[redacted]	9.8%	3.7%
Only PCSK9i	3.2	[redacted]	5.969	[redacted]	4.2%	1.5%
PCSK9i at >3.5 mmol/L	2.2	[redacted]	6.047	[redacted]	31.2%	13.2%

	Optimal target	Cost	QALYs	Net health benefit (£20k per QALY)	% ezetim.	% inclis.
Atorvastatin cholesterol distribution	2.2	[redacted]	7.753	[redacted]	20.7%	8.9%
Exclude unstable angina	2.2	[redacted]	6.059	[redacted]	31.2%	13.2%
Exclude TIA	2.2	[redacted]	6.046	[redacted]	31.2%	13.2%
Previous statin model Utilities	2.2	[redacted]	5.800	[redacted]	31.2%	13.2%
Inclisiran TA Utilities	2.0	[redacted]	6.338	[redacted]	42.3%	18.8%
Ezetimibe 80% adherence	2.4	[redacted]	6.021	[redacted]	17.9%	9.8%
Ezetimibe 50% adherence	2.7	[redacted]	5.993	[redacted]	4.9%	5.9%
Ezetimibe 0% adherence	3.1	[redacted]	5.985	[redacted]	0%	5.9%
Injectables 80% adherence	2.0	[redacted]	6.063	[redacted]	42.3%	15%
Injectables 50% adherence	1.9	[redacted]	6.053	[redacted]	50.6%	11.8%
Injectables 0% adherence	0.8	[redacted]	6.042	[redacted]	99.6%	0%
Different CVD event costs	2.2	[redacted]	6.202	[redacted]	31.0%	12.9%
Volume discounted inclisiran price	1.9	[redacted]	6.095	[redacted]	50.6%	23.7%
Higher inclisiran escalation cost	2.2	[redacted]	6.046	[redacted]	31.2%	13.2%
Pharmacist fee with ezetimibe	2.2	[redacted]	6.046	[redacted]	31.2%	13.2%
3-cycles LDL-c change adjusted for gender and baseline LDL-c	2.1	[redacted]	6.053	[redacted]	32.9%	14.0%
Statin intolerance	2.2	[redacted]	6.045	[redacted]	37.5%	15.8%
Non-HDL-c						
Base case	2.9	[redacted]	6.006	[redacted]	30.7%	13.1%
£30k per QALY threshold	2.2	[redacted]	6.115	[redacted]	66.1%	42.9%
CVD mortality RR	3.7	[redacted]	5.946	[redacted]	8.0%	3.2%
Only PCSK9i	4.2	[redacted]	5.922	[redacted]	3.2%	1.6%
Atorvastatin cholesterol distribution	3.1	[redacted]	7.660	[redacted]	16.7%	7.9%
Exclude unstable angina	2.9	[redacted]	6.018	[redacted]	30.7%	13.1%
Exclude TIA	2.9	[redacted]	6.006	[redacted]	30.7%	13.1%
Previous statin model Utilities	2.9	[redacted]	5.761	[redacted]	30.7%	13.1%
Inclisiran TA Utilities	2.9	[redacted]	6.263	[redacted]	30.7%	13.1%
Ezetimibe 80% adherence	3.2	[redacted]	5.968	[redacted]	13.4%	8.0%
Ezetimibe 50% adherence	3.5	[redacted]	5.957	[redacted]	6.5%	8.0%
Ezetimibe 0% adherence	4.3	[redacted]	5.928	[redacted]	0%	3.2%
Injectables 80% adherence	2.8	[redacted]	6.006	[redacted]	33.7%	13.4%
Injectables 50% adherence	2.5	[redacted]	6.015	[redacted]	50.6%	13.5%
Injectables 0% adherence	1.3	[redacted]	5.997	[redacted]	99.6%	0%
Different CVD event costs	2.9	[redacted]	6.006	[redacted]	30.7%	13.1%
Volume discounted inclisiran price	2.7	[redacted]	6.034	[redacted]	39.5%	20.2%

	Optimal target	Cost	QALYs	Net health benefit (£20k per QALY)	% ezetim.	% inclis.
Higher inclisiran escalation cost	2.9	[redacted]	6.006	[redacted]	30.7%	13.1%
Pharmacist fee with ezetimibe	2.9	[redacted]	6.006	[redacted]	30.7%	13.1%

A further sensitivity analysis was undertaken including people who are intolerant to statin (see 2.5.1). Table 29 shows that the inclusion of people who are intolerant to statin does not affect the optimal targets which remain 2.2 mmol/L at a threshold of £20,000 per QALY. Table 30 compares the levels of escalation and outcomes of the statin intolerant and statin tolerant populations in the analysis.

Table 30: Single target of 2.2 mmol/l LDL-c – statin intolerance sensitivity analyses

	Weight	Cost	QALYs	Net health benefit (£20k per QALY)	% ezetim.	% bemped oic acid	% inclis.
Intolerant	9.1%	[redacted]	6.032	[redacted]	100%	68%	42%
Tolerant	90.9%	[redacted]	6.046	[redacted]	31%	0%	13%
All	100.0%	[redacted]	6.045	[redacted]	37%	6%	16%

Table 31 show the probabilistic results for the single target analysis. It shows that a target of 1.8 mmol/litre was the most cost effective of the 3 LDL-c targets (1.8, 2.0, 2.2) in only 3% of simulations and cost above £20,000 per extra QALY gained.

Table 31: Probabilistic analysis of selected targets

		Single LDL-C Target		
		1.8	**2.0**	**2.2**
Mean costs		[redacted]	[redacted]	[redacted]
Mean QALYs		6.116	6.080	6.048
Probability cost-effective at £20k per QALY gained		3%	38%	59%
		Mean	**2.5th centile**	**97.5th centile**
Cost per QALY gained 2.0 vs 2.2		[redacted]	[redacted]	[redacted]
Cost per QALY gained 1.8 vs 2.0		[redacted]	[redacted]	[redacted]

Finally, Table 32 shows that treating to a single target was not found to be cost effective compared to giving ezetimibe to everyone and then treating to the optimal inclisiran treatment threshold.

1 **Table 32: Single target compared with inclisiran target and ezetimibe for all**

	Inclisiran target	Single target	Incr. cost	Incr QALY	Diff eze	Diff Incl	Cost per QALY
LDL-c							
Base case	3.1	2.2	[redacted]	-0.01	-69%	12%	[redacted]
£30k per QALY threshold	2.2	1.7	[redacted]	0.04	-39%	20%	[redacted]
CVD mortality RR	4.0	2.7	[redacted]	-0.03	-90%	3%	[redacted]
Only PCSK9i	4.0	3.2	[redacted]	-0.08	-96%	1%	[redacted]
PCSK9i at >3.5 mmol/L	3.1	2.2	[redacted]	-0.01	-69%	12%	[redacted]
Atorvastatin cholesterol distribution	3.5	2.2	[redacted]	-0.02	-79%	8%	[redacted]
Exclude unstable angina	3.1	2.2	[redacted]	-0.01	-69%	12%	[redacted]
Exclude TIA	3.1	2.0	[redacted]	-0.01	-69%	12%	[redacted]
Previous statin model Utilities	3.4	2.2	[redacted]	0.00	-69%	12%	[redacted]
Inclisiran TA Utilities	3.0	2.0	[redacted]	0.03	-58%	17%	[redacted]
Ezetimibe 80% adherence	3.2	2.4	[redacted]	-0.01	-78%	8%	[redacted]
Ezetimibe 50% adherence	3.1	2.7	[redacted]	-0.03	-90%	2%	[redacted]
Injectables 80% adherence	3.1	2.0	[redacted]	0.01	-58%	17%	[redacted]
Injectables 50% adherence	3.1	1.9	[redacted]	0.01	-49%	22%	[redacted]
Different CVD costs	3.4	2.2	[redacted]	0.00	-69%	12%	[redacted]
Volume discounted inclisiran price	2.9	1.9	[redacted]	0.04	-49%	20%	[redacted]
Higher inclisiran escalation cost	3.1	2.2	[redacted]	-0.01	-69%	12%	[redacted]
Pharmacist fee with ezetimibe	3.1	2.2	[redacted]	-0.01	-69%	12%	[redacted]
3-cycles LDL-c change adjusted for gender and baseline LDL-c	3.8	2.1	[redacted]	-0.01	-67%	13%	[redacted]
Non-HDL-c							
Base case	4.0	2.9	[redacted]	0.00	-69%	11%	[redacted]
Base case 30k	3.1	2.2	[redacted]	0.07	-34%	33%	[redacted]
CVD mortality RR	4.5	3.7	[redacted]	-0.04	-92%	2%	[redacted]
Atorvastatin cholesterol distribution	4.2	3.1	[redacted]	-0.03	-83%	6%	[redacted]
Exclude unstable angina	4.1	2.9	[redacted]	0.00	-69%	11%	[redacted]
Exclude TIA	4.1	2.9	[redacted]	0.00	-69%	11%	[redacted]
Previous statin model utilities	4.5	2.9	[redacted]	0.00	-69%	11%	[redacted]
Inclisiran TA utilities	4.0	2.9	[redacted]	0.00	-69%	11%	[redacted]

	Inclisiran target	Single target	Incr. cost	Incr QALY	Diff eze	Diff Incl	Cost per QALY
Ezetimibe 80% adherence	4.2	3.2	[redacted]	-0.02	-83%	6%	[redacted]
Ezetimibe 50% adherence	4.4	3.5	[redacted]	0.00	-87%	6%	[redacted]
Injectable 80% adherence	4.0	2.8	[redacted]	0.00	-66%	15%	[redacted]
Injectable 50% adherence	4.0	2.5	[redacted]	0.01	-49%	25%	[redacted]
Different event unit costs	4.5	4.2	[redacted]	0.00	-69%	11%	[redacted]
Volume discounted inclisiran price	4.0	2.7	[redacted]	0.02	-61%	19%	[redacted]
Higher inclisiran escalation cost	4.1	2.9	[redacted]	0.00	-69%	11%	[redacted]
Pharmacist fee with ezetimibe	4.0	2.9	[redacted]	0.00	-69%	11%	[redacted]

3.5 Overview

Table 33 shows the most cost-effective treatment thresholds / targets in the base case analysis. If treating to a single target, then the optimal targets at £20,000 per QALY gained were 2.2 mmol/litre LDL cholesterol or 2.9 mmol/litre non-HDL cholesterol. If giving ezetimibe to everyone, then inclisiran was cost effective above 3.1 mmol/litre LDL cholesterol or 4.0 mmol/litre non-HDL cholesterol. Table 34 shows the proportion of patients that could reach different targets, assuming full adherence. So for example, half would have <1.8 mmol/litre LDL cholesterol with a statin alone, 69% with stain plus ezetimibe, 70% with the optimal inclisiran target and 79% by escalating everyone when above 2.0 mmol/litre.

Table 33: Most cost-effective cholesterol treatment thresholds at £20,000 per QALY gained – Base case analyses

	Ezetimibe analysis		Inclisiran (ezetimibe for all)		Single target/threshold*		
	Threshold	Eze %	Threshold	Incl %	Threshold	Eze %	Incl %
LDL-c	0.3	100%	3.1	1.5%	2.2	31%	13%
Non-HDL-c	0.8	100%	4.0	1.6%	2.9	31%	13%

Eze %= escalated to ezetimibe; Incl % = escalated to inclisiran
* Ezetimibe if above target then inclisiran if still above target

Table 34: People achieving hypothetical targets by treatment strategy

	LDL<1.5	LDL<1.8	LDL<2.0	LDL<2.5	LDL<3.0
Statin	26%	49%	58%	81%	92%
Statin+ezetemibe	49%	69%	81%	93%	97%
Statin+ezetemibe then inclisiran if LDL>3.1 (see table above)	49%	70%	82%	95%	98%
Statin then single LDL target>2.2 (see table above)	38%	62%	83%	100%	100%
Statin then	43%	79%	99%	100%	100%

	LDL<1.5	LDL<1.8	LDL<2.0	LDL<2.5	LDL<3.0
single LDL target>2.0					
Statin then single LDL target>1.8 (QOF 2023)	56%	99%	99%	100%	100%

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4 Discussion

4.1 Summary of results

Using a combination of treatment effects from randomised controlled trials and real-world evidence on patient characteristics and event rates, the most cost-effective treatment targets were estimated for people with CVD being treated with statins. This cost-utility analysis showed that:

- Adding ezetimibe to a statin was cost effective at all baseline levels of cholesterol.
- Adding inclisiran to ezetimibe and a statin was cost effective above an LDL cholesterol of 3.1 mmol/litre or above a non-HDL cholesterol of 4.0 mmol/litre.
- The most cost-effective single targets were LDL cholesterol = 2.2 mmol/litre and non-HDL cholesterol = 2.9 mmol/litre. This was found to be only slightly more cost-effective than a target of 2.0 (cost per QALY for 2.0 vs 2.2 = [redacted]) which was the most cost-effective target in 38% of the probabilistic analysis simulations.
- Treating to a single target was not cost-effective compared with ezetimibe for everyone and using an inclisiran threshold: both LDL-c and non-LDL-c single targets were dominated by the inclisiran specific thresholds.

The LDL cholesterol analysis was deemed to be directly applicable with minor limitations. The non-HDL cholesterol analysis was deemed to be directly applicable but with potentially serious limitations due to the weaker evidence base for treatment effects.

The results were robust to sensitivity analysis, except that:

- The inclisiran treatment threshold was lower when alternative utility scores were used.
- Both the inclisiran target and the single target were lower if a £30,000 per QALY threshold was used.
- The single target was higher when people were less adherent to ezetimibe and lower if people were less adherent to inclisiran.
- Both the injectables target and the single target were higher if PCSK9 inhibitors were used instead of inclisiran.
- Both the inclisiran target and the single target were higher if mortality reduction was based upon ‘modifiable CVD mortality’ rather than all-cause mortality.

However, the committee were satisfied that the base case analyses were based on the most plausible assumptions.

4.2 Limitations and interpretation

4.2.1 Treatment effects

There was some inconsistency between the results of the LDL cholesterol analysis and those of the non-HDL cholesterol analysis. This is apparent because at the optimal non-HDL cholesterol target fewer people were being escalated than at the optimal LDL cholesterol target. The data on LDL cholesterol are almost certainly more robust for the following reasons:

- Firstly, LDL cholesterol is the most frequently reported measure of cholesterol in clinical trials while non-HDL cholesterol tends to be under-reported, particularly in trials involving ezetimibe. This prompted us to adjust the ezetimibe treatment effect on non-HDL to make it more consistent with the LDL cholesterol effect.
- In addition, CTT’s collaboration studies that were used to estimate the risk reduction associated with a reduction of cholesterol reported exclusively LDL cholesterol relative

risks, so the corresponding non-HDL cholesterol relative risks had to be extrapolated using the ratio of effect sizes from the LDL cholesterol analysis.

Therefore, despite the adjustments made, the LDL cholesterol target should be regarded as the most reliable of the two. Using the distribution of cholesterol in our population, it is possible to estimate an equivalent non-HDL cholesterol target that would result in the same proportion of people being escalated to ezetimibe. In the case of a single LDL cholesterol target of 2 mmol/litre, the corresponding equivalent non-HDL cholesterol target was 2.6 mmol/litre. The corresponding equivalent non-HDL cholesterol target for an inclisiran LDL cholesterol target of 3.1 mmol/litre was 4.2 mmol/litre.

In common with previous studies, this analysis used a **cholesterol-mediated approach** to evaluate the health consequences of lipid-lowering therapies. Wisløff and colleagues[57] showed that an analysis solely based on direct outcomes observed in a clinical trial can yield different results compared to an equivalent analysis employing a cholesterol-mediated approach. This is due to the nature of cholesterol accumulation, which is a slow process of lipid accumulating in the arterial wall (atherosclerosis) that increases the risk of cardiovascular diseases in the long-term. Reducing cholesterol is a major factor in slowing or even reversing the process, but it takes time and yields health benefits later in life. Consequently, clinical trials tend to underestimate the impact of lipid-lowering therapies on CVD as the average follow-up duration is insufficient to capture the gradual process of cholesterol reduction. Hence, a cholesterol-mediated approach seems to be the most appropriate when conducting an analysis with a life-time horizon. However, as Table 35 shows for ezetimibe and the PCSK9 inhibitors the relative reduction in the model was very similar to that observed the trials.

Table 35: Major cardiovascular events risk reduction - model results compared with clinical trials

	Model - entire cohort (lifetime)	Randomised controlled trials (meta-analyses from evidence review – various follow-up points)
Ezetimibe	-7%	-6%
Inclisiran	-16%	-26%
PCSK9 inhibitors	-17%	-17%

Inclisiran is a relatively recently approved drug and although its effect on reducing cholesterol has been adequately proven, there is a scarcity of trials showing its effects on cardiovascular events. As a result, some health care professionals have developed a lower level of trust in inclisiran, which may explain the low uptake of this medicine in primary care. However, recent trials like ORION-10 and ORION-11[46] have demonstrated that inclisiran reduces major cardiovascular events. Table 35 shows that for inclisiran the relative reduction in major cardiovascular events was larger than for the other medicines and larger than predicted by the model using the CTTC risk reduction. However, the major cardiovascular events outcome from the inclisiran trials was exploratory and were not adjudicated by an independent clinical committee. The Committee did not place great weight on the magnitude of the trial cardiovascular risk reduction for inclisiran because the outcome measure was less well defined and less objective.

Although Table 35 provides some validation for the use of the CTTC risk reduction equations, but it is less certain that they are applicable across the entire range of cholesterol measurement especially at the tail ends. For example, some of the age-specific mortality rates for a few of the subgroups at the lower end of the LDL distribution were better than the general population in England, even though they have CVD. This could be real if LDL cholesterol is also correlated with other risk factors, or it could be that the CTTC risk

reduction is less applicable at very low levels of LDL cholesterol. Either way, this was not considered a major limitation, since the proportion of patients with below average mortality was small.

4.2.2 Baseline rates

The baseline characteristics of the population of interest were derived from CPRD-HES-ONS linked dataset which serves as an ideal source for conducting longitudinal analyses on demographics, laboratory results, diagnoses and prescriptions. However, it is important to acknowledge the limitations of using this dataset.

Firstly, as hospitalisation is not always required for **TIA**, diagnoses in primary care were initially used However, the resulting rates were deemed implausibly high, almost certainly due to double counting of the same episode during subsequent primary care visit. Consequently, TIA rates were calculated using an external study [49] instead.

Similarly, the rates of **angina admissions** were perceived to be excessively high by the committee, potentially encompassing admissions for undifferentiated chest pain that would not benefit from a lipid-lowering therapy. To address this concern, the rate was adjusted using the ratio of unstable to stable angina admissions from the most recent national Hospital Episode Statistics (HES) data to estimate the number of admissions specifically for unstable angina. Given the uncertainty surrounding the risk of TIA and angina, these two events were excluded in scenario analyses although the impact on the results was negligible.

4.2.3 Mortality

The CPRD analysis that informed baseline mortality rates included people on a statin that were censored whenever they were escalated to a new treatment or discontinued the statin treatment. As such, the model assumes a 100% adherence to statin and no discontinuation. In the real world, people might discontinue statins for a variety of reason, and this might affect their survival and their risk of developing new CVD events. Therefore, it is possible that the model is not accurately capturing real-world survival of people in secondary prevention.

Two methods of capturing the impact of cholesterol lowering drugs on mortality were considered:

- A treatment effect from the CTTC was applied to all deaths (as used in the base case)
- A different (larger) treatment effect was applied but just to deaths where cardiovascular disease was the underlying cause. Cardiovascular mortality was defined quite narrowly to identify those deaths that would be potentially preventable using lipid-lowering therapy, so for example, deaths due to pulmonary embolism or haemorrhagic stroke were not included.

The first approach is not ideal as the model population is likely to have more comorbidities than the CTTC trials populations and so the all-cause mortality risk reduction might be less applicable. However, it was considered preferable to trying to define modifiable CVD mortality. The second approach was conducted in a sensitivity analysis and the life-years gained were substantially less. The CPRD analysis showed that the non-CVD mortality was increased after an event, such as an MI, even more than the CVD mortality, which suggested that this approach would under-estimate modifiable mortality. However, the committee were satisfied that the base case approach was more robust.

There are two distinct ways an intervention affects mortality in the model:

- A direct effect through the all-cause mortality treatment effect discussed above,
- An indirect effect through CVD relative risk reduction. This is because an intervention, by preventing new episodes of CVD, also reduces the probability of dying during an acute event.

- To ensure accurate estimation and avoid any potential inaccuracies resulting from the simultaneous application of these two effects on mortality, the results were calibrated. An adjustment factor was applied to the all-cause mortality treatment effect, ensuring that the calculated mortality reduction per mmol/litre reduction within the model precisely reflects the mortality reduction observed in the trials included in the CTTC analysis.

4.2.4 Cholesterol measurement

In the model, escalation is based on a single annual measurement of cholesterol above the target, however, observed cholesterol levels might vary due to measurement error or short-term biological variation, as well as the effects of treatment and diet. Basing escalation decisions on a single measurement could mean that too many people are escalated in the longer-term. This could be costly for the NHS, especially as there are no indications for de-escalation. Whereas having multiple measurements would be more accurate but would also be costly for the NHS and time-consuming for patients. This could be the subject of future research.

It was assumed that cholesterol levels will increase gradually over time and at a constant rate. However, it is possible that there is regression to the mean, such that the increase over time could be higher for those people with a low cholesterol at baseline and might even fall over time for those with a high cholesterol at baseline. Therefore, a further model adjusted for baseline cholesterol values was specified and tested in a scenario analysis. With this model, the single target decreased slightly to 2.1 mmol/L.

With the exception of LDL-c values calculated using the Friedewald formula, all the LDL-c values used in the model were reported directly from NHS general practices and, as such, suffer from approximation and other recording biases. For instance, a few observations were reported in the subgroups ranging between 1.8 and 1.999 or between 2.1 to 2.199. On the other hand, the subgroup 2.0 - 2.099 is among the most populous subgroups in our sample, which suggests that some clinicians approximate the observed LDL-c values to 2.0 when reporting cholesterol results. This had some untintended consequences in this analysis. For instance, in the full incremental analysis of the single target in Table 28, the LDL-c target of 2.1 is dominated by the LDL-c target of 2.0 and, as such, it is never the optimal target, even if costs and other relevant parameters are modified. This is because when the target is reduced from 2.2 to 2.1, only a small subset of individuals become eligible to the highly cost-effective ezetimibe treatment; by contrast, the substantial increase of people receiving inclisiran makes this target less preferable than a target of 2.0, where a significantly higher proportion of people receive ezetimibe. While it may appear perplexing, this enhances the external validity of the model. Consequently, while the cholesterol values used in the model may not precisely reflect actual cholesterol levels of individuals, they do mirror the values recorded in clinical practice, which ultimately determine therapeutic decisions.

4.2.5 Implementation of event rates

The way the model uses event rate data has strengths and limitations. Its strength is that mortality and event rates have been measured for the same population with the same background therapy. There was no censoring at first event so the total number of admissions and the number of deaths should be estimated precisely, and these have been stratified by age, sex. It was difficult to apply a further level of stratification relating to the pathway, without making the analysis quite complex. Furthermore, since the whole population has CVD and it is a prevalent population, it is difficult to differentiate those patients who have greater severity than others. Therefore, the same mortality rates were applied to individuals of the same age and sex, regardless of their pathway (number of admissions and types of admissions), unless they had an event in the last 12 months. Consequently, while the model exactly measures precisely overall admission rates and overall mortality, it may over-restimate the life expectancy of individuals in post-CVD states with an unfavourable prognosis. This implies that long-term costs associated with severe diseases, such as stroke,

could be overestimated as well as their impact on QALYs. However, the impact on incremental costs and QALYs is likely to be very small.

Secondly, although in practice people can have multiple admissions in a single year, the model does not include post states for composite CVD events or combinations of two or more events. This is primarily due to a lack of available data to accurately estimate risks, healthcare costs and quality of life for people have experienced multiple events. However, this is not an important limitation because the model estimates precisely the number of admissions and deaths that occur for the cohort and does not need to predict the pathway of individual patients. Furthermore, the ranking system in the Markov model prevents people from transitioning from any post-state to a less severe post-state. This should help ensure that the impact on quality of life and healthcare costs of those who experience multiple events is not underestimated.

Finally, it is worth noting that the formula used to prevent people from transitioning from any post-state to a less severe post-state does not take into account people who experience less severe CV events in two or more consecutive years. Nevertheless, the occurrence of such cases is anticipated to be relatively uncommon so this limitation is not expected to significantly affect the outcomes of the model and if it has an effect, it will be to mitigate the first limitation.

4.3 Generalisability to other populations or settings

The population of the base case analysis is people with CVD who are on a statin. A sensitivity analysis that included people intolerant to statin was conducted and found no difference in the value of the optimal single target. The results cannot be generalised to people using statin for primary prevention as their risk of having CVD events would be much lower.

Although, the population of interest in the base case scenario are people on any statin, NICE guideline CG181 specifically recommends atorvastatin 80mg. A sensitivity analysis using the age/sex/cholesterol distribution for the subgroup on 80mg atorvastatin found similar, albeit slightly higher inclisiran treatment thresholds, suggesting that this model's findings might be generalisable to those on an optimised statin therapy.

Medicines were assumed to be administered in primary care, except for PCSK9 inhibitors, which require an outpatient appointment before prescription. The results of the model would not be applicable if the therapies are administered in secondary care where the costs might be higher.

Finally, this analysis used UK-specific cholesterol distribution, admission rates and unit costs. Moreover, the prices of inclisiran and PCSK9i used in the model were negotiated between NHS England and pharmaceutical companies. As such, this analysis cannot be generalised to other countries.

4.4 Comparisons with other studies

4.4.1 Published literature

A systematic search was conducted to identify economic analyses on lipid medication therapies for people already on statins, primarily to discover:

- how treatment effects have been modelled, and
- if cholesterol treatment thresholds or targets had been modelled.

A total of 40 full papers were identified, with the majority focusing on ezetimibe and PCSK9 inhibitors and a few on inclisiran, bempedoic acid or a combination of therapies.

Two economic evaluations on lipid targets were identified. A Swedish study[23] evaluated the predicted impact of reducing the LDL cholesterol of a sample of people from a Swedish national register below 1.8 mmol/litre compared to doing nothing; however, the study included only on the benefits and cost savings of cholesterol reduction and not the costs of the therapies needed to achieve the desired reduction. A German study[4] sought to quantify the demand for PCSK9 inhibitors and the related cost required to attain the revised LDL cholesterol target (1.4 mmol/litre) outlined by the European Society of Cardiology (ESC)[29]. The authors found that reaching the increased demand for PCSK9 inhibitors would pose significant affordability challenges for any healthcare system. Therefore, they proposed an allocation strategy that identifies a tailored target population for PCSK9 inhibitors as the optimal approach. These findings are consistent with the present analysis that found that adopting treatment-specific targets is the most cost-effective approach.

Among those undertaking an economic modelling approach, the vast majority (26 studies) used an LDL-mediated treatment effect whereas one third (12 studies) used direct effects from clinical trials. Hence, the approach undertaken in this analysis is commonly applied in the literature.

Most of the studies relied on publications from the CTT collaboration to estimate the relative risk reductions associated with 1 mmol/litre decreased in LDL cholesterol. A minority of studies, primarily those published before 2010, used the Framingham risk equations. Notably, no analysis specifically targeting the reduction of non-HDL cholesterol was identified.

Only five analyses from the UK were identified. Three studies[2, 47, 48] explored the cost-effectiveness of ezetimibe for primary or secondary prevention but are relatively outdated and not directly applicable to the current NHS setting, particularly since the price of ezetimibe significantly decreased when the drug became generic. One is a critical review from the Evidence Review Group (ERG) on the NICE TA on evolocumab that found evolocumab clinically and cost-effective in certain patient subgroups[7]. Lastly, a recent cost-effectiveness analysis[31] comparing various lipid modification therapy concluded that PCSK9 inhibitors are not cost-effective at currently listed prices compared to ezetimibe in the UK. The analysis also found that ezetimibe is cost-effective compared to statins only at a £20,000 threshold, which is consistent with the present study that identified a treatment-specific threshold for ezetimibe close to 0.

4.4.2 Inclisiran technology appraisal

The NICE technology appraisal on inclisiran (TA733) was based upon a manufacturers model, which found inclisiran to be cost effective as an adjunct to statin in people with CVD, at a threshold of £20,000 per QALY. A cut-off of 2.6 mmol/litre LDL cholesterol was specified in the TA, based on the entry criteria in the clinical trials rather than based on an incremental analysis of baseline LDL cholesterol, as conducted for this guideline. When comparing the inputs and outcomes of the ERG-revised version of the TA model with a similar cohort (with the same baseline LDL cholesterol and same age/sex distribution) in this guideline model, the following were noted:

- The treatment effect for inclisiran was a bit higher than what was found in the guideline's network meta-analysis.
- The TA model applied a treatment effect to CVD mortality rather than all-cause mortality. The life-years gained in the TA model were greater because the baseline risk of modifiable CVD mortality was much higher. Like the guideline model, the TA model included CPRD-HES-ONS data, but patients followed only for one year and then extrapolated over the lifetime increasing the CVD mortality risk by 5% every year, whereas for the guideline, patients were followed up for 7 years and mortality was stratified by age/sex group to estimate lifetime risk.

- Non-cardiovascular mortality was lower in the TA model, being based upon the general population rather than a CVD population. Unlike the guideline model which estimates non-cardiovascular mortality from the same population, this would exaggerate the life-years gained from averting CVD mortality because that approach under-estimates the competing risks associated with comorbidity.
- Strokes and MIs and coronary revascularisations averted were similar in the two models. The TA model did not include non-vascular revascularisations or TIAs. However, it had a much higher baseline rate of unstable angina admissions and therefore a greater number of admissions averted. The rate was high enough to suggest that it included admissions for stable as well as unstable angina. The committee were concerned that this would include cases of undifferentiated chest pain that might not be modifiable with lipid lowering medicines.
- The utilities in the acute states in the TA model, which were sourced from the alirocumab TA model, were mostly lower than in this model. For the non-acute states, they were mainly higher in the TA model than in this model. This meant that the TA model was giving a greater weighting to years of life gained.
- The price of medicines were the same. The unit costs were typically lower in the TA model. Stroke had a significantly lower cost because it did not include social care costs.

Overall, while the committee accepted that there might be some uncertainty about the most appropriate unit costs and utilities, the guideline approach was rigorous, particularly regarding the estimation of events and treatment effects.

4.5 Conclusions

This cost-utility analysis aimed to determine the most cost-effective cholesterol target for people with CVD who are on statin therapy. Two distinct approaches were undertaken, and a cost-effective strategy within each approach was identified:

- The treatment-specific targets analysis found that it was most cost-effective to give ezetimibe to everyone and prescribe inclisiran solely to those with a LDL cholesterol exceeding 3.1 mmol/litre;
- The single target analysis found that it was most cost-effective for people to have their therapy escalated if their LDL cholesterol is above 2.2 mmol/litre. However, a target of 2.0 mmol/litre was found to be cost-effective in a sizeable proportion of simulations in the probabilistic sensitivity analysis.

Costs and QALYs were also modelled based on non-HDL cholesterol treatment effects and the base case the results were consistent with those of the LDL cholesterol model in the base case analysis. However, generally the LDL cholesterol model results were generally considered more reliable as the treatment effects are based on more robust evidence. Including population who are intolerant to statin did not affect the optimal value of a single LDL-c target.

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1 Appendices

2 Appendix A: Search strategy

3 Health economic evidence was identified by conducting searches using terms for a broad
4 cardiovascular diseases population. The following databases were searched: NHS Economic
5 Evaluation Database (NHS EED - this ceased to be updated after 31st March 2015), Health
6 Technology Assessment database (HTA - this ceased to be updated from 31st March 2018)
7 and The International Network of Agencies for Health Technology Assessment (INAHTA).
8 Searches for recent evidence were run on Medline and Embase from 2014 onwards for
9 health economics, and all years for quality-of-life and modelling studies.

10 **Table 36: Database parameters, filters and limits applied**

Database	Dates searched	Search filters and limits applied
Medline (OVID)	Health Economics 1 January 2014 – 16 November 2022	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
	Quality of Life 1946 – 16 November 2022	
	Models 1946 – 16 November 2022	
Embase (OVID)	Health Economics 1 January 2014 – 16 November 2022	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
	Quality of Life 1974 – 16 November 2022	
	Models 1974 – 16 November 2022	
NHS Economic Evaluation Database (NHS EED) (Centre for Research and Dissemination - CRD)	Inception –31 March 2015	
Health Technology Assessment Database (HTA) (Centre for Research and Dissemination – CRD)	Inception – 31 March 2018	

Database	Dates searched	Search filters and limits applied
The International Network of Agencies for Health Technology Assessment (INAHTA)	Inception - 16 November 2022	English language

1 **Medline (Ovid) search terms**

1.	*Cardiovascular Diseases/
2.	*Heart diseases/
3.	*Myocardial Ischemia/
4.	exp *Angina Pectoris/
5.	*Coronary Disease/
6.	*Coronary Artery Disease/
7.	exp *Coronary Stenosis/
8.	*Myocardial Infarction/
9.	exp *Heart Failure/
10.	*Arrhythmias, cardiac/ or *Atrial fibrillation/
11.	*Vascular Diseases/
12.	*Hypertension/
13.	*Atherosclerosis/
14.	*Peripheral Arterial Disease/
15.	*Peripheral Vascular Diseases/
16.	*Arteriosclerosis/
17.	*Cerebrovascular Disorders/
18.	exp *Stroke/
19.	exp *brain ischemia/
20.	exp *heart arrest/
21.	((cardiovascular or cardio vascular) adj3 (event* or disease* or disorder*)).ti,ab.
22.	((coronary or peripheral vascular or heart or peripheral arter*) adj3 (disease* or event* or disorder*)).ti,ab.
23.	(MI or myocardial infarct*).ti,ab.
24.	((heart or cardiopulmonary or cardiac) adj3 (death* or arrest* or attack*)).ti,ab.
25.	(CVD or CHD or CAD or PAD or CVA).ti,ab.
26.	(hypertension or hypertensive*).ti,ab.
27.	((high or raised or elevated) adj2 (blood pressure or bp)).ti,ab.
28.	(atheroscleros* or arterioscleros*).ti,ab.
29.	(cerebrovascular accident* or cerebrovascular disorder* or strokes or stroke).ti,ab.
30.	(ACS or angina or acute coronary syndrome*).ti,ab.
31.	(AF or atrial fibrillation).ti,ab.
32.	((chronic or congestive) adj2 heart failure).ti,ab.
33.	or/1-32
34.	letter/
35.	editorial/
36.	news/

37.	exp historical article/
38.	Anecdotes as Topic/
39.	comment/
40.	Case reports/
41.	(letter or comment*).ti.
42.	or/34-41
43.	randomized controlled trial/ or random*.ti,ab.
44.	42 not 43
45.	animals/ not humans/
46.	exp Animals, Laboratory/
47.	exp Animal Experimentation/
48.	exp Models, Animal/
49.	exp Rodentia/
50.	(rat or rats or mouse or mice or rodent*).ti.
51.	or/44-50
52.	33 not 51
53.	limit 52 to English language
54.	exp Ezetimibe/
55.	*Anticholesteremic Agents/
56.	(ezetimib or ezetimibe or ezetrol or bempedoic).ti,ab,kf.
57.	Nilemdo.ti,ab,kf.
58.	*RNA, Small Interfering/
59.	inclisiran.ti,ab,kf.
60.	Leqvio.ti,ab,kf.
61.	*PCSK9 Inhibitors/
62.	alirocumab.ti,ab,kf.
63.	Praluent.ti,ab,kf.
64.	evolocumab.ti,ab,kf.
65.	Repatha.ti,ab,kf.
66.	or/54-65
67.	limit 66 to English language
68.	67 not 51
69.	((target* or goal* or level* or optimum or optimal) adj2 (lipid* or cholesterol or LDL or HDL or lipoprotein* or lipo-protein*)).ti,ab,kf.
70.	53 and 69
71.	economics/
72.	value of life/
73.	exp "costs and cost analysis"/
74.	exp Economics, Hospital/
75.	exp Economics, medical/
76.	Economics, nursing/
77.	economics, pharmaceutical/
78.	exp "Fees and Charges"/

79.	exp budgets/
80.	budget*.ti,ab.
81.	cost*.ti.
82.	(economic* or pharmaco?economic*).ti.
83.	(price* or pricing*).ti,ab.
84.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
85.	(financ* or fee or fees).ti,ab.
86.	(value adj2 (money or monetary)).ti,ab.
87.	or/71-86
88.	exp models, economic/
89.	*Models, Theoretical/
90.	*Models, Organizational/
91.	markov chains/
92.	monte carlo method/
93.	exp Decision Theory/
94.	(markov* or monte carlo).ti,ab.
95.	econom* model*.ti,ab.
96.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
97.	or/88-96
98.	quality-adjusted life years/
99.	sickness impact profile/
100.	(quality adj2 (wellbeing or well being)).ti,ab.
101.	sickness impact profile.ti,ab.
102.	disability adjusted life.ti,ab.
103.	(qal* or qtime* or qwb* or daly*).ti,ab.
104.	(euroqol* or eq5d* or eq 5*).ti,ab.
105.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
106.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
107.	(hui or hui1 or hui2 or hui3).ti,ab.
108.	(health* year* equivalent* or hye or hyes).ti,ab.
109.	discrete choice*.ti,ab.
110.	rosser.ti,ab.
111.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
112.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
113.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
114.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
115.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
116.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
117.	or/98-116
118.	87 and (68 or 70)
119.	68 and 97
120.	68 and 117

1 **Embase (Ovid) search terms**

1.	*cardiovascular disease/
2.	*coronary artery disease/
3.	*vascular disease/
4.	*coronary artery atherosclerosis/
5.	*peripheral vascular disease/
6.	*peripheral occlusive artery disease/
7.	*arteriosclerosis/
8.	*ischemic heart disease/
9.	exp *Stroke/ or *stroke patient/
10.	*coronary artery obstruction/
11.	*hypertension/
12.	*heart disease/
13.	*heart arrhythmia/
14.	*heart fibrillation/ or *heart atrium fibrillation/
15.	*heart failure/ or exp *congestive heart failure/
16.	*acute coronary syndrome/ or exp *angina pectoris/ or *heart infarction/
17.	*cerebrovascular disease/
18.	*cerebrovascular accident/
19.	exp *brain ischemia/
20.	exp *heart arrest/ or *heart death/
21.	*brain infarction/
22.	*atherosclerosis/
23.	((cardiovascular or cardio vascular) adj3 (event* or disease* or disorder*)).ti,ab.
24.	((coronary or peripheral vascular or heart or peripheral arter*) adj3 (disease* or event* or disorder*)).ti,ab.
25.	(MI or myocardial infarct*).ti,ab.
26.	((heart or cardiopulmonary or cardiac) adj3 (death* or arrest* or attack*)).ti,ab.
27.	(CVD or CHD or CAD or PAD or CVA).ti,ab.
28.	(hypertension or hypertensive*).ti,ab.
29.	((high or raised or elevated) adj2 (blood pressure or bp)).ti,ab.
30.	(atheroscleros* or arterioscleros*).ti,ab.
31.	(cerebrovascular accident* or cerebrovascular disorder* or strokes or stroke).ti,ab.
32.	(ACS or angina or acute coronary syndrome*).ti,ab.
33.	(AF or atrial fibrillation).ti,ab.
34.	((chronic or congestive) adj2 heart failure).ti,ab.
35.	or/1-34
36.	letter.pt. or letter/
37.	note.pt.
38.	editorial.pt.
39.	Case reports/ or case study/
40.	(letter or comment*).ti.
41.	(conference abstract or conference paper).pt.

42.	or/36-41
43.	randomized controlled trial/ or random*.ti,ab.
44.	42 not 43
45.	animal/ not human/
46.	nonhuman/
47.	exp Animal Experiment/
48.	exp Experimental Animal/
49.	animal model/
50.	exp Rodent/
51.	(rat or rats or mouse or mice or rodent*).ti.
52.	or/44-51
53.	35 not 52
54.	limit 53 to English language
55.	*ezetimibe/
56.	hypocholesterolemic agent/
57.	(ezetimib or ezetimibe or ezetrol or bempedoic).ti,ab,kf.
58.	*bempedoic acid/
59.	Nilemdo.ti,ab,kf.
60.	*small interfering RNA/
61.	*inclisiran/
62.	inclisiran.ti,ab,kf.
63.	Leqvio.ti,ab,kf.
64.	PCSK9 inhibitor/
65.	*alirocumab/
66.	alirocumab.ti,ab,kf.
67.	Praluent.ti,ab,kf.
68.	*evolocumab/
69.	evolocumab.ti,ab,kf.
70.	Repatha.ti,ab,kf.
71.	or/55-70
72.	limit 71 to English language
73.	72 not 52
74.	((target* or goal* or level* or optimum or optimal) adj2 (lipid* or cholesterol or LDL or HDL or lipoprotein* or lipo-protein*)).ti,ab,kf.
75.	54 and 74
76.	quality-adjusted life years/
77.	"quality of life index"/
78.	short form 12/ or short form 20/ or short form 36/ or short form 8/
79.	sickness impact profile/
80.	(quality adj2 (wellbeing or well being)).ti,ab.
81.	sickness impact profile.ti,ab.
82.	disability adjusted life.ti,ab.
83.	(qal* or qtime* or qwb* or daly*).ti,ab.

84.	(euroqol* or eq5d* or eq 5*).ti,ab.
85.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
86.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
87.	(hui or hui1 or hui2 or hui3).ti,ab.
88.	(health* year* equivalent* or hye or hyes).ti,ab.
89.	discrete choice*.ti,ab.
90.	rosser.ti,ab.
91.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
92.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
93.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
94.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
95.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
96.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
97.	or/76-96
98.	health economics/
99.	exp economic evaluation/
100.	exp health care cost/
101.	exp fee/
102.	budget/
103.	funding/
104.	budget*.ti,ab.
105.	cost*.ti.
106.	(economic* or pharmaco?economic*).ti.
107.	(price* or pricing*).ti,ab.
108.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
109.	(financ* or fee or fees).ti,ab.
110.	(value adj2 (money or monetary)).ti,ab.
111.	or/98-110
112.	statistical model/
113.	exp economic aspect/
114.	112 and 113
115.	*theoretical model/
116.	*nonbiological model/
117.	stochastic model/
118.	decision theory/
119.	decision tree/
120.	monte carlo method/
121.	(markov* or monte carlo).ti,ab.
122.	econom* model*.ti,ab.
123.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
124.	or/114-123
125.	111 and (73 or 75)

126.	73 and 124
127.	73 and 97

1 **NHS EED and HTA (CRD) search terms**

#1.	MeSH DESCRIPTOR Cardiovascular Diseases EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Heart Diseases EXPLODE ALL TREES
#3.	MeSH DESCRIPTOR Myocardial Ischemia EXPLODE ALL TREES
#4.	MeSH DESCRIPTOR Angina Pectoris EXPLODE ALL TREES
#5.	MeSH DESCRIPTOR Coronary Artery Disease EXPLODE ALL TREES
#6.	MeSH DESCRIPTOR Coronary Disease EXPLODE ALL TREES
#7.	MeSH DESCRIPTOR Coronary Stenosis EXPLODE ALL TREES
#8.	MeSH DESCRIPTOR Myocardial Infarction EXPLODE ALL TREES
#9.	MeSH DESCRIPTOR Heart Failure EXPLODE ALL TREES
#10.	MeSH DESCRIPTOR Arrhythmias, Cardiac EXPLODE ALL TREES
#11.	MeSH DESCRIPTOR Atrial Fibrillation EXPLODE ALL TREES
#12.	MeSH DESCRIPTOR Vascular Diseases EXPLODE ALL TREES
#13.	MeSH DESCRIPTOR Hypertension EXPLODE ALL TREES
#14.	MeSH DESCRIPTOR Atherosclerosis EXPLODE ALL TREES
#15.	MeSH DESCRIPTOR Peripheral Arterial Disease EXPLODE ALL TREES
#16.	MeSH DESCRIPTOR Peripheral Vascular Diseases EXPLODE ALL TREES
#17.	MeSH DESCRIPTOR Arteriosclerosis EXPLODE ALL TREES
#18.	MeSH DESCRIPTOR Cerebrovascular Disorders EXPLODE ALL TREES
#19.	MeSH DESCRIPTOR Stroke EXPLODE ALL TREES
#20.	MeSH DESCRIPTOR Brain Ischemia EXPLODE ALL TREES
#21.	MeSH DESCRIPTOR Heart Arrest EXPLODE ALL TREES
#22.	(((cardiovascular or cardio vascular) adj3 (event* or disease* or disorder*)))
#23.	(((coronary or peripheral vascular or heart or peripheral arter*) adj3 (disease* or event* or disorder*)))
#24.	((MI or myocardial infarct*))
#25.	(((heart or cardiopulmonary or cardiac) adj3 (death* or arrest* or attack*)))
#26.	((CVD or CHD or CAD or PAD or CVA))
#27.	((hypertension or hypertensive*))
#28.	(((high or raised or elevated) adj2 (blood pressure or bp)))
#29.	((atheroscleros* or arterioscleros*))
#30.	((cerebrovascular accident* or cerebrovascular disorder* or strokes or stroke))
#31.	((ACS or angina or acute coronary syndrome*))
#32.	((AF or atrial fibrillation))
#33.	(((chronic or congestive) adj2 heart failure))
#34.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33
#35.	MeSH DESCRIPTOR Ezetimibe EXPLODE ALL TREES
#36.	MeSH DESCRIPTOR Anticholesteremic Agents EXPLODE ALL TREES
#37.	((ezetimib or ezetimibe or ezetrol or bempedoic))
#38.	(Nilemdo)
#39.	MeSH DESCRIPTOR RNA, Small Interfering EXPLODE ALL TREES
#40.	(inclisiran)

#41.	(Leqvio)
#42.	(alirocumab)
#43.	(Praluent)
#44.	(evolocumab)
#45.	(Repatha)
#46.	#35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45
#47.	(((target* or goal* or level* or optimum or optimal) adj2 (lipid* or cholesterol or LDL or HDL or lipoprotein* or lipo-protein*)))
#48.	#34 AND #47
#49.	#46 OR #48

1 **INAHTA search terms**

1.	(("cardiovascular diseases"[mh])) OR ("Heart diseases"[mh]) OR ("Myocardial Ischemia"[mh]) OR ("Angina Pectoris"[mh]) OR ("Coronary Disease"[mh]) OR ("Coronary Artery Disease"[mh]) OR ("Coronary Stenosis"[mh]) OR ("Myocardial Infarction"[mh]) OR ("Heart Failure"[mh]) OR ("Arrhythmias, cardiac"[mh]) OR ("Atrial fibrillation"[mh]) OR ("Vascular Diseases"[mh]) OR ("Hypertension"[mh]) OR ("Atherosclerosis"[mh]) OR ("Peripheral Arterial Disease"[mh]) OR ("Peripheral Vascular Diseases"[mh]) OR ("Arteriosclerosis"[mh]) OR ("Cerebrovascular Disorders"[mh]) OR ("stroke"[mh]) OR ("brain ischemia"[mh]) OR ("heart arrest"[mh]) OR (((cardiovascular or cardio vascular) and (event* or disease* or disorder*))) OR (((coronary or peripheral vascular or heart or peripheral arter*) and (disease* or event* or disorder*))) OR ((MI or myocardial infarct*)) OR (((heart or cardiopulmonary or cardiac) and (death* or arrest* or attack*))) OR ((CVD or CHD or CAD or PAD or CVA)) OR ((hypertension or hypertensive*)) OR (((high or raised or elevated) and (blood pressure or bp))) OR ((atheroscleros* or arterioscleros*)) OR ((cerebrovascular accident* or cerebrovascular disorder* or strokes or stroke)) OR ((ACS or angina or acute coronary syndrome*)) OR ((AF or atrial fibrillation)) OR (((chronic or congestive) and heart failure))
1.	("ezetimibe"[mhe]) OR ("Anticholesteremic Agents"[mh]) OR ((ezetimib or ezetimibe or ezetrol or bempedoic)) OR (Nilemdo) OR ("RNA, Small Interfering"[mh]) OR (inclisiran) OR (Leqvio) OR ("PCSK9 Inhibitors"[mh]) OR (alirocumab) OR (Praluent) OR (evolocumab) OR (Repatha)
2.	(((target* or goal* or level* or optimum or optimal) and (lipid* or cholesterol or LDL or HDL or lipoprotein* or lipo-protein*)))
3.	1 and 3
4.	2 or 4

2
3

Appendix B: Cholesterol statistical analysis plan

Statistical analysis plan for CPRD lipids project

02/03/2023

Background

This document outlines a proposed analysis of CPRD data. The analysis will provide parameters and statistics to be used in the health economic modelling of different target cholesterol thresholds for CVD secondary prevention, in support of the lipid modification guideline.

The dataset for the analysis is an event level file of each measurement of cholesterol in the study population taken in general practice, and other patient information current at the time of each cholesterol measurement. Each record in the file includes a unique patient identifier, a cholesterol measurement, information on the measurement type (e.g. HDL, non-HDL, LDL, etc), the patient's time since entering the analysis cohort, their gender, their age, and their current statin and its dose.

Patients only enter the cohort after they have met all of the following conditions:

- they have a record of an established CVD event/diagnosis;
- they have a record of being prescribed a statin within primary care after the CVD event/diagnosis and after 01/01/2013;
- the measurement of the cholesterol must have occurred after 01/01/2013 and after the initiation of a statin following the CVD event/diagnosis

Patients are censored at death, or if they discontinue the statin, or are prescribed another cholesterol lowering drug, or at 28/02/2020. They are also censored at the end of their registration at the primary care practice or their practice's last collection date.

Analysis plan

All analyses described below will be conducted in full twice; once using only LDL cholesterol measurements and once using non-HDL cholesterol measurements. For subgroup analyses, the number of subgroups will remain the same in both analyses, but the cut-offs for inclusion in the groups will change.

The data items will be inspected, for missing values and plausibility. The distribution of cholesterol measurements and statin dosages will be visualised, and other variables will be tabulated. The percentage of records with implausible or missing values will be calculated. The analysis will proceed excluding these records, but their impact on the validity of results will be considered. Where non-HDL or LDL cholesterol for a patient is not available, but can be derived from other measurements taken on the same day, these will be derived from those other measurements.

Part 1. Baseline characteristics of patients in different cholesterol groups

The distribution (count and percentage) and mean and median age of people in different subgroups defined by gender and post-statin initiation cholesterol group will be calculated (groupings still to be finalised but will be similar to e.g. 1-1.99, 2-2.99 mmol/litre etc). The groups will be chosen so that there are approximately 10 groups total for each gender; a constant range of cholesterol measurements in each cholesterol group apart from the upper and lower tails; and no less than 30 patients in any cholesterol group.

The statistics will then be calculated from the event-level file as follows. Every patient's first cholesterol measurement which is after 3 months since entering the cohort will be taken, to avoid any effects from discontinuation, swapping treatments, or delayed effects immediately after statin initiation. The median cholesterol reading in each specified cholesterol group will then be calculated for each gender, along with the mean and median age in that group, and the proportion of all patients in that group. Normal approximation-derived 95% confidence intervals for the mean age will be generated.

Separately, for each defined cholesterol group and gender, the proportion of the patient population belonging to each 5-year age group will be calculated, stratified by sex. Age groups will be combined if data are sparse (<10).

Part 2. Average annual change in cholesterol when on treatment

This analysis will be done as follows. The first and last instances in a sequence of records where a patient has a cholesterol measurement which are both a) at least 3 months after entering the cohort b) such that the statin prescribed and dosage is the same in the first and last measurements in the sequence and all those in between, will be identified. If there is more than one sequence of measurements meeting these requirements for a patient, the first sequence only will be taken. The arithmetic difference between the first and last cholesterol measurements will be taken for each patient, and average annual change across all patients (with 95% confidence intervals) will be the estimated annual change. The analyses will be stratified by gender.

Part 3. 95% Confidence intervals for rates provided by CPRD

CPRD will provide mortality and hospitalisation rates, but not confidence intervals for these. These intervals will be derived based on the normal approximation to the Poisson distribution using the follow-up time and event data provided. The rates will be provided by CPRD by individual age; sparse data may prove a problem for calculating rates and confidence intervals at that level, and in that case regrouping into age groups will be necessary. This will be to ensure at least 10 events in each age group.

Appendix C: Data quality report

NICE data suitability assessment tool (DataSAT)

This document provides an assessment of the data suitability for an analysis to provide information for health economic modelling of lipid modification strategies for the 2023 NICE cardiovascular disease secondary prevention guideline. The data analysis was conducted by CPRD and commissioned and specified by NICE.

Research question

What are the rates of cardiovascular events and mortality, by age and sex, amongst people taking statins for secondary prevention of cardiovascular disease in England?

Provenance

Item	Response
Data sources	Clinical Practice Research Datalink (CPRD) Aurum, Hospital Episode Statistics (HES) Admitted Patient Care (APC), and Office for National Statistics (ONS) Death Registration data.
Data linkage and data pooling	Records were linked using NHS Digital's Master Person Service [1]. This uses a deterministic algorithm to match patients in different health datasets by NHS number and then, if that is missing, a match on demographic information.
Type of data source	CPRD is database of information extracted from patient's primary care electronic health records. HES inpatients is an administrative database of all secondary care admissions. ONS death registrations is a database of all registered deaths.
Purpose of data collection	In primary care, prescriptions, symptoms, diagnoses, and test results are recorded for clinician's and patient's records, and for certain reimbursement schemes such as the Quality Outcomes Framework.

Item	Response
	In secondary care, HES captures high-level information on the diagnoses and procedures associated with each hospital admission to determine the reimbursement tariff for that admission. The ONS collate key information on all deaths as part of civil registration, including cause of death, which is also used for service evaluation and epidemiological research.
Data collection	In participating primary care practices which use the EMIS IT system, information including symptoms, test results, diagnoses, inbound and outbound referrals, are all recorded in distinct observation records, many of which can be sub-categorised into the observations associated with referrals, problems, and drug issue [2]. Observations are coded using READ and SNOMED codes. Drug and device prescriptions are also recorded separately. Free text information recorded by GPs is not extracted due to patient privacy concerns. HES inpatients is based on information extracted by clinical coders from clinician's records of diagnoses and procedures associated with an admission to an NHS hospital [3]. The coders extract sufficient information to identify the reimbursement tariff each admission is eligible for. This will usually include the primary diagnosis for the admission (ICD-10 code), and any major procedures done (using OPCS-4 codes). ONS death registrations are usually certified by a medical practitioner and the death certificate is submitted to the registrar, usually by a near relative of the deceased. HES and ONS deaths cover the whole of the UK. CPRD covers a representative sample of all GP practices in England. Only practices where it was possible to link information from each patient to their records in both the national HES and ONS datasets were included in this analysis [4].
Care setting	CPRD covers primary care; HES covers secondary care; and death registrations cover deaths in any setting.
Geographical setting	A representative sample of all GP practices from all regions in England, and any data on hospitalisations in England and mortality anywhere in the UK of patients registered at those practices.
Population coverage	CPRD Aurum includes data on over 13 million current patients (as of 2019) across 1,345 practices [4]. HES inpatients data covers all NHS hospital admissions in England. Death registrations covers the whole UK population.

Item	Response
Time period of data	CPRD Aurum captures data from 1995 to present; HES has collected admitted patient care data since 1989; and UK deaths have been registered since 1837. For this analysis, records of patients who had a first CVD event at any time, who were also at risk of a subsequent event during 2013-2020, have all their healthcare records from during 2013-2020 from CPRD, HES, and ONS analysed.
Data preparation	CPRD, HES, and ONS deaths dates are cleaned, transformed, and linked prior to analysis.
Data governance	The CPRD, which provided all the data used in this analysis, is a joint venture from the Medicines and Healthcare Regulatory Agency (MHRA) and the National Institute for Health Research (NIHR). The CPRD is owned by the UK Department of Health and operates within the MHRA.
Data specification	The detailed specification of the CPRD and HES datasets can be found in the CPRD Aurum data specification [5], and in the HES data dictionary [6].
Data management plan and quality assurance methods	CPRD conduct validation and quality assurance checks covering data integrity, structure, and format [4]. Issues highlighted are addressed before being incorporated into CPRD Aurum. These checks include: - That all expected data files are supplied from each GP practice, that data elements in each file are of the correct type, length, and format. Duplicate records are removed and observation records without an associated patient are removed. - That basic data on a given patient is consistent, for example with respect to their data of birth, practice registration date, and transfer out date. HES undergoes automatic data cleaning and derivation [6, 7] checks. These include: - Checks of validity of individual data items (e.g. date of birth is a valid date), and removal or reclassification of records with errors. - Removal of duplicate records.

Item	Response
Other documents	CPRD maintain a list of published studies which have used CPRD data. https://cprd.com/bibliography

1

2 **Data quality**

Study variable	Target concept	Operational definition	Quality dimension	How assessed	Assessment result
Age	Patient's age whilst at risk of a CVD event and death.	Recorded age in CPRD	Accuracy and completeness	We are not aware of any studies which have evaluated the accuracy of age recording in CPRD against an external standard, but it is expected to be as accurate as age data is in GP records in England generally. CPRD perform checks that date of birth is consistent between data items on the same patient in their dataset [5]. Analysis results were stratified by age group, and patients whose date of birth was not known were excluded prior to the production of the analysis results.	N/A
Sex	Sex	Recorded sex in CPRD	Accuracy and completeness	We are not aware of any studies which have evaluated the accuracy of sex recording in CPRD against an external standard, but it is expected to be as accurate as sex data is in GP records in England generally. Patients whose sex was not known were excluded prior to production of the results.	N/A
Current statin prescription	Patient currently taking a statin (of	In CPRD there is a record of the patient being prescribed	Accuracy and completeness	Within primary care statin prescriptions issued by the GP are automatically recorded alongside the	N/A

Study variable	Target concept	Operational definition	Quality dimension	How assessed	Assessment result
	a specified substance and dose).	a statin in primary care (of a specified substance and dose) within 90 days prior to the current date.		BNF code, dosage, and quantity [8]. Statin discontinuation is defined as starting 28 days following the start of a gap of at least 90 days between statin prescriptions. Information on prescriptions is here used as a proxy for statin exposure, as information on dispensing or actual adherence was not available.	
LDL cholesterol measurement	Current measured LDL cholesterol levels	Measured LDL cholesterol from a test initiated in primary care.	Accuracy and completeness	The accuracy of cholesterol measurements was not evaluated against an external standard, nor are we aware of any evaluations of whether tests results in primary care are completely recorded in CPRD.	N/A
Non-HDL cholesterol measurement	Current measured non-HDL cholesterol levels	Measured non-HDL cholesterol from a test initiated in primary care.	Accuracy and completeness	The accuracy of cholesterol measurements was not evaluated against an external standard, nor are we aware of any evaluations of whether tests results in primary care are completely recorded in CPRD.	N/A
Cardiovascular disease death	Death where cardiovascular disease was the underlying cause.	Death registration from the ONS which has a cardiovascular disease ICD-10 code as the underlying cause of death.	Accuracy and completeness	All deaths in the UK must be registered. Cause of death must be certified by a registered medical practitioner or coroner. Accuracy of cardiovascular death categorisation is not known. Small studies have reported on accuracy of cause death recording in different settings; for example, one pilot study has reported underlying cause of death was misclassified in up to 10% of death registrations [9], and one small study of prostate cancer patients reported a similar misclassification	Uncertain but expected to be highly complete and with accuracy for cause of death around ~90-95% or higher.

Study variable	Target concept	Operational definition	Quality dimension	How assessed	Assessment result
				percentage in cause of death [10]. In the present analysis only CVD deaths which are misclassified as non-CVD and vice versa will introduce error. Deaths abroad of people living in Britain are not automatically registered. It is not clear how much misclassification is likely to be introduced from this.	
Non-cardiovascular disease death	Death where cardiovascular disease was not the underlying cause.	Death registration from the ONS which does not have a cardiovascular disease ICD-10 code as the underlying cause of death.	Accuracy and completeness	All deaths in the UK must be registered. Cause of death must be certified by a registered medical practitioner or coroner. Accuracy of cardiovascular death categorisation is not known. Small studies have reported on accuracy of cause death recording in different settings; for example, one pilot study has reported underlying cause of death was misclassified in up to 10% of death registrations [9], and one small study of prostate cancer patients reported a similar misclassification percentage in cause of death [10]. In the present analysis only CVD deaths which are misclassified as non-CVD and vice versa will introduce error. Deaths abroad of people living in Britain are not automatically registered. It is not clear who much misclassification is likely to be introduced from this.	Uncertain but expected to be highly complete and with accuracy for cause of death around ~90-95% or higher.
Hospital admission with ischaemic stroke	Hospital admission with ischaemic stroke.	Patient has a record of an inpatient admission to an NHS-funded hospital where the primary diagnosis had an	Accuracy and completeness	Acute and emergency care in England is overwhelmingly provided by NHS hospitals, which need to record key information on each admission to be compensated under the payment by results (PbR) system. Accuracy of primary diagnosis	Expected to be around 95% accurate and expected

Study variable	Target concept	Operational definition	Quality dimension	How assessed	Assessment result
		ICD-10 code for ischaemic stroke.		recording of HES admissions has been reported at around 95% from 2002 onwards [11, 12].	to be highly complete.
Transient ischaemic attack diagnosed by a clinician in primary or secondary care	Record of TIA in hospital or primary care	Patient has a record of an inpatient admission to an NHS-funded hospital where the primary diagnosis had an ICD-10 code for TIA, or they had a record of an NHS GP observation for TIA coded using READ codes.	Accuracy and completeness	Accuracy of primary diagnosis recording of HES admissions has been reported at around 95% from 2002 onwards [11, 12]. If a GP recorded a diagnosis of TIA it would be expected to appear in primary care records, but we are not aware of validation studies on this topic.	Uncertain
Hospital admission with peripheral artery disease	Hospital admission with peripheral artery disease	Patient has a record of an inpatient admission to an NHS-funded hospital where the primary diagnosis had an ICD-10 code for peripheral artery disease.	Accuracy and completeness	Acute and emergency care in England is overwhelmingly provided by NHS hospitals, which need to record key information on each admission to be compensated under the payment by results (PbR) system. Accuracy of primary diagnosis recording of HES admissions has been reported around 95% from 2002 onwards [11, 12], though the accuracy of different CVD events is not reported.	Expected to be around 95% accurate and expected to be highly complete.
Hospital admission for non-coronary revascularisation	Hospital admission for non-coronary revascularisation	Patient has a record of an inpatient admission to an NHS-funded hospital with an OPCS-4 procedure code for non-coronary revascularisation.	Accuracy and completeness	Acute and emergency care in England is overwhelmingly provided by NHS hospitals, which need to record key information on each admission to be compensated under the payment by results (PbR) system. One analysis from 2012-13 reported that errors leading to an incorrect payment tariff were found in 8% of HES records, though these were typically due to omission of relevant	Uncertain but expected to be highly accurate and complete

Study variable	Target concept	Operational definition	Quality dimension	How assessed	Assessment result
				comorbidities and not misclassification or omission of major procedures done during the admission [12, 13].	
Hospital admission for myocardial infarction	Hospital admission for myocardial infarction	Patient has a record of an inpatient admission to an NHS-funded hospital where the primary diagnosis had an ICD-10 code for myocardial infarction.	Accuracy and completeness	Acute and emergency care in England is overwhelmingly provided by NHS hospitals, which need to record key information on each admission to be compensated under the payment by results (PbR) system. Accuracy of primary diagnosis recording of HES admissions has been reported around 95% from 2002 onwards [11, 12].	Expected to be around 95% accurate and expected to be highly complete.
Hospital admission for unstable angina	Hospital admission for unstable angina	Patient has a record of an inpatient admission to an NHS-funded hospital where the primary diagnosis had an ICD-10 code for unstable angina.	Accuracy and completeness	Acute and emergency care in England is overwhelmingly provided by NHS hospitals, which need to record key information on each admission to be compensated under the payment by results (PbR) system. Accuracy of primary diagnosis recording of HES admissions has been reported around 95% from 2002 onwards [11, 12].	Expected to be around 95% accurate and expected to be highly complete.
Hospital admission for elective coronary revascularisation	Hospital admission for elective coronary revascularisation	Patient has a record of an inpatient admission to an NHS-funded hospital with an OPCS-4 code for coronary revascularisation and an elective admission method.	Accuracy and completeness	Acute and emergency care in England is overwhelmingly provided by NHS hospitals, which need to record key information on each admission to be compensated under the payment by results (PbR) system. One analysis from 2012-13 reported that errors leading to an incorrect payment tariff were found in 8% of HES records, though these were typically due to omission of relevant comorbidities and not misclassification or omission	Uncertain but expected to be highly accurate and complete

Study variable	Target concept	Operational definition	Quality dimension	How assessed	Assessment result
				of major procedures done during the admission [12, 13].	

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1 **Data relevance to research question**

Item	Response
Population	The target population for this analysis is people attending primary care in the UK and being treated with lipid modification following a cardiovascular event, as that is the population the guideline being developed applies to. The patients included in the CPRD comprise a representative sample of this population in primary care. What is not fully understood is the extent to which patients with lipid modification records and prescription records (required for characterising the cohort and as part of cohort entry for time-to-event analyses respectively) missing due to clerical omissions or errors may be different to those with it present. Neither the analysis as commissioned by CPRD or a separate conducted at NICE could address these questions, as they were both restricted to patients with prescribing and lipid modification data available.
Care setting	The data used are from primary and secondary care and mortality records in the UK, therefore are directly applicable to the care settings of interest.
Treatment pathway	All the data are UK-based records, with HES and CPRD coming from patient care contacts and episodes, and so fully reflect the pathway of care in the UK.
Availability of key study elements	The purpose of this analysis is to characterise the UK CVD secondary prevention population and estimate their rates of hospitalisation and mortality, by age and sex, whilst on treatment with a statin. All key study elements for each of the relevant settings (HES for hospitalisation, ONS death registrations for mortality, CPRD for statin prescriptions) was available.
Study period	Data were available from 2013 to 2020, and hence current to the UK population prior to the COVID-19 pandemic.
Timing of measurements	The timing of measurements reflects the exact dates of cholesterol measurements, hospitalisation, and death, and so is appropriate to the analysis question.
Follow-up	Patients have between 0 and 7 years follow up. The analysis is however structured to estimate rates by age using the whole population at risk during 2013-2020, so estimates results by age group using a period approach analysis.
Sample size	There was no minimum clinically important difference requiring a sample size or power calculation for this analysis. Estimates of different types of hospitalisation and mortality were estimated by five year age group. Where data were too sparse for robust estimation of rates, result were aggregated up to larger age groups. Confidence intervals were calculated and uncertainty associated with these incorporated into the economic modelling.

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1 Appendix D: CPRD data analysis results

2 **Table 37: Admission rates by age and type of admission – men***

	Person-years	Admissions	Rate	Rate - Lower 95% CL	Rate – upper 95% CL
	Ischaemic stroke				
18-44	11,990	60	0.0050	0.0039	0.0064
45-49	21,896	104	0.0047	0.0039	0.0058
50-54	45,156	213	0.0047	0.0041	0.0054
55-59	71,734	392	0.0055	0.0049	0.0060
60-64	99,160	628	0.0063	0.0059	0.0068
65-69	138,615	850	0.0061	0.0057	0.0066
70-74	154,737	1,270	0.0082	0.0078	0.0087
75-79	149,005	1,716	0.0115	0.0110	0.0121
80-84	127,111	1,875	0.0148	0.0141	0.0154
85-89	77,389	1,420	0.0183	0.0174	0.0193
90+	31,887	762	0.0239	0.0223	0.0257
	Myocardial infarction				
18-44	11,990	142	0.0118	0.0100	0.0140
45-49	21,896	230	0.0105	0.0092	0.0120
50-54	45,156	531	0.0118	0.0108	0.0128
55-59	71,734	840	0.0117	0.0109	0.0125
60-64	99,160	1,104	0.0111	0.0105	0.0118
65-69	138,615	1,409	0.0102	0.0096	0.0107
70-74	154,737	1,849	0.0119	0.0114	0.0125
75-79	149,005	2,040	0.0137	0.0131	0.0143
80-84	127,111	2,162	0.0170	0.0163	0.0177
85-89	77,389	1,638	0.0212	0.0202	0.0222
90+	31,887	916	0.0287	0.0269	0.0306
	Unstable angina				
18-44	11,990	106	0.0088	0.0073	0.0107
45-49	21,896	200	0.0091	0.0080	0.0105
50-54	45,156	384	0.0085	0.0077	0.0094
55-59	71,734	514	0.0072	0.0066	0.0078
60-64	99,160	669	0.0067	0.0063	0.0073
65-69	138,615	786	0.0057	0.0053	0.0061
70-74	154,737	756	0.0049	0.0045	0.0052
75-79	149,005	795	0.0053	0.0050	0.0057
80-84	127,111	675	0.0053	0.0049	0.0057
85-89	77,389	404	0.0052	0.0047	0.0058
90+	31,887	158	0.0050	0.0042	0.0058
	Non-coronary revascularisation				
18-44	11,990	47	0.0039	0.0029	0.0052
45-49	21,896	85	0.0039	0.0031	0.0048
50-54	45,156	309	0.0068	0.0061	0.0077
55-59	71,734	556	0.0078	0.0071	0.0084

	Person-years	Admissions	Rate	Rate - Lower 95% CL	Rate – upper 95% CL
60-64	99,160	909	0.0092	0.0086	0.0098
65-69	138,615	1,333	0.0096	0.0091	0.0101
70-74	154,737	1,432	0.0093	0.0088	0.0097
75-79	149,005	1,293	0.0087	0.0082	0.0092
80-84	127,111	932	0.0073	0.0069	0.0078
85-89	77,389	431	0.0056	0.0051	0.0061
90+	31,887	122	0.0038	0.0032	0.0046
	Elective coronary revascularisation				
18-44	11,990	264	0.0220	0.0195	0.0248
45-49	21,896	590	0.0269	0.0249	0.0292
50-54	45,156	1,182	0.0262	0.0247	0.0277
55-59	71,734	1,736	0.0242	0.0231	0.0254
60-64	99,160	2,051	0.0207	0.0198	0.0216
65-69	138,615	2,187	0.0158	0.0151	0.0165
70-74	154,737	2,102	0.0136	0.0130	0.0142
75-79	149,005	1,677	0.0113	0.0107	0.0118
80-84	127,111	873	0.0069	0.0064	0.0073
85-89	77,389	276	0.0036	0.0032	0.0040
90+	31,887	33	0.0010	0.0007	0.0015

1 * Men with CVD on a statin but not on other lipid lowering therapy

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3 **Table 38: Admission rates by age and type of admission – women***

Person-years	Admissions	Rate	Rate - Lower 95% CL	Rate – upper 95% CL
Ischaemic stroke				
5,002	50	0.0100	0.0076	0.0132
8,668	82	0.0095	0.0076	0.0117
17,398	109	0.0063	0.0052	0.0076
27,425	171	0.0062	0.0054	0.0072
40,018	294	0.0073	0.0066	0.0082
60,693	408	0.0067	0.0061	0.0074
79,618	774	0.0097	0.0091	0.0104
92,582	1,265	0.0137	0.0129	0.0144
98,470	1,734	0.0176	0.0168	0.0185
78,778	1,856	0.0236	0.0225	0.0247
50,480	1,522	0.0302	0.0287	0.0317
Myocardial infarction				
5,002	42	0.0084	0.0062	0.0114
8,668	79	0.0091	0.0073	0.0114
17,398	159	0.0091	0.0078	0.0107
27,425	191	0.0070	0.0060	0.0080
40,018	314	0.0078	0.0070	0.0088
60,693	473	0.0078	0.0071	0.0085

Person-years	Admissions	Rate	Rate - Lower 95% CL	Rate – upper 95% CL
79,618	659	0.0083	0.0077	0.0089
92,582	1,044	0.0113	0.0106	0.0120
98,470	1,336	0.0136	0.0129	0.0143
78,778	1,302	0.0165	0.0157	0.0175
50,480	992	0.0197	0.0185	0.0209
Unstable angina				
5,002	56	0.0113	0.0087	0.0146
8,668	89	0.0102	0.0083	0.0126
17,398	152	0.0087	0.0074	0.0102
27,425	214	0.0078	0.0068	0.0089
40,018	254	0.0063	0.0056	0.0072
60,693	331	0.0055	0.0049	0.0061
79,618	428	0.0054	0.0049	0.0059
92,582	460	0.0050	0.0045	0.0054
98,470	499	0.0051	0.0046	0.0055
78,778	354	0.0045	0.0040	0.0050
50,480	214	0.0042	0.0037	0.0048
Non-coronary revascularisation				
5,002	23	0.0046	0.0031	0.0069
8,668	56	0.0065	0.0050	0.0084
17,398	130	0.0075	0.0063	0.0089
27,425	191	0.0070	0.0060	0.0080
40,018	269	0.0067	0.0060	0.0076
60,693	365	0.0060	0.0054	0.0067
79,618	484	0.0061	0.0056	0.0066
92,582	648	0.0070	0.0065	0.0076
98,470	524	0.0053	0.0049	0.0058
78,778	323	0.0041	0.0037	0.0046
50,480	136	0.0027	0.0023	0.0032
Elective coronary revascularisation				
5,002	38	0.0076	0.0055	0.0104
8,668	103	0.0119	0.0098	0.0144
17,398	216	0.0124	0.0109	0.0142
27,425	324	0.0118	0.0106	0.0132
40,018	423	0.0106	0.0096	0.0116
60,693	557	0.0092	0.0084	0.0100
79,618	617	0.0077	0.0072	0.0084
92,582	595	0.0064	0.0059	0.0070
98,470	353	0.0036	0.0032	0.0040
78,778	123	0.0016	0.0013	0.0019
50,480	24	0.0005	0.0003	0.0007

1 * Women with CVD on a statin but not on other lipid lowering therapy

Table 39: Mortality rates by age and type of event in last 12 months – men*

	Person-years	NCV deaths	CV deaths	All deaths	Rate	Rate - Lower 95% CL	Rate – upper 95% CL
	Male	Ischaemic stroke					
18-44	121	1	1	2	0.0165	0.0041	0.0659
45-49	155	1	7	8	0.0517	0.0258	0.1033
50-54	303	11	6	17	0.0560	0.0348	0.0901
55-59	412	11	24	35	0.0850	0.0610	0.1184
60-64	610	27	27	54	0.0886	0.0678	0.1156
65-69	783	66	60	126	0.1608	0.1351	0.1915
70-74	1,067	99	77	176	0.1650	0.1423	0.1912
75-79	1,246	172	147	319	0.2559	0.2293	0.2856
80-84	1,294	241	268	509	0.3935	0.3607	0.4292
85-89	883	216	295	511	0.5784	0.5303	0.6308
90+	418	154	208	362	0.8653	0.7806	0.9591
	Male	Myocardial infarction					
18-44	310	3	0	3	0.0097	0.0031	0.0300
45-49	426	8	3	11	0.0258	0.0143	0.0466
50-54	771	15	12	27	0.0350	0.0240	0.0510
55-59	1,058	27	11	38	0.0359	0.0261	0.0494
60-64	1,194	64	17	81	0.0678	0.0545	0.0843
65-69	1,419	128	34	162	0.1141	0.0979	0.1332
70-74	1,532	221	60	281	0.1834	0.1631	0.2061
75-79	1,518	309	91	400	0.2635	0.2389	0.2906
80-84	1,494	434	128	562	0.3763	0.3464	0.4087
85-89	1,020	433	153	586	0.5743	0.5296	0.6227
90+	519	351	104	455	0.8768	0.7999	0.9612
	Male	Unstable angina					
18-44	227	0	1	1	0.0044	0.0006	0.0312
45-49	416	1	2	3	0.0072	0.0023	0.0224
50-54	768	3	3	6	0.0078	0.0035	0.0174
55-59	1,074	15	4	19	0.0177	0.0113	0.0277
60-64	1,257	23	5	28	0.0223	0.0154	0.0322
65-69	1,502	33	8	41	0.0273	0.0201	0.0371
70-74	1,499	55	23	78	0.0520	0.0417	0.0650
75-79	1,567	91	33	124	0.0791	0.0663	0.0943
80-84	1,361	123	44	167	0.1227	0.1054	0.1428
85-89	827	116	50	166	0.2008	0.1725	0.2338
90+	327	73	27	100	0.3060	0.2515	0.3722
	Male	Non-coronary revascularisation					
18-44	37	0	1	1	0.0268	0.0038	0.1900
45-49	74	3	0	3	0.0405	0.0131	0.1256
50-54	235	7	3	10	0.0426	0.0229	0.0791
55-59	460	9	8	17	0.0370	0.0230	0.0595
60-64	710	21	7	28	0.0394	0.0272	0.0571
65-69	1,003	64	20	84	0.0837	0.0676	0.1037

	Person-years	NCV deaths	CV deaths	All deaths	Rate	Rate - Lower 95% CL	Rate – upper 95% CL
70-74	1,078	102	33	135	0.1253	0.1058	0.1483
75-79	935	114	38	152	0.1626	0.1387	0.1906
80-84	692	104	35	139	0.2008	0.1701	0.2372
85-89	312	94	24	118	0.3788	0.3163	0.4537
90+	90	32	7	39	0.4326	0.3161	0.5921
	Male	Elective coronary revascularisation					
18-44	251	0	0	0	0.0000		
45-49	537	0	2	2	0.0037	0.0009	0.0149
50-54	1,104	3	2	5	0.0045	0.0019	0.0109
55-59	1,610	3	5	8	0.0050	0.0025	0.0099
60-64	1,928	6	8	14	0.0073	0.0043	0.0123
65-69	2,020	16	12	28	0.0139	0.0096	0.0201
70-74	1,974	38	12	50	0.0253	0.0192	0.0334
75-79	1,561	44	31	75	0.0480	0.0383	0.0602
80-84	825	43	13	56	0.0679	0.0522	0.0882
85-89	259	21	3	24	0.0928	0.0622	0.1385
90+	35	6	0	6	0.1718	0.0772	0.3823
	Male	No event in last 12 months					
18-44	6,834	28	4	32	0.0046	0.0033	0.0066
45-49	13,613	49	21	70	0.0051	0.0041	0.0065
50-54	29,894	176	55	231	0.0077	0.0068	0.0088
55-59	49,439	410	114	523	0.0106	0.0097	0.0115
60-64	69,732	859	222	1,081	0.0155	0.0146	0.0165
65-69	99,029	1,603	517	2,120	0.0214	0.0205	0.0223
70-74	110,185	2,706	706	3,411	0.0310	0.0299	0.0320
75-79	105,509	3,958	1,034	4,992	0.0473	0.0460	0.0486
80-84	89,281	5,285	1,382	6,668	0.0747	0.0729	0.0765
85-89	53,852	5,269	1,374	6,643	0.1234	0.1204	0.1264
90+	21,968	3,759	1,003	4,763	0.2168	0.2107	0.2230
	Male	All					
18-44	7,780	32	7	39	0.0050	0.0036	0.0068
45-49	15,221	62	35	97	0.0064	0.0052	0.0078
50-54	33,076	215	81	296	0.0089	0.0080	0.0100
55-59	54,053	475	166	640	0.0118	0.0110	0.0128
60-64	75,432	1,000	286	1,286	0.0170	0.0161	0.0180
65-69	105,756	1,910	651	2,561	0.0242	0.0233	0.0252
70-74	117,334	3,221	911	4,131	0.0352	0.0342	0.0363
75-79	112,337	4,688	1,374	6,062	0.0540	0.0526	0.0553
80-84	94,946	6,230	1,870	8,101	0.0853	0.0835	0.0872
85-89	57,153	6,149	1,899	8,048	0.1408	0.1378	0.1439
90+	23,358	4,375	1,349	5,725	0.2451	0.2388	0.2515
All	696,446	28,356	8,630	36,986			

1 * Men with CVD on a statin but not on other lipid lowering therapy

1 CV= modifiable cardiovascular deaths; NCV=all other deaths

2 **Table 40: Mortality rates by age and type of event in last 12 months – women***

	Person-years	NCV deaths	CV deaths	All deaths	Rate	Rate - Lower 95% CL	Rate – upper 95% CL
	Female	Ischaemic stroke					
18-44	101	2	0	2	0.0199	0.0050	0.0794
45-49	105	3	1	4	0.0382	0.0143	0.1017
50-54	158	4	3	7	0.0442	0.0211	0.0927
55-59	198	8	3	11	0.0556	0.0308	0.1004
60-64	286	22	11	33	0.1152	0.0819	0.1621
65-69	394	46	33	79	0.2004	0.1607	0.2498
70-74	625	66	63	129	0.2064	0.1737	0.2452
75-79	926	126	134	260	0.2809	0.2488	0.3172
80-84	1,195	222	258	480	0.4015	0.3672	0.4391
85-89	1,143	287	366	653	0.5714	0.5292	0.6169
90+	745	315	468	783	1.0514	0.9803	1.1277
	Female	Myocardial infarction					
18-44	91	1	1	2	0.0220	0.0055	0.0881
45-49	124	3	2	5	0.0404	0.0168	0.0971
50-54	219	9	2	11	0.0503	0.0278	0.0908
55-59	279	17	1	18	0.0645	0.0406	0.1024
60-64	356	27	10	37	0.1039	0.0753	0.1434
65-69	494	59	12	71	0.1436	0.1138	0.1812
70-74	621	85	19	104	0.1674	0.1381	0.2028
75-79	822	141	51	192	0.2337	0.2029	0.2692
80-84	958	295	65	360	0.3758	0.3389	0.4167
85-89	879	320	88	408	0.4642	0.4213	0.5115
90+	615	355	89	444	0.7215	0.6574	0.7918
	Female	Unstable angina					
18-44	127	1	0	1	0.0079	0.0011	0.0557
45-49	200	1	1	2	0.0100	0.0025	0.0399
50-54	355	1	0	1	0.0028	0.0004	0.0200
55-59	484	4	3	7	0.0145	0.0069	0.0303
60-64	586	2	4	6	0.0102	0.0046	0.0228
65-69	704	16	5	21	0.0298	0.0195	0.0458
70-74	955	29	6	35	0.0366	0.0263	0.0510
75-79	993	46	13	59	0.0594	0.0460	0.0767
80-84	1,062	76	28	104	0.0979	0.0808	0.1187
85-89	774	75	27	102	0.1318	0.1086	0.1600
90+	459	78	30	108	0.2353	0.1948	0.2841
	Female	Non-coronary revascularisation					
18-44	19	1	0	1	0.0522	0.0074	0.3708
45-49	40	2	0	2	0.0495	0.0124	0.1979
50-54	91	1	0	1	0.0110	0.0016	0.0781
55-59	163	8	1	9	0.0552	0.0287	0.1061

	Person-years	NCV deaths	CV deaths	All deaths	Rate	Rate - Lower 95% CL	Rate – upper 95% CL
60-64	205	8	5	13	0.0633	0.0368	0.1090
65-69	288	27	2	29	0.1005	0.0699	0.1447
70-74	370	28	4	32	0.0866	0.0612	0.1224
75-79	478	58	10	68	0.1423	0.1122	0.1804
80-84	402	54	20	74	0.1840	0.1465	0.2311
85-89	234	48	6	54	0.2308	0.1768	0.3014
90+	113	36	7	43	0.3801	0.2819	0.5125
	Female	Elective coronary revascularisation					
18-44	37	0	0	0	0.0000		
45-49	88	0	1	1	0.0114	0.0016	0.0807
50-54	206	2	0	2	0.0097	0.0024	0.0389
55-59	299	2	2	4	0.0134	0.0050	0.0357
60-64	396	11	3	14	0.0353	0.0209	0.0596
65-69	528	5	2	7	0.0133	0.0063	0.0278
70-74	572	12	4	16	0.0280	0.0171	0.0456
75-79	557	14	4	18	0.0323	0.0204	0.0513
80-84	329	4	5	9	0.0273	0.0142	0.0525
85-89	126	2	6	8	0.0637	0.0318	0.1273
90+	26	1	0	1	0.0385	0.0054	0.2730
	Female	No event in last 12 months					
18-44	3,116	21	2	23	0.0073	0.0048	0.0110
45-49	5,629	30	13	42	0.0075	0.0056	0.0102
50-54	11,807	98	12	110	0.0093	0.0077	0.0112
55-59	19,068	181	27	208	0.0109	0.0095	0.0125
60-64	27,350	376	63	439	0.0160	0.0146	0.0176
65-69	41,519	761	126	888	0.0214	0.0200	0.0228
70-74	54,545	1,328	226	1,554	0.0285	0.0271	0.0299
75-79	62,893	2,196	400	2,596	0.0413	0.0397	0.0429
80-84	66,930	3,498	817	4,315	0.0645	0.0626	0.0664
85-89	53,186	4,531	1,007	5,539	0.1041	0.1014	0.1069
90+	34,057	5,412	1,301	6,714	0.1971	0.1925	0.2019
	Female	All					
18-44	3,491	26	3	29	0.0082	0.0057	0.0118
45-49	6,186	39	18	56	0.0091	0.0070	0.0118
50-54	12,835	115	17	132	0.0103	0.0086	0.0122
55-59	20,491	220	37	257	0.0125	0.0111	0.0141
60-64	29,181	446	96	542	0.0186	0.0171	0.0202
65-69	43,928	914	180	1,095	0.0249	0.0235	0.0264
70-74	57,689	1,548	322	1,870	0.0324	0.0310	0.0339
75-79	66,668	2,581	612	3,193	0.0479	0.0463	0.0496
80-84	70,877	4,149	1,193	5,342	0.0754	0.0734	0.0774
85-89	56,341	5,263	1,500	6,764	0.1201	0.1172	0.1229
90+	36,015	6,197	1,895	8,093	0.2247	0.2199	0.2297
All	403,701	21,497	5,874	27,371			

1 * Women with CVD on a statin but not on other lipid lowering therapy

2 CV= modifiable cardiovascular deaths; NCV=all other deaths