Online supplementary file 4: Cost and health benefits of diagnosis of individuals with familial hypercholesterolaemia in the long term

Contents

• Model structure

Similarly to the analysis in the Section 8.2[1]. Coronary revascularisation was excluded because, as a non-elective procedure for the management of some types of ACS, it will be partly captured in the ACS events; because the effect of coronary revascularisation on the risk of ACS is unclear from the literature [2-5], and due to lack of evidence on the direction of effect of diagnosis and subsequent LLT on the probability of elective coronary revascularisation.

The model does not consider recurring events explicitly, in contrast with some of the previous cost-effectiveness models in both people with FH [6-10] and in the general population [11-14] . We took this approach given the limited data on recurrent events from the CPRD cohort, and because the purpose of our model is to capture the impact of diagnosis, which is primarily in individuals who have not yet experienced a CV event. Once individuals have experienced a CV event, the role of diagnosis is likely to be less important as individuals with CV history will generally be in receipt of LLT.

• Model inputs

Effect of diagnosis on cholesterol

Table 1: Effect of diagnosis on low-density lipoprotein cholesterol

Relative reduction in low-density lipoprotein cholesterol	Average	Standard error	Number of individuals
In the newly treated individuals following diagnosis for familial hypercholesterolaemia	32.60%	0.89%	1291
In those who started treatment prior diagnosis for familial hypercholesterolaemia	34.50%	0.97%	844
Source: Analysis of CPRD data (see Chapter [CPRD]) Distribution for probabilistic sensitivity analysis: normal for relative reduction; beta for proportion of individuals.			

Risk of first major cardiovascular event

Table 2: Coefficients of risk equations used in the cost-effectiveness model

Parameter	**Model**	
	Scenario: Exponential	**Base-case: Generalised Gamma**
mu	N/A	13.1896
sigma	N/A	2.2144
Q	N/A	0.4970
constant	0.0001	N/A
sex (=0 if female; =1 if male)	0.7848	-1.2077
age at diagnosis, in years	0.0504	-0.0724
LDLC pre-treatment, in mmol/L	0.2838	-0.4426
CV history at diagnosis (=1 if yes)	1.4728	-2.5750
CV: cardiovascular; LDLC: low density lipoprotein cholesterol; N/A: not applicable		

Obtained from the analysis of time to first major cardiovascular event reported in Section 11.2. For hazard ratios, see Chapter Section 11.2 Distribution for probabilistic sensitivity analysis: multivariate normal.

Table 3: Cholesky decomposition for the exponential risk equation

Parameters	constant	male	age	PT-LDLC	CV history
constant	0.620				
male	-0.080	0.164			
age	-0.006	0.000	0.004		
PT-LDLC	-0.034	-0.012	-0.034	0.015	
CV history	0.014	-0.024	-0.057	-0.084	0.207
CV: Cardiovascular; PT-LDLC: Pre-Treatment Low Density Lipoprotein Cholesterol					

Table 4: Cholesky decomposition for the generalised gamma risk equation

Parameters	mu	sigma	Q	male	age	PT-LDLC	CV history
mu	1.353						
sigma	0.154	0.268					
Q	-0.141	-0.343	0.079				
male	-0.160	0.012	0.010	0.253			
age	-0.010	0.004	0.001	0.000	0.007		
PT-LDLC	-0.070	0.006	0.016	-0.019	-0.055	0.025	
CV history	-0.231	-0.372	-0.039	-0.016	-0.092	-0.134	0.356
CV: Cardiovascular; PT-LDLC: Pre-Treatment Low Density Lipoprotein Cholesterol							

Table 5: Distribution of individuals by type of 1st CV event

Parameters	**N**	**Proportion**
Death	15	11%
Non-fatal acute coronary syndrome	91	65%
Non-fatal transient ischaemic attack or ischaemic stroke	35	25%
Obtained from the analysis of time to first major cardiovascular event reported in Section 11.2 Distribution for probabilistic sensitivity analysis: Dirichlet		

Table 6: Calculation of risk adjustment from Perak et al[15]

Population	Time, years	Survival	Cumulative hazard	Hazard rate	Hazard ratio
Age = 30 years	10.20	0.99	0.01	0.00	N/A

	20.69	0.94	0.06	0.00	4.13
	29.93	0.88	0.12	0.01	6.44
Age = 40 years	10.20	0.94	0.06	0.00	N/A
	19.99	0.86	0.15	0.01	1.48
	29.95	0.76	0.27	0.01	2.00
Age = 50 years	9.85	0.94	0.06	0.01	N/A
	20.63	0.86	0.15	0.01	1.47
	29.81	0.77	0.26	0.01	2.03
Age = 60 years	9.97	0.88	0.13	0.01	N/A
	20.41	0.71	0.34	0.02	1.51
	28.67	0.51	0.68	0.04	3.04

Time and Survival read from curves reported in Perak et al [15].

Cumulative hazard calculated as 1 – Survival.

Hazard rate calculated as the ratio between the differences in cumulative hazards.

Hazard ratio calculated as the ratio between the hazard rate at approximately 20 and 30 years to the hazard rate at 10 years.

Hazard ratio used in the model corresponds to the hazard ratio calculated in the population aged 30 years, and the average of the hazard ratios calculated from the population aged 40-60 years.

N/A: Not applicable

Not included in the probabilistic sensitivity analysis

Table 7: Effect of reducing low-density lipoprotein cholesterol by 1 mmol/L on the risk of non-cardiovascular death

Average	95% confidence interval	Distribution for probabilistic sensitivity analysis	Source
0.96	0.92 to 1.01	Lognormal	CTTC 2019 Webfigure 4A [16]

Survival post-1st major cardiovascular event

We compared the survival after the 1st non-fatal acute coronary syndrome and after the 1st non-fatal ischaemic stroke/transient ischaemic attack observed in the CPRD cohort and predicted by the Lewsey equations [17] given the average age at the event and sex of the CPRD cohort (Figures 1 and 2). We concluded that Lewsey equations overestimated survival after the 1st non-fatal acute coronary syndrome but fitted well to the observed survival after the 1st non-fatal ischaemic stroke/transient ischaemic attack. Therefore, we calibrated the Lewsey equations for survival after the 1st non-fatal acute coronary syndrome by applying the hazard ratio of the observed hazard rate to the Lewsey predicted hazard rate at 1.3 years, at 2.91.

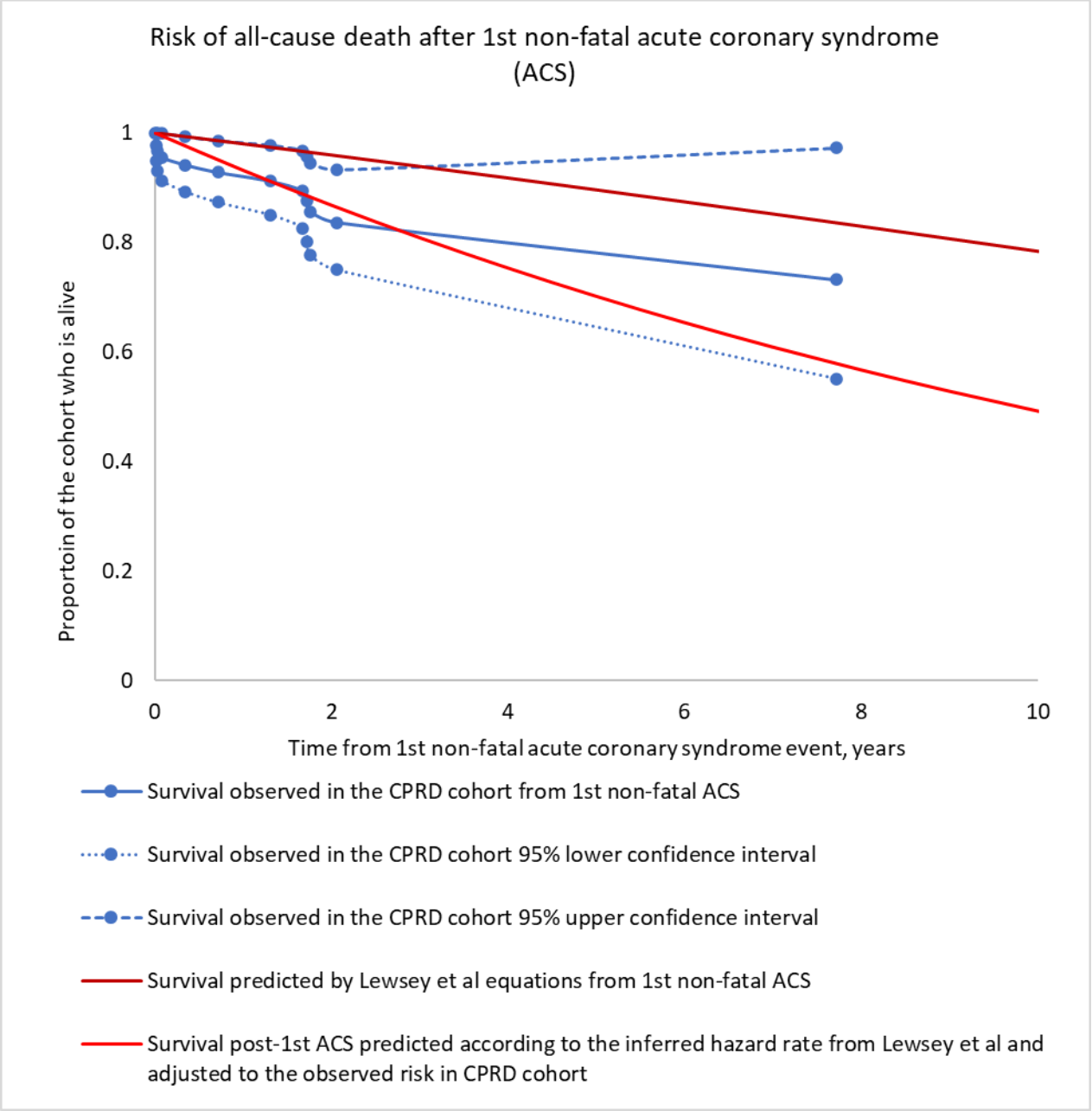


Figure 1: Comparison of observed survival in CPRD cohort after first non-fatal acute coronary syndrome event to Lewsey et al [17] risk equations for death after first non-fatal coronary heart disease given age and sex of the CPRD cohort

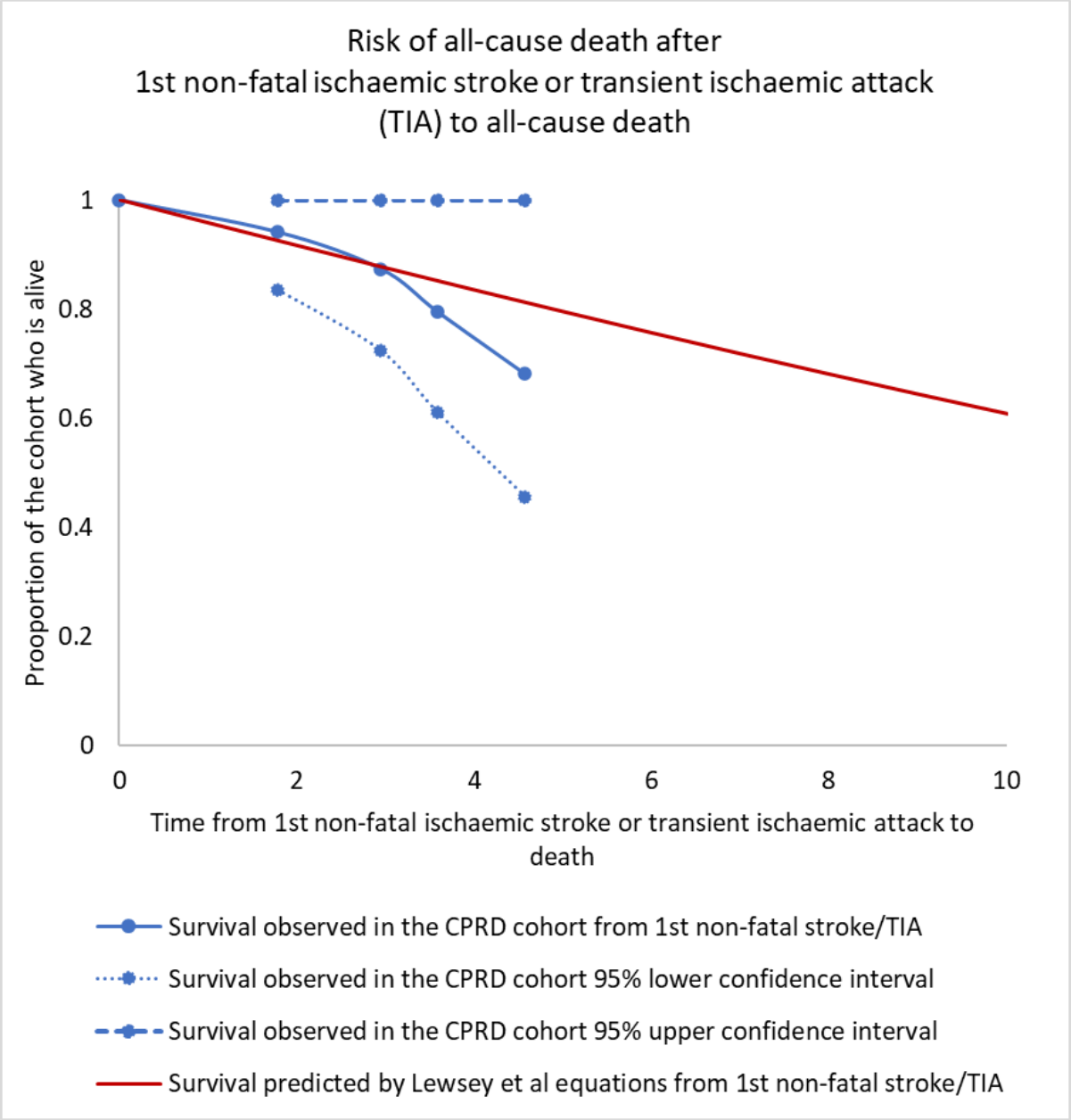


Figure 2: Comparison of observed survival in CPRD cohort after first non-fatal ischaemic stroke or transient ischaemic attack event to Lewsey et al [17] risk equations for death after first non-fatal cerebrovascular event given age and sex of the CPRD cohort

To avoid having yearly tunnel states from the first non-fatal event, we assumed that the hazard rate at 10 years from the Lewsey equations [17], calculated at 10-year age intervals for the age at which the CV event had occurred, was generalisable over the long-term. The predictions using this hazard rate compared well with the original Lewsey equations [17] (see Figures 3 and 4 for males; figures for females not presented but similar).

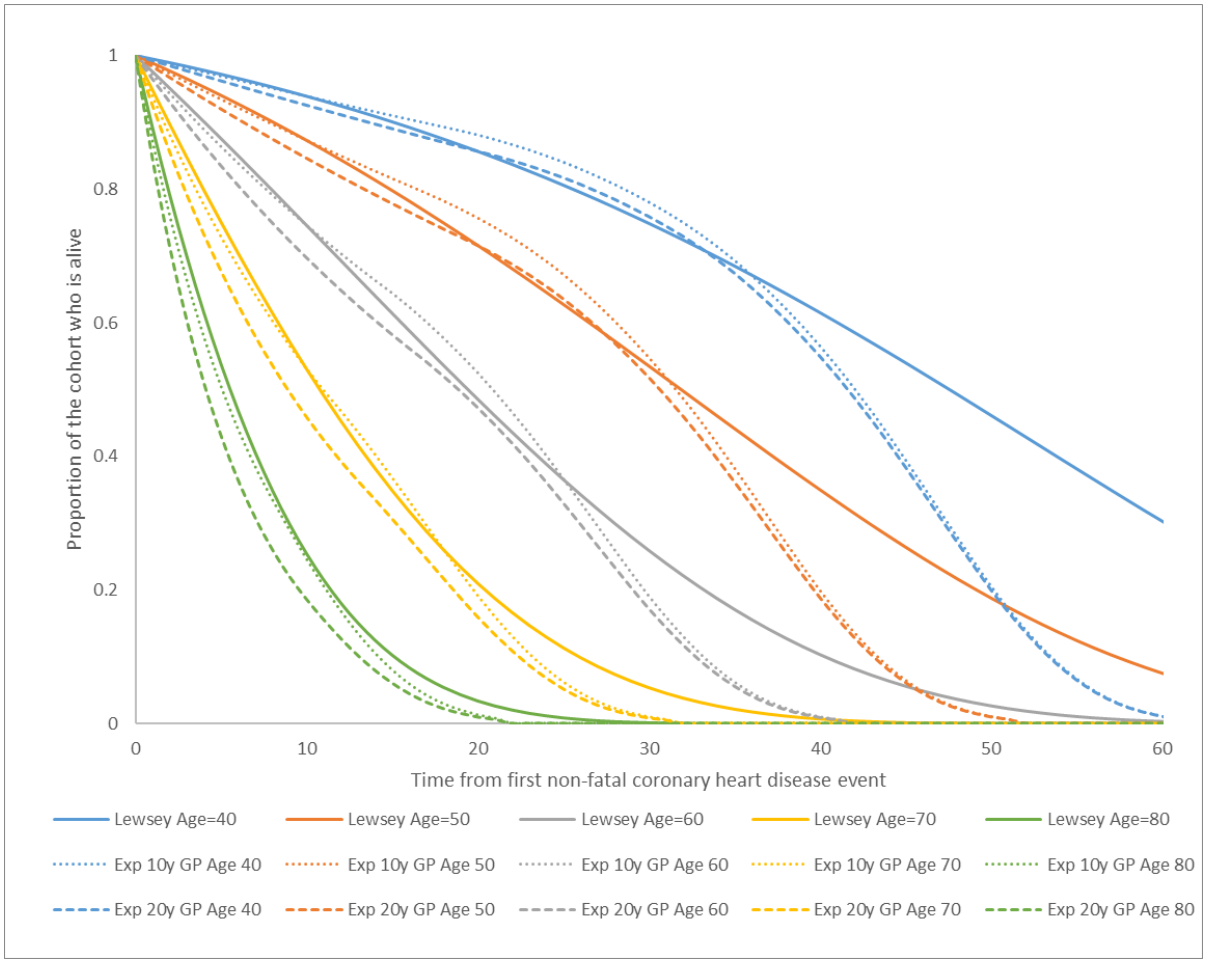
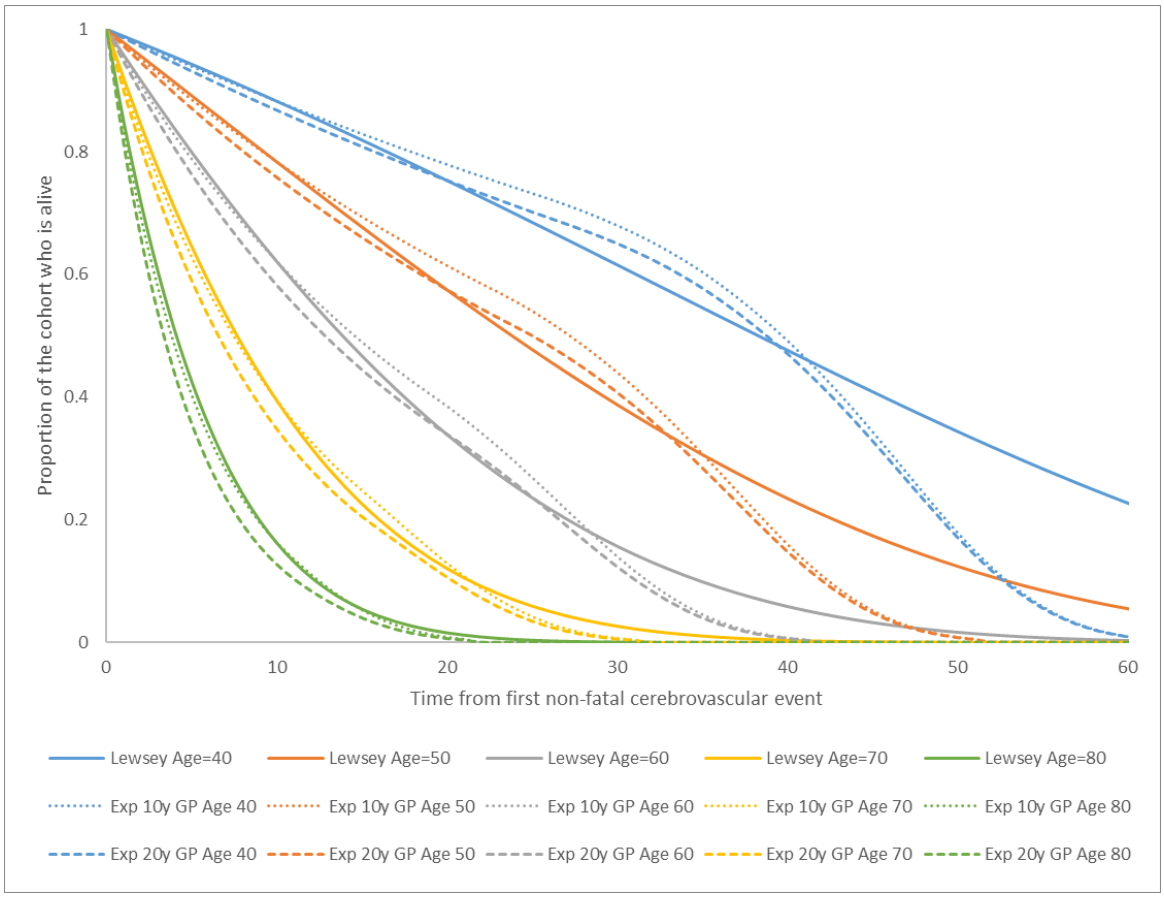


Figure 3: Comparison of predictions by the Lewsey et al [17] risk equation for time from first non-fatal coronary heart disease to death to equations using inferred hazard rate at 10 and at 20 years in males adjusted for general-population mortality; all given age at the event

Legend:

- Lewsey Age = 40, 50, 60, 70, 80: predictions using Lewsey et al equation if individuals had the coronary heart disease event at 40, 50, 60, 70 or 80 years of age.
- Exp 10y GP Age 40, 50, 60, 70, 80: predictions using a constant hazard rate inferred from the Lewsey et al rate at 10 years, constrained by the age- and sex-matched general population mortality, if individuals had the coronary heart disease event at 40, 50, 60, 70 or 80 years of age.
- Exp 20y GP Age 40, 50, 60, 70, 80: predictions using a constant hazard rate inferred from the Lewsey et al rate at 20 years, constrained by the age- and sex-matched general population mortality, if individuals had the coronary heart disease event at 40, 50, 60, 70 or 80 years of age.

Figure 4: Comparison of predictions by the Lewsey et al [17] risk equation for time from first non-fatal cerebrovascular disease event to death to equations using inferred hazard rate at 10 and at 20 years in males adjusted for general-population mortality; all given age at the event



Legend:

- Lewsey Age = 40, 50, 60, 70, 80: predictions using Lewsey et al equation if individuals had the cerebrovascular disease event at 40, 50, 60, 70 or 80 years of age.
- Exp 10y GP Age 40, 50, 60, 70, 80: predictions using a constant hazard rate inferred from the Lewsey et al rate at 10 years, constrained by the age- and sex-matched general population mortality, if individuals had the cerebrovascular disease event at 40, 50, 60, 70 or 80 years of age.
- Exp 20y GP Age 40, 50, 60, 70, 80: predictions using a constant hazard rate inferred from the Lewsey et al rate at 20 years, constrained by the age- and sex-matched general population mortality, if individuals had the cerebrovascular disease event at 40, 50, 60, 70 or 80 years of age.

Table 8: Probability of all-cause death following the 1st non-fatal cardiovascular event

Event at age	< 45 years	45 – 54 years	55 – 64 years	65 – 74 years	75+ years
After non-fatal acute coronary syndrome					
Males	0.018	0.039	0.082	0.168	0.328
Females	0.014	0.029	0.061	0.123	0.240
After non-fatal ischaemic stroke/ transient ischaemic attack					
Males	0.012	0.024	0.046	0.089	0.166
Females	0.011	0.022	0.044	0.087	0.167
Distribution for probabilistic sensitivity analysis: Multivariate normal for the risk from Lewsey equations [17].					

Other inputs

Table 9: Probability of non-cardiovascular death per annum by sex and age used in the cost-effectiveness model [18]

Age	Male	Female
Aged under 1	0.0038	0.0031
Aged 1 to 4	0.0001	0.0001
Aged 5 to 9	0.0001	0.0001
Aged 10-14	0.0001	0.0001
Aged 15-19	0.0003	0.0001
Aged 20-24	0.0004	0.0002
Aged 25-29	0.0005	0.0003
Aged 30-34	0.0007	0.0004
Aged 35-39	0.0009	0.0006
Aged 40-44	0.0012	0.0008
Aged 45-49	0.0016	0.0013
Aged 50-54	0.0021	0.0018
Aged 55-59	0.0029	0.0027
Aged 60-64	0.0047	0.0042
Aged 65-69	0.0078	0.0064
Aged 70-74	0.0122	0.0102
Aged 75-79	0.0221	0.0175
Aged 80-84	0.0384	0.0316
Aged 85-89	0.0940	0.0917
Fixed in the probabilistic sensitivity analysis		

Table 10: Distribution and unit costs of lipid lowering therapy

Type of lipid lowering therapy	Number of individuals	Unit cost	Drug used for costing
low statin	48	£0.79	Simvastatin 10 mg 28 tablets
low statin + non-statin	2	£2.65	Simvastatin 10 mg 28 tablets + ezetimibe 10 mg 28 tables
medium statin	609	£0.86	Atorvastatin 10 mg 28 tables
medium statin + non-statin	50	£2.72	Atorvastatin 10 mg 28 tablets + ezetimibe 10 mg 28 tables
high statin	562	£1.82	Atorvastatin 80 mg 28 tables
high statin + non-statin	159	£3.68	Atorvastatin 80 mg 28 tablets + ezetimibe 10 mg 28 tables
non-statin	12	£1.86	Ezetimibe 10 mg 28 tables
Source			
Source for the number of individuals: Analysis of CPRD cohort Source for the unit costs: Drug Tariff December 2019 [19] Distribution for the probabilistic sensitivity analysis: Dirichlet for distribution of individuals by lipid lowering treatment categories; unit costs fixed.			

Table 11: Monitoring pattern and costs in the base-case

Individual group	Number of appointments	Mean cost	Standard Error [1]
			Adults
Primary care Year 1: number of appointments (& lipid tests)	3.0	£137	£35
Primary care Year 2+: number of appointments (& lipid tests)	1.0	£35	£9
Secondary care Year 1: number of appointments (& lipid tests)	3.0	£556	£142
Secondary care Year 2+: number of appointments (& lipid tests)	1.0	£170	£43
Children and adolescents: not treated post diagnosis			
Year 1: number of appointments (& lipid tests)	1.0	£272	£69
Year 2: number of appointments (& lipid tests)	0.5	£112	£29
Children and adolescents: treated post diagnosis			
Year 1: number of appointments (& lipid tests)	3.0	£723	£184
Year 2: number of appointments (& lipid tests)	1.5	£336	£86
[1] Standard error calculated assuming that 95% CI correspond to +/- 50% mean. Distribution for the probabilistic sensitivity analysis: Gamma.			

Table 12: Unit costs to calculate the costs of blood tests

Item	Unit cost	First year of treatment	Subsequent years of treatment
Appointment with healthcare assistant to take blood	£7.05	1	1
Total cholesterol test	£1.09	1	1
High Density Lipoprotein cholesterol test	£1.09	1	1
Transaminase test	£1.09	1	0
HbA1c test	£2.46	1	1
Cost of blood test		£12.79	£11.70
Source: NICE CG181 [12], updated to 2019 prices [20,21]			

Table 13: Calculation of cost of appointments in secondary care

Type of appointment	**Clinical area**	**cost**	**Attendances**
Adults			
Non-Admitted Face-to-Face Attendance, First	Chemical pathology	£146	14281
Non-Admitted Face-to-Face Attendance, First	Endocrinology	£212	152584
Non-Admitted Face-to-Face Attendance, First	General medicine	£201	343385
Cost of first appointment; adults		**£203**	N/A
Non-Admitted Face-to-Face Attendance, Follow-up	Chemical Pathology	£130	38,098
Non-Admitted Face-to-Face Attendance, Follow-up	Endocrinology	£152	423,726
Non-Admitted Face-to-Face Attendance, Follow-up	General Medicine	£176	347,462
Non-Admitted Non-Face-to-Face Attendance, Follow-up	Chemical Pathology	£31	228
Non-Admitted Non-Face-to-Face Attendance, Follow-up	Endocrinology	£103	27,702
Non-Admitted Non-Face-to-Face Attendance, Follow-up	General Medicine	£135	8,983
Multiprofessional Non-Admitted Face-to-Face Attendance, Follow-up	Chemical Pathology	£173	497
Multiprofessional Non-Admitted Face-to-Face Attendance, Follow-up	Endocrinology	£140	12,333
Multiprofessional Non-Admitted Face-to-Face Attendance, Follow-up	General Medicine	£179	8,517
Multiprofessional Non-Admitted Non-Face-to-Face Attendance, Follow-up	Chemical Pathology	£26	1
Multiprofessional Non-Admitted Non-Face-to-Face Attendance, Follow-up	Endocrinology	£69	2,665
Multiprofessional Non-Admitted Non-Face-to-Face Attendance, Follow-up	General Medicine	£63	122
Non-Admitted Face-to-Face Attendance, Follow-up	Chemical Pathology	£130	38,098
Cost of follow-up appointments; adults		**£159**	N/A
Children			
Non-Admitted Face-to-Face Attendance, First, consultant led	General paediatrics	£259	620,218
Non-Admitted Face-to-Face Attendance, First, consultant led	Paediatric metabolic	£796	1516

	disease		
Cost of first appointment; children		£260	N/A
Non-Admitted Face-to-Face Attendance, Follow-up	General paediatrics	£211	689,355
Non-Admitted Face-to-Face Attendance, Follow-up	Paediatric metabolic disease	£407	11,832
Non-Admitted Non-Face-to-Face Attendance, Follow-up	General paediatrics	£123	22,440
Non-Admitted Non-Face-to-Face Attendance, Follow-up	Paediatric metabolic disease	£481	15
Multiprofessional Non-Admitted Face-to-Face Attendance, Follow-up	General paediatrics	£220	25,569
Multiprofessional Non-Admitted Face-to-Face Attendance, Follow-up	Paediatric metabolic disease	£417	1,472
Multiprofessional Non-Admitted Non-Face-to-Face Attendance, Follow-up	General paediatrics	£110	58
Multiprofessional Non-Admitted Non-Face-to-Face Attendance, Follow-up	Paediatric metabolic disease	N/A	0
Cost of follow-up appointments; children		**£212**	N/A
Source: NHS Reference Costs 2019 [21]			

Table 14: Unit costs to calculate the costs of blood tests

Item	Unit cost	Source
Appointment with general practitioner	£33	NICE CG181 [12], updated to 2019 prices [20,21]
Appointment with nurse	£14	PSSRU unit cost book [20] band 6 staff, page 125, £84 per individual-related work; 10-minute appointment

Table 15: Calculations of the cost of health states

Item	Original cost	Cost per year	Inflated to 2019
Non-fatal myocardial infarction (assumed equivalent to non-fatal acute coronary syndrome)			
first 90-day period	4854	7378 [1]	8195
second 90-day period	1209		
third 90-day period	640		
fourth 90-day period	675		
subsequent periods	481	1924 [2]	2137
Non-fatal ischaemic stroke (assumed equivalent to non-fatal ischaemic stroke and transient ischaemic attack)			
first 90-day period	5957	8322 [1]	9244
second 90-day period	1151		
third 90-day period	675		
fourth 90-day period	539		
subsequent periods	448	1792 [2]	1990
Fatal cardiovascular event			

One-off cost	2071	N/A	2300
Death (not related to cardiovascular event)			
One-off cost	1737	N/A	1929
[1] Cost in the first year calculated as the sum of the costs in the first four 90-day periods. [2] Cost in subsequent years calculated as the cost of subsequent (90-day periods) multiplied by 4. Source of original costs is Walker et al [22], inflated to 2019 [20] Distribution for the probabilistic sensitivity analysis: Gamma.			

Table 16: Calculations for health-related quality of life weights post-event

Health state	Original mean value	Original standard error	Proportion of cases in CPRD cohort	Used in the model
Post-first non-fatal acute coronary syndrome				
Unstable angina (year 1)	0.77	0.038	15 (45%)	0.76
Myocardial infarction (year 1)	0.76	0.018	18 (55%)	
Post-unstable angina (year 2+)	0.88	0.018	15 (45%)	0.88
Post-myocardial infarction (year 2+)	0.88	0.018	18 (55%)	
Post-first non-fatal ischaemic stroke or transient ischaemic attack				
Stroke	0.63	0.04	23 (76%)	0.72
Transient ischaemic attack	0.90	0.025	12 (34%	
Source of the original values is the NICE CG181 [12]. Values used in the model are the weighted average of the original values weighted with the relative proportion of cases in the CPRD cohort. Distribution for the probabilistic sensitivity analysis: Beta.				

Scenario analysis

List of scenario analyses

Table 17: Scenario analyses

Base-case	Scenario	Justification for scenario analysis
Scenarios on the effect of FH diagnosis on health outcomes		
FH diagnosis reduces LDLC proportionally as observed before and after diagnosis in the entire CPRD cohort.	1. FH diagnosis reduces LDLC by 50% in line with the NICE CG71 target [6].	The LDLC reduction observed in the CPRD cohort may not reflect the effect of FH diagnosis via cascade testing given the observational nature of the data and because it reflects past practice in primary care.
	2. FH diagnosis reduces LDLC to the EAS targets of 3.5 mmol/L in children and adolescents, 1.8 mmol/L in adults in primary prevention and 1.4 mmol/L in adults in secondary prevention [23].	
	3. FH diagnosis reduces LDLC by 40%, which is 80% of the NICE CG71 target [6].	To reflect discontinuation and adherence in clinical practice.
	4. FH diagnosis reduces LDLC depending on PT-LDLC, from 5% in those with PT-LDLC 1 mol/L to 40% in those with PT-LDLC = 8 mmol/L, in 5% increments.	Individuals may be treated more or less intensively depending on their pre-treatment LDLC, which will result in different proportional reductions in LDLC due to FH diagnosis. Additionally, data from general population suggests that the proportional reduction is greater in patients with greater PT-LDLC [24].
Lower LDLC reduces the risk of non-CV death as estimated by the 2019 CTTC meta-analysis [16]	5. Lower LDLC does not affect the risk of non-CV death.	The CTTC estimates are not statistically significant [16], hence are uncertain, and may not generalise to the FH population.
Individuals have the health benefits and costs of FH diagnosis and treatment, irrespective of their pre-treatment LDLC.	6. Diagnosed individuals have no benefits and no costs of treatment if their pre-treatment LDLC < EAS target of 1.8 mmol/L in adults in primary prevention and 1.4 mmol/L in adults in secondary prevention [23].	Individuals with low pre-treatment LDLC may not be started on LLT, but the treatment thresholds in clinical practice are unclear.
	7. Diagnosed individuals have no benefits and no costs of treatment if their pre-treatment LDLC < 3 mmol/L for primary prevention and < 2 mmol/L for secondary prevention.	
LDLC burden included as estimated by the EAS relationship; that is, the effect of LDLC on CV risk increases over time.	8. LDLC burden is not included, and the effect of LDLC on CV risk is obtained from the relationship estimated by the CTTC meta-analysis [16]: rate ratio = 0.79 for major vascular events per 1 mmol/L LDLC reduction.	The LDLC effect size is uncertain, with the estimate of the effect of LDLC reductions on CV risk from the CTTC meta-analysis being a conservative estimate [16].
	9. The effect of LDLC reduction on CV event risk is greater that what was estimated in the CTTC relationship (30% vs 21%) [16].	The CTTC relationship may not reflect the reduction in risk in individuals with FH.
	10. The CTTC relationship [16] holds up to a maximum pre-treatment	It is uncertain whether the CTTC relationship holds in

Base-case	Scenario	Justification for scenario analysis
	LDLC of 6 mmol/L and beyond this threshold the effect of greater LDLC reductions the effect is the same.	individuals with high pre-treatment LDLC, as they were underrepresented in the primary studies.
FH diagnosis does not affect the risk of all-cause death over and above the effect via the reduction of LDLC.	11. FH diagnosis reduces the risk of non-CV death (prior to a 1st CV event) by 1% (hazard ratio = 0.99).	Once diagnosed, individuals with FH may adopt healthier lifestyles, which may reduce the risk of death via mechanisms other than LDLC reduction.
Children who are diagnosed with FH are treated with LLT from 10 years of age.	12. Individuals who are diagnosed with FH are treated with LLT from 18 years of age.	Although the NICE CG71 and the Heart UK consensus statement recommend treatment from 10 years of age [6,25], some individuals and families may prefer to defer starting LLT until adulthood.
Prior FH diagnosis and treatment has no effect on the risk of death after the first-non-fatal CV event.	13. Prior FH diagnosis and treatment reduces LDLC after the first non-fatal CV event by 50%, in line with the NICE CG181 [12], while individuals who did not have a prior diagnosis have the base-case risk of death (calculated from the Lewsey equations).	Individuals who have a prior diagnosis of FH who have a first non-fatal CV event may be treated more intensely than individuals who have not been diagnosed, despite the NICE target for secondary prevention for individuals with and without FH being the same at 50% LDLC reduction.
	14. Prior FH diagnosis and treatment reduces LDLC after the first non-fatal CV event to the EAS target of 1.4 mmol/L. [23], while individuals who did not have a prior diagnosis have the base-case risk of death (calculated from the Lewsey equations).	
LLT, and specifically statins, cause earlier onset of cases of diabetes type 2, which is reflected in additional costs.	15. In addition to causing earlier onset of cases of diabetes type 2, statins cause additional cases of diabetes, with implications for costs and quality-adjusted life expectancy as per the scenario in the cost-effectiveness analysis informing NICE CG181 [12], updated to 2019 [20,21].	We follow the assumptions made for the base-case and scenario analysis of NICE CG181 for adverse effects of LLT [12].
Scenarios on the risk of the first CV event		
Individuals are at risk of CV events, hence experience the benefits of treatment, from 25 years of age.	16. Individuals are at risk of CV events from age 35, as per Perak et al [15].	There is uncertainty in the age when individuals with FH are at risk of CV events. Perak et al suggests that individuals are at little risk from CV events until 35 years of age, hence we test this age in a scenario [15].
The generalised gamma risk equation informs the risk of the first CV event	17. The exponential model informs the risk of CV events.	Although the best fitting model is the generalised gamma, the exponential model was considered a realistic alternative for long-term extrapolation as the generalized gamma predicted reductions in risk over time.
The risk of the first CV event in the long-term is based on the risk equations	18. The risk of the first CV event after 10 years is based on the risk equations estimated from the CPRD cohort, without the upwards	There is uncertainty in the risk beyond 10 years, with the estimates obtained from the CPRD cohort (without

Base-case	Scenario	Justification for scenario analysis
estimated from the CPRD cohort, adjusted upwards with hazard ratios calculated from Perak et al [15].	adjustment.	adjustment) being a conservative estimate.
	19. The risk of the first CV event is adjusted upwards with the standardised mortality ratio obtained from comparing the Simon Broome cohort with the general population mortality risk, and assuming that this ratio can be applied to the hazard rate [26].	There is uncertainty in whether the risk observed in the CPRD cohort represents the risk of individuals with FH in the long-term. The adjustment with the Simon Broome standardised mortality ratio represents a worst-case scenario.
The probability of death due to the first CV event is the observed probability in the CPRD cohort irrespective of age at the event.	20. The probability of death due to the first CV event depends on age: lower for younger ages and larger for older ages, as inferred from the probability of death following acute myocardial infarction in the general population [27].	The probability of death due to the first CV event may not be independent from age at the event, but the number of events in the CPRD cohort is insufficient to inform age-dependent probabilities.
To estimate the counterfactual risk of death after the first non-fatal CV event, we assume that individuals in Lewsey et al [17] had the same LDLC reduction as the CPRD cohort before and after diagnosis.	21. Doubling the risk of death post-first non-fatal CV event compared to the base-case.	To account for the increased risk of individuals with FH.
The hazard rate for death after the first non-fatal CV event at 10-years is generalisable to the entire time horizon.	22. The hazard rate for death after the first non-fatal CV event at 20-years is generalisable to the entire time horizon.	The hazard rate at 10 years may not be generalisable to the entire time horizon.
Scenarios on costs		
Children are monitored from diagnosis.	23. Individuals are monitored only from 10 years of age.	Following the Heart UK consensus statement[25], we assumed that children are monitored from diagnosis in the base-case. However, some clinicians may choose to start monitoring when LLT is started, at 10 years of age.
Individuals diagnosed with FH and are treated have 3 monitoring appointments in the first year after treatment initiation, then 1 appointment per year thereafter if adults or 1.5 if children and adolescents.	24. Low intensity monitoring: 2 appointments in the first year after treatment initiation, then 0.75 appointments per year if adults or 1 appointment per year if children and adolescents. Children and adolescents who are not treated have 1 appointment (and 1 lipid test) in the year of diagnosis and none thereafter until treatment.	Given the variation in the frequency of monitoring across the country, we present a low-intensity and a high-intensity monitoring scenario.
Children and adolescents who are not treated have 1 monitoring appointment in the year of diagnosis and 1 appointment every other year subsequently until treatment.	25. High intensity monitoring: individuals have 3 appointments (and lipid tests) in the first year after treatment initiation, then 1.2 appointments per year if adults or 2 appointments per year if children and adolescents. Children and adolescents who are not treated have 1 appointment (and 1 lipid test) every year until treatment.	
75% of adult individuals who are diagnosed	26. 50% of adult individuals who are diagnosed with FH are	We assumed that 75% of adult individuals who are diagnosed

Base-case	Scenario	Justification for scenario analysis
with FH are monitored in primary care.	monitored in primary care.	with FH are monitored in primary care as per Pears et al regarding the Wessex FH service [28], but there is variability across the country.
The costs of care post-CV events are generalisable from individuals with stable coronary artery disease (Walker, 2016) to individuals with FH.	27. The costs are generalisable from the NICE CG181 [12], updated to 2019 [20,21].	The Walker et al costs may not be generalisable to FH individuals. The NICE CG181 are an alternative, given that they were validated by the guideline development group (albeit for the general population rather than not specifically individuals with FH) [12] .
The costs of care post-CV events are constant over time.	28. Increased costs of care (by 25%) to account for the increased risk of recurrent events compared to the general population.	The Walker et al [22]costs may not reflect the long-term risk of recurrent events experienced by FH individuals compared to individuals with stable coronary artery disease after a first CV event. Nanchen et al, which compared the hazard rates of recurrent events of individuals with and without FH following an ACS, reports hazard ratios of 2.46-3.53 depending on the definition of FH [29].
Scenarios on health-related quality of life		
We obtain health-related quality of life weights for the health states from the NICE CG181.	29. We obtain the weights from Ara et al, given that these were used for TA393 [13,30].	The base-case uses the HRQoL used in the NICE CG181 (and CG71) analysis [6,12], given that these values were validated in NICE Committees and is consistent with the approach used for the non-FH individuals. Ara et al is an alternative, given that it was based on UK general population EQ-5D data [30].
CG71: Clinical Guideline 71. CG181: Clinical Guideline 181. CPRD: Clinical Practice Research Datalink. CTTC: Cholesterol Treatment Trialists' Collaboration. CV: Cardiovascular. EAS: European Atherosclerosis Society. FH: Familial Hypercholesterolaemia. LDLC: Low Density Lipoprotein Cholesterol. LLT: Lipid Lowering Treatment. NICE: National Institute for Health and Care Excellence. TA393: Technology Appraisal 393.		

Model inputs for scenario analyses

Table 18: Model inputs for scenario 15: including the costs and QALY consequences related to new cases of type 2 diabetes caused by statins, obtained from NICE CG181 updated to 2019

Analysis	**Input**
Costs in primary prevention, per individual started on lipid lowering treatment	
Years 3 to 6 from treatment initiation	£4.60
Years 7 to 11 from treatment initiation	£2.05
Years 13+ from treatment initiation	£5.24
Costs in secondary prevention, per individual started on lipid lowering treatment	
Years 3 to 6 from treatment initiation	£9.19
Years 7 to 11 from treatment initiation	£4.11
Years 13+ from treatment initiation	£10.49
QALY losses, per individual started on lipid lowering treatment	
Primary prevention, all years	-0.0001
Secondary prevention, all years	-0.0002
Source: NICE CG181 [12], updated to 2019 [20,21].	

Table 19: Model inputs for scenario 19: The risk of the first CV event is adjusted upwards with the standardised mortality ratio

Individual group	**Input**
Males	
Aged 40-59 years	5.47
Aged 60+ years	5.20
Females	
Aged 40-59 years	8.58
Aged 60+ years	8.46
Source: Humphries et al [26].	

Table 20: Model inputs for scenario 20: The probability of death due to the first CV event depends on age

Age at 1st cardiovascular event	**Change from base-case in %**
Males	
Age < 45 years	-0.62
Age 45-54 years	-0.47
Age 55 – 64 years	0.00
Age 65 – 74 years	1.00
Age 75+ years	2.89
Females	
Age < 45 years	-0.42

Age 45-54 years	-0.35
Age 55 – 64 years	0.00
Age 65 – 74 years	0.92
Age 75+ years	2.44
Source: Calculated from the proportion of admissions for myocardial infarction which resulted in death within 28 days from Asaria et al [27]., as the relative change compared to proportion of deaths in age 55-64 years, given that the average age at the 1st major cardiovascular event in the CPRD cohort was 57 years in males and 64 years in females.	

Table 21: Model inputs for scenario 24: low-intensity monitoring

Individual group	**Number of appointments**	**Cost**
Adults		
Primary care Year 1: number of appointments (& lipid tests)	2.0	£92
Primary care Year 2+: number of appointments (& lipid tests)	0.8	£26
Secondary care Year 1: number of appointments (& lipid tests)	2.0	£386
Secondary care Year 2+: number of appointments (& lipid tests)	0.8	£128
Children and adolescents: not treated post diagnosis		
Year 1: number of appointments (& lipid tests)	1.0	£272
Year 2: number of appointments (& lipid tests)	0.0	£0
Children and adolescents: treated post diagnosis		
Year 1: number of appointments (& lipid tests)	2.0	£498
Year 2: number of appointments (& lipid tests)	1.0	£224

Table 22: Model inputs for scenario 25: high-intensity monitoring

Individual group	**Number of appointments**	**Cost**
Adults		
Primary care Year 1: number of appointments (& lipid tests)	3.0	£137
Primary care Year 2+: number of appointments (& lipid tests)	1.2	£42
Secondary care Year 1: number of appointments (& lipid tests)	3.0	£556
Secondary care Year 2+: number of appointments (& lipid tests)	1.2	£204
Children and adolescents: not treated post diagnosis		
Year 1: number of appointments (& lipid tests)	1.0	£272
Year 2: number of appointments (& lipid tests)	1.0	£224
Children and adolescents: treated post diagnosis		
Year 1: number of appointments (& lipid tests)	3.0	£723
Year 2: number of appointments (& lipid tests)	2.0	£448

Table 23: Model inputs for scenario 27: costs obtained from the NICE CG181

Health state	Cost (per annum)
Non-fatal ACS year 1	£3791
Non-fatal ACS year 2 and beyond	£860
Non-fatal IS/TIA year 1	£3054
Non-fatal IS/TIA year 2 and beyond	£249
CV death	£1058
ACS: Acute Coronary Syndrome; CV: Cardiovascular; IS: Ischaemic Stroke; NICE: National Institute for Health and Care Excellence; TIA: Transient Ischaemic Attack. To calculate these costs, we recalculated the costs as per the NICE CG181 model [12], updated to 2019 [20,21], and calculated the weighted average of the costs of myocardial infarction and unstable angina, and of ischaemic stroke and transient ischaemic attack based on the proportions in the CPRD cohort.	

Table 24: Model inputs for scenario 28: Increased costs of recurrent events

Health state	Cost (per annum)
Non-fatal ACS year 1	£10,244
Non-fatal ACS year 2 and beyond	£4,186
Non-fatal IS/TIA year 1	£11,554
Non-fatal IS/TIA year 2 and beyond	£4,301
CV death	£2300 (=base-case)
Non-CV death	£1929 (=base-case)
Any death: average of CV and non-CV death	£2115 (=base-case)
ACS: Acute Coronary Syndrome; CV: Cardiovascular; FH: Familial Hypercholesterolaemia; IS: Ischaemic Stroke; NICE: National Institute for Health and Care Excellence; TIA: Transient Ischaemic Attack.	

Table 25: Model inputs for scenario 29, in which the health-related quality of life weights are obtained from Ara et al [13,30].

Health state	Input
Non-fatal ACS year 1	0.72
Non-fatal ACS year 2 and beyond	0.74
Non-fatal IS/TIA year 1	0.63
Non-fatal IS/TIA year 2 and beyond	0.67
ACS: Acute Coronary Syndrome; IS: Ischaemic Stroke; TIA: Transient Ischaemic Attack.	

Validation

Advishe checklist [31]

Table 26: Advishe checklist for the cost-effectiveness model on the long-term health outcomes and costs of individuals with FH

Question	Answer
Part A: Validation of the conceptual model	
A1: Have experts been asked to judge the appropriateness of the conceptual model?	Yes, the stakeholder group agreed that the conceptual model was appropriate.
A2: Has this model been compared to other conceptual models found in the literature or clinical textbook?	Yes, we compared our conceptual model to other models in the literature. This is reported under Model structure.
Part B: Input data validation	
B1: Have experts been asked to judge the appropriateness of the input data?	Yes, the same experts as in A1 reviewed the input data. The experts agreed that the appropriate data was used.
B2: When input parameters are based on regression models, have statistical tests been performed?	Yes, the statistical tests are reported in Section 11.2.
Part C: Validation of the computerised model	
C1: Has the computerised model been examined by modelling experts?	Yes, the computerised model was examined by Beth Woods. BW is not an independent expert as she supervised the development of the cost-effectiveness model and collaborated in all economic analyses. This verification identified issues around the implementation of scenarios on the effect of diagnosis on LDLC reductions, on the calculation of the number of deaths, on the calculation of the hazard rate for 1st major CV event, the calculation of costs for the scenario accounting for recurrent events and in the calculation of costs of monitoring. These issues were addressed prior to conducting the tests reported in the TECH-VER checklist.
C2: Has the model been run for specific, extreme sets of parameter values in order to detect any coding errors?	Yes, the tests are reported in the TECH-VER checklist below.
C3: Have individuals been tracked through the model to determine whether its logic is correct?	Yes, the individuals were tracked through the model at various ages.
C4: Have individual submodules of the computerised model been tested?	Yes, the model trace was tested independently from the model macros. The model is functioning as expected.
Part D: Operational validation	
D1: Have experts been asked to judge the appropriateness of the model outcomes?	Yes, the stakeholder group reviewed the predictions of the model for individuals diagnosed with FH and agreed that these had face validity.
D2: Have the model outcomes been compared to the outcomes of other models that address similar problems?	Yes, this is reported in the discussion.
D3: Have the model outcomes been compared to the outcomes obtained when using alternative input data?	Yes, via the scenario analysis (e.g. using alternative costs for health states, alternative source of health-related quality of life)
D4: Have the model outcomes been compared to empirical data?	Yes, by comparing the outcomes of the model for two individual profiles to the outcomes predicted by the risk equations estimated from the CPRD data.

Part E: Other validation techniques	
E1: Have any other validation techniques been performed?	No.
Advishe: Assessment of the Validation Status of Health-Economic decision models. CV: Cardiovascular. CPRD: Clinical Practice Research Datalink. LDLC: Low Density Lipoprotein Cholesterol. TECH-VER: TECHnical VERification checklist.	

TECH-VER checklist [32]

Table 27: TECH-VER checklist

Test description	**Expected result**	**Result**
Pre-analysis calculations		
Does the technology (drug/device, etc.) acquisition cost increase with higher prices?	Yes	Yes. Tested by increasing the unit cost of LLT drugs. The cost of LLT increased.
Does the probability of an event, derived from an OR/RR/HR and baseline probability, increase with higher OR/RR/HR?	Yes	Yes. Tested in scenarios 8-10. When LDLC burden is not considered, and the CTTC relationship is used to inform the effect of LDLC reductions in CV risk, the counterfactual CV risk in undiagnosed/untreated individuals increases.
Additional check not in TECH-VER: Do the survival model predictions in Excel match those obtained from R?	Yes	Yes, tested for 2 individual profiles.
Event-state calculations		
The sum of the number of individuals at each health state should add up to the cohort size	Yes	Yes. Calculated in the trace.
Check if all probabilities and number of individuals in a state are greater than or equal to 0	Yes	Yes. Calculated in the trace.
Check if all probabilities are smaller than or equal to 1	Yes	Yes. Observed in the trace.
Are the number of dead individuals in the previous period smaller than the number of dead individuals in the subsequent period	Yes	Yes. Calculated in the trace.
In case of lifetime horizon, check if all individuals are dead at the end of the time horizon	Yes	Yes. Calculated in the trace.
Are the QALYs equal to the life years if the utilities are set to 1?	Yes	Yes. Tested by setting the baseline utility = 1 and the utility related to post-events to zero.
Are the QALYs equal to zero if the utilities are set to zero?	Yes	Yes. Tested by setting the baseline utility = 0.
If state utilities are lower, are QALYs lower?	Yes	Yes. Tested by setting the utility related to post-events to a lower value.
Are costs zero if all costs are set to zero?	Yes	Yes. Tested by setting all costs to zero.
If mortality risk is set to zero, do individuals die?	No	No. Tested by setting the mortality risk to zero.
If mortality risk is set to 1, do all individuals die in the first cycle?	Yes	Yes. Tested by changing the transition probability to death in cycle 1 to 1.
If all decision options have the same effectiveness, are life years and QALYs the same?	Yes	Yes. Tested by changing the reduction of LDLC due to diagnosis to zero.

If all decision options have the same effectiveness and costs, are all results the same?	Yes	Yes. Tested by changing the reduction of LDLC due to diagnosis to zero and setting costs of monitoring, treatment and adverse effects to zero.
Is the number of individuals alive in the model, the same or lower as in the general population?	Yes	Yes, if individuals are not diagnosed and treated. The number of individuals alive in the model and the QALYs are similar to the general population if individuals are treated.
Is the QALY at each cycle, the same or lower than the general population?	Yes	
If the inflation rate is higher, are the costs which are based on a reference from previous years higher too?	Yes	Yes. Tested by increasing the inflation factor of 2018/19.
Is the sum of all ingoing and outgoing transition probabilities in a state in a given cycle the same as the change in number of individuals?	Yes	Yes. Tested in the well state.
Are the number of individuals entering a tunnel state the same as the number of individuals leaving the tunnel state?	Yes	Yes. Tested in the trace.
If the treatment acquisition cost is greater, are the costs greater?	Yes	Yes. Tested by increasing the costs of LLT.
Are the time conversions for probabilities conducted correctly?	Yes	Not applicable as cycle is annual.
Result calculations		
Do the more effective decision options yield greater QALYs and life years?	Yes	Yes. Tested in scenario 1.
Do the more costly decision options yield greater treatment costs?	Yes	Yes. Tested in scenario 25.
Are the total life years greater than the total QALYs?	Yes	Yes. Observed in the results
Are the undiscounted results greater than the discounted results?	Yes	Yes. Observed in the results
Is the ratio of the undiscounted total QALYs to the undiscounted total life years within the max and min of the utility inputs?	Yes	Yes. Calculated.
Subgroup analysis results: Do subgroups with better baseline health have better outcomes?	Yes	Yes. Observed in the results.
Do the disaggregated results sum to the total results?	Yes	Yes. Observed in the results.
Are the life years with half-cycle correction lower than the life years without?	Yes	Not calculated because life-years without half-cycle correction not recorded.
Are the discounted results equal to undiscounted if the discount rate is set to zero?	Yes	Yes. Observed in the results.
If discount rates are higher, are the discounted results smaller?	Yes	Yes. Observed in the results.
Is the ratio of the total undiscounted treatment cost to the average duration of treatment similar to the treatment-related unit acquisition cost?	Yes	No, it is lower. This is likely because the treatment-related costs are only recorded in the well state, and the proportion of people in the well state reduces over time.
If the effect of the decision option is doubled, is the incremental effect approximately doubled?	Yes	Yes. Calculated.

Uncertainty analysis		
Are all necessary parameters subject to uncertainty included in the OWSA?	Yes	Not applicable as OWSA not conducted
Does the OWSA include any parameters associated with joint uncertainty?	Yes	
Are the upper and lower bounds used in the one-way sensitivity analysis using confidence intervals based on the statistical distribution assumed for that parameter?	Yes	
Are the resulting ICER, incremental costs/QALYs with upper and lower bound of a parameter plausible and in line with a priori expectations?	Yes	
Do all parameters used in the sensitivity analysis have appropriate associated distributions – upper and lower bounds should surround the deterministic value (i.e. upper bound ≥ mean ≥ lower bound)	Yes	
Standard error and not standard deviation used in sampling	Yes	Yes, checked.
Lognormal/gamma distribution for HRs and costs/resource use	Yes	Yes, checked.
Beta for utilities and proportions/probabilities	Yes	Yes, checked.
Dirichlet for multinomial	Yes	Yes, checked.
Multivariate normal for correlated inputs	Yes	Yes, checked.
Normal for other variables as long as samples do not violate the requirement to remain positive when appropriate	Yes	Yes: lognormal for rate ratios.
Check PSA output mean costs, QALYs, and ICER compared with the deterministic results. Is there a large discrepancy?	No	No. Observed in the results.
If you take new PSA runs from the Microsoft Excel model do you get similar results?	Yes	Yes.
Is(are) the CEAC line(s) in line with the CE scatter plots and the efficient frontier?	Yes	Yes, in line with the scatter plots. Not compared with the efficiency frontier.
Does the PSA cloud demonstrate an unexpected behaviour or have an unusual shape?	No	No
Is the sum of all CEAC lines equal to 1 for all WTP values?	Yes	Not calculated as only two comparators.
Do the explored scenario analyses provide a balanced view on the structural uncertainty (i.e. not always looking at more optimistic scenarios)?	Yes	Yes.
Are the scenario analysis results plausible and in line with a priori expectations?	Yes	Yes.
Check the correlation between two PSA results (i.e. costs/QALYs under the SoC and costs/QALYs under the comparator). Should be very low (very high) if different (same) random streams are used for different arms	High	Correlation is close to 1 as same random streams are used for each arm.
If a certain seed is used for random number generation (or previously generated random numbers	Yes	Not applicable as seed not used.

are used), check if they are scattered evenly between 0 and 1 when they are plotted		
Is the mean of the parameter samples generated by the model similar to the point estimate for that parameter? Use graphical methods to examine distributions, functions	Yes	Not conducted due to time constraints.
Do sensitivity analyses include any parameters associated with methodological/structural uncertainty?	Yes	E.g. Whether effect of LDLC reduction depends on duration of reduction.
Value of information analysis if applicable: Was this implemented correctly?	Yes	Yes, checked.
Which types of analysis?		EVPI only.
Is EVPI larger than all individual EVPPIs?	Yes	Not applicable as only EVPI calculated as EVPI low.
Is EVPPI for a (group of) parameters larger than the EVSI of that (group) of parameter(s)?	Yes	
Are the results from EVPPI in line with OWSA or other parameter importance analysis (e.g. ANCOVA)?	Yes	
Did the electronic model pass the black-box tests of the previous verification stages in all PSA iterations and in all scenario analysis settings?	Yes	Not conducted due to time constraints.
Check if all sampled input parameters in the PSA are correctly linked to the corresponding event/state calculations	Yes	Yes, via input sheet.

Advishe: Assessment of the Validation Status of Health-Economic decision models. CEAC: Cost-Effectiveness Acceptability Curve. CPRD: Clinical Practice Research Datalink. CTTC: Cholesterol Treatment Trialists' Collaboration. CV: Cardiovascular. EVPI: Expected Value of Perfect Information. EVPPI: Expected Value of Perfect Parameter Information. EVSI: Expected Value of Sample Information. HR: Hazard Ratio. ICER: Incremental Cost-Effectiveness Ratio. LDLC: Low Density Lipoprotein Cholesterol. LLT: Lipid Lowering Treatment. OR: Odds Ratio.

OWSA: One-Way Sensitivity Analysis. PSA: Probabilistic Sensitivity Analysis. QALYs: Quality-Adjusted Life Years. RR: Risk Ratio. SoC: Standard of Care. TECH-VER: TECHnical VERification checklist. WTP: Willingness To Pay

Results

Impact of diagnosis on health outcomes

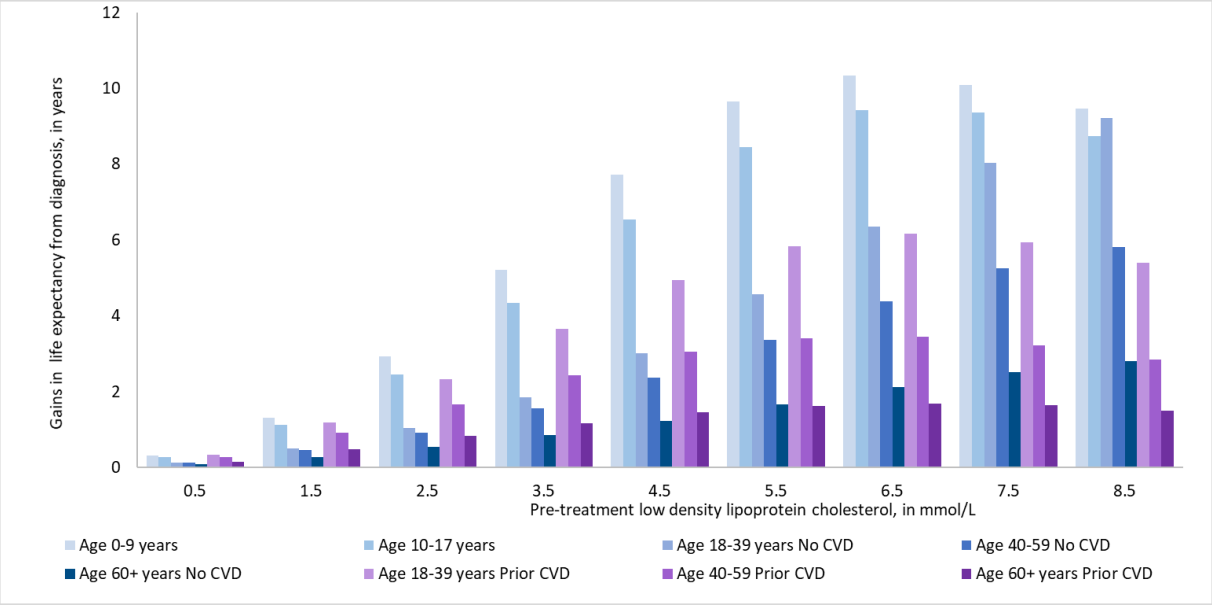


Figure 5A: Gains in life expectancy due to diagnosis in males

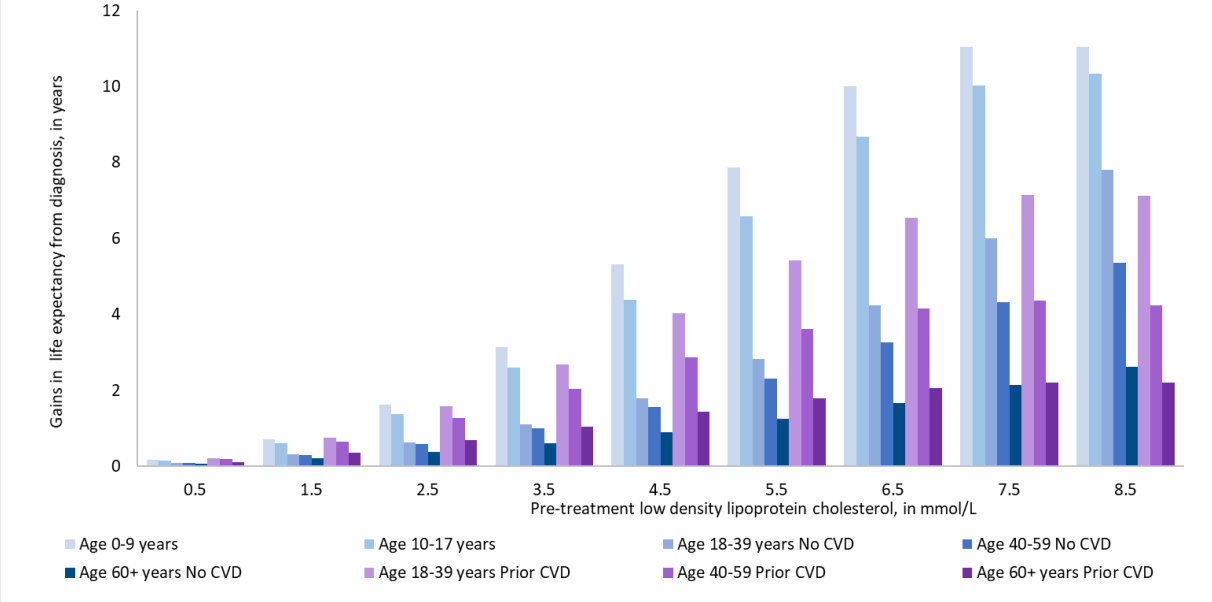


Figure 5B: Gains in life expectancy due to diagnosis in females

Figure 5: Gains in life expectancy due to diagnosis (undiscounted)

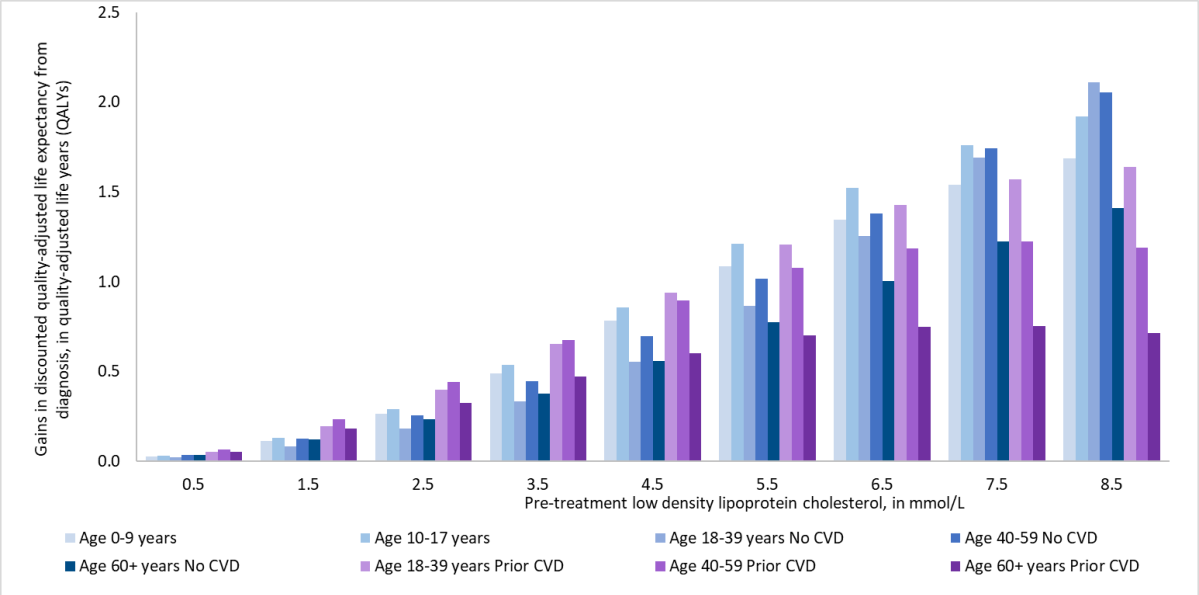


Figure 6A: Gains in quality-adjusted life expectancy (discounted) in males

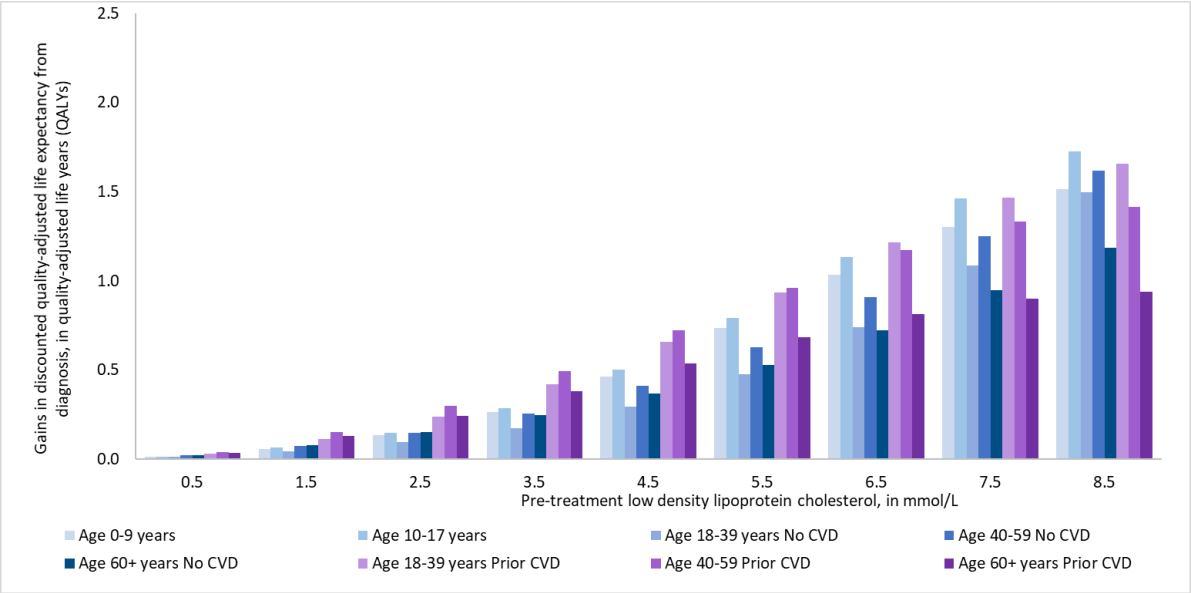


Figure 6B: Gains in quality-adjusted life expectancy (discounted) in females

Figure 6: Gains in quality-adjusted life expectancy (discounted)

Impact of diagnosis on costs

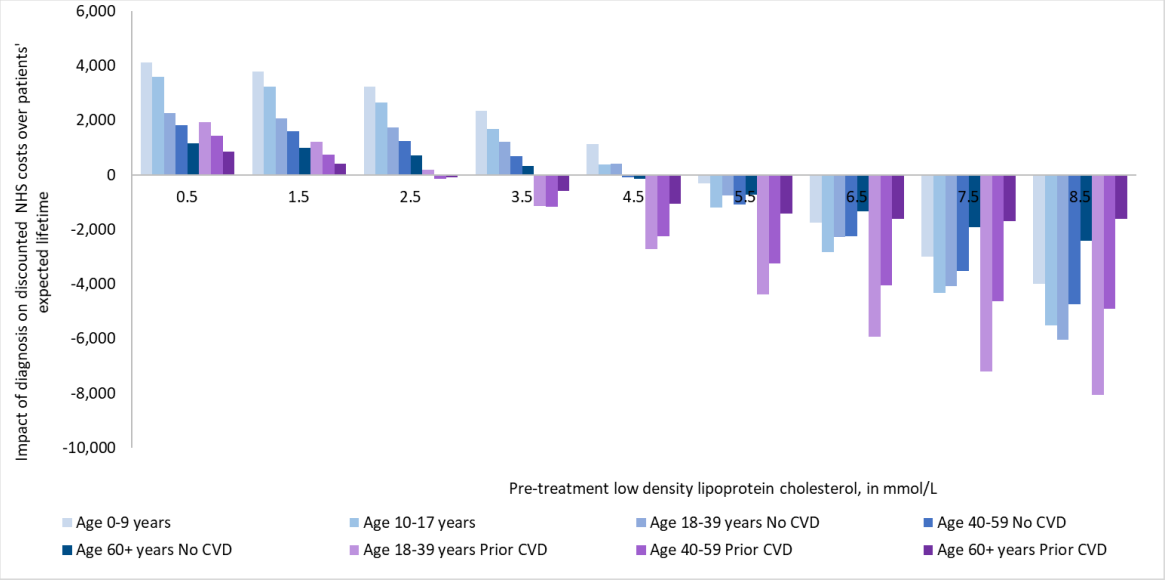


Figure 7A: Impact of diagnosis on discounted costs in males

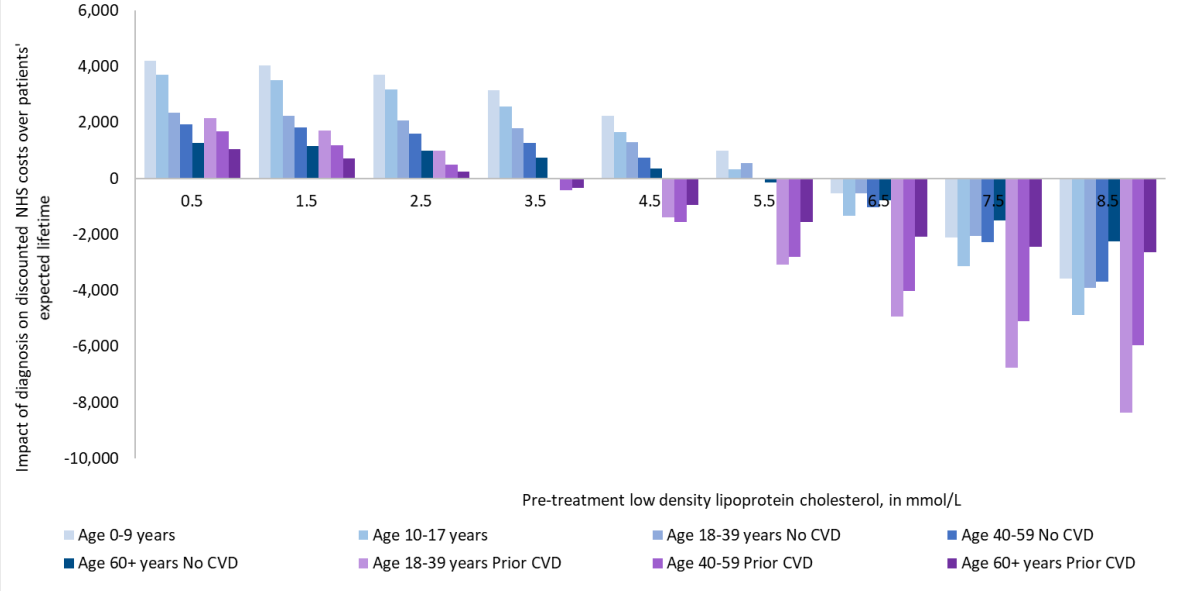


Figure 7B: Impact of diagnosis on discounted costs in females

Figure 7: Impact of diagnosis on discounted costs

Impact of diagnosis on net health gain

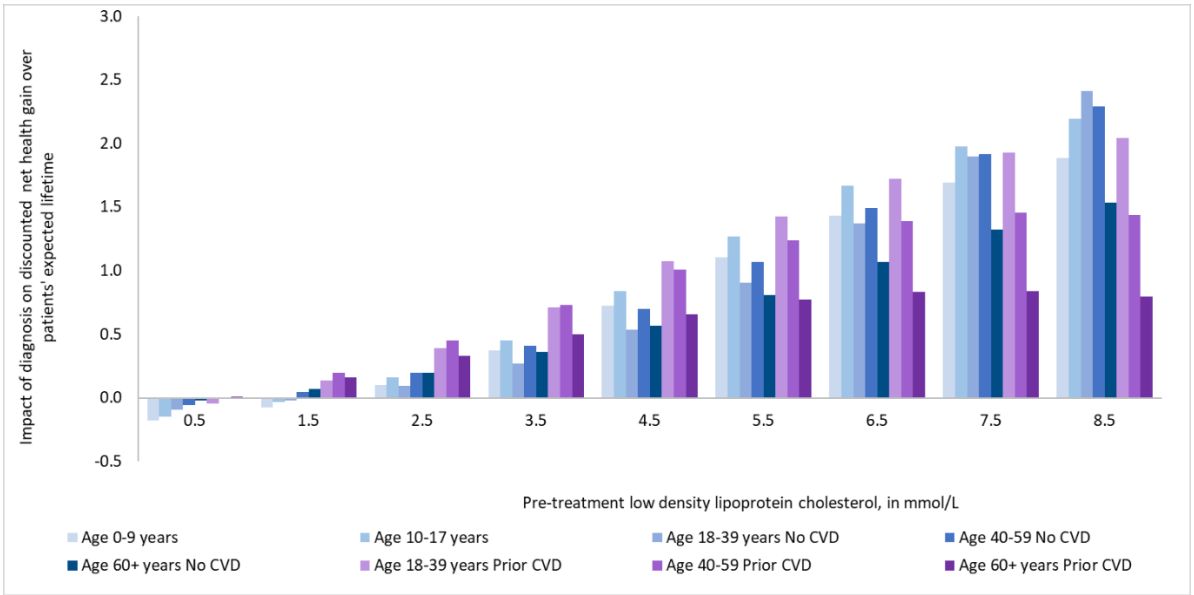


Figure 8A: Impact of diagnosis on net health gain at the £20,000/QALY threshold in males

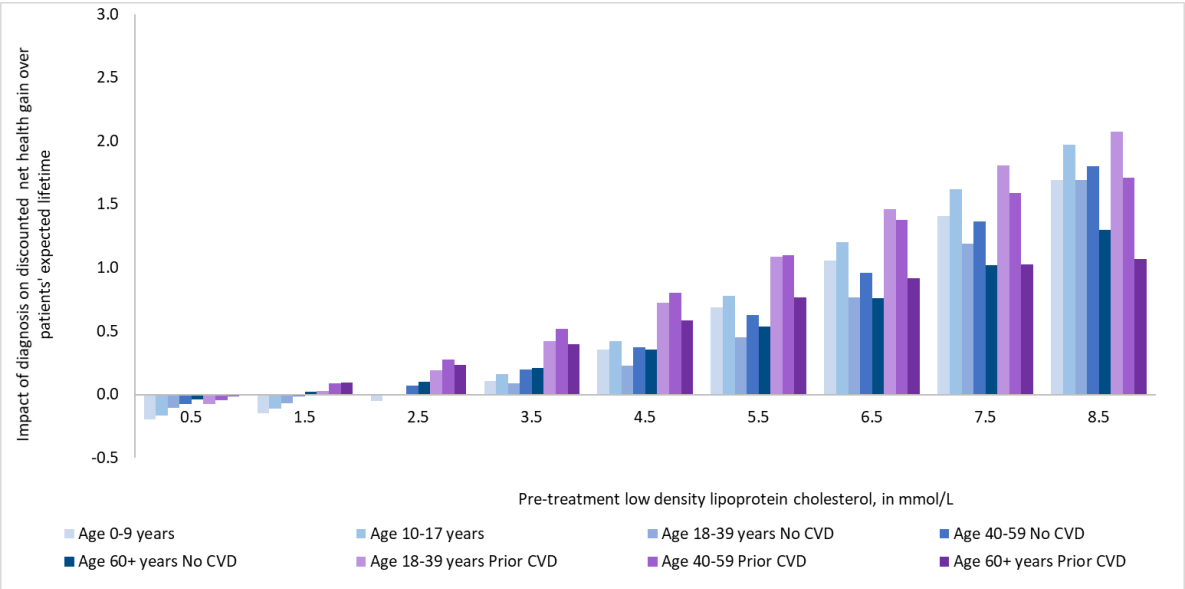


Figure 8B: Impact of diagnosis on net health gain at the £20,000/QALY threshold in females

Figure 8: Impact of diagnosis on net health gain at the £20,000/QALY threshold (discounted to present values)

Probability that diagnosis is a net health gain for the NHS

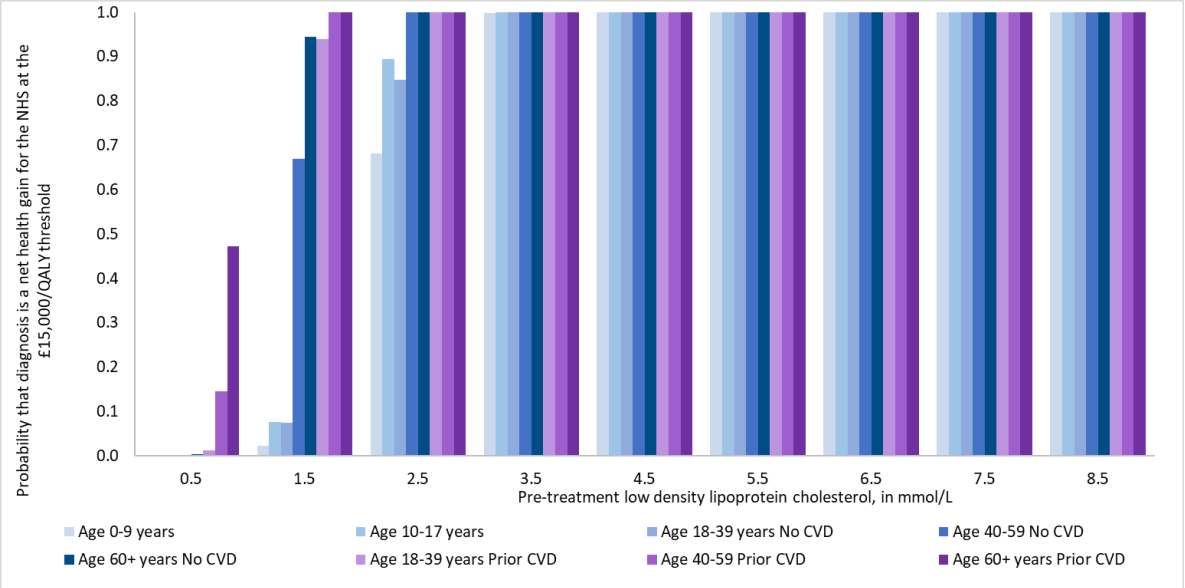


Figure 9A: Probability that diagnosis is a net health gain for the NHS in males

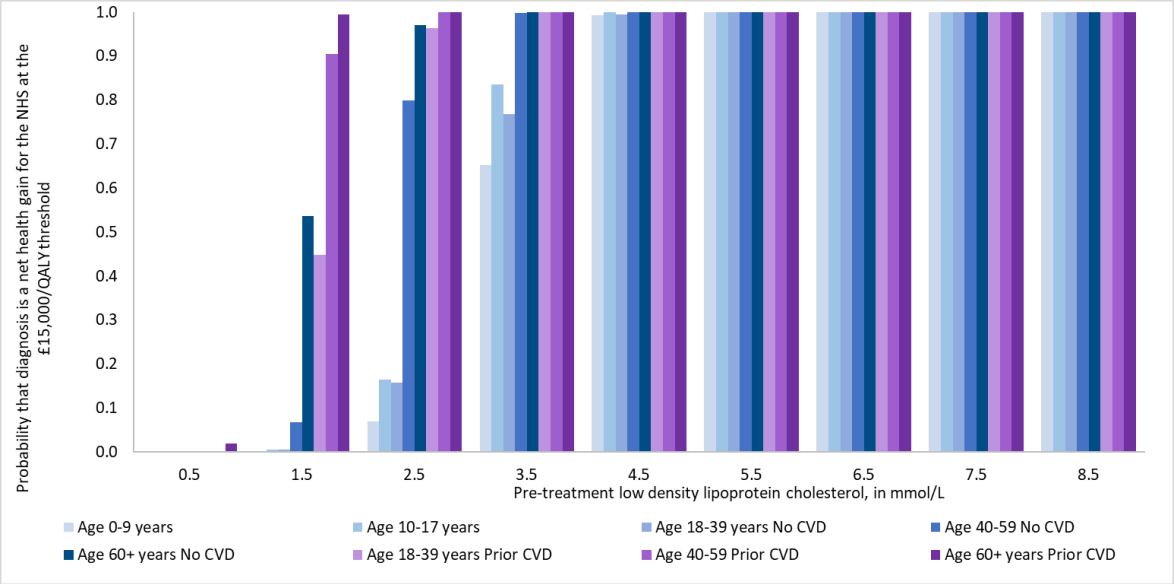


Figure 9B: Probability that diagnosis is a net health gain for the NHS in females

Figure 9: Probability that diagnosis is a net health gain for the NHS at the cost-effectiveness threshold of £15,000/QALY

Results of the scenario analysis

Table 28: Change in the number of subgroups for whom diagnosis is a net health gain compared to the base-case, at a cost-effectiveness threshold of £15,000/QALY

Scenario	Change in number of subgroups
Scenarios on the effects of diagnosis on health outcomes	
1. FH diagnosis reduces LDLC by 50% in line with the NICE CG71 target [6].	4
2. FH diagnosis reduces LDLC to the EAS targets of 3.5 mmol/L in children and adolescents, 1.8 mmol/L in adults in primary prevention and 1.4 mmol/L in adults in secondary prevention [23].	-8
3. FH diagnosis reduces LDLC by 40%, which is 80% of the NICE CG71 target [6].	3
4. FH diagnosis reduces LDLC depending on PT-LDLC, from 5% in those with PT-LDLC 1 mol/L to 40% in those with PT-LDLC = 8 mmol/L, in 5% increments.	3
5. Lower LDLC does not affect the risk of non-CV death.	-4
6. Diagnosed individuals have no benefits and no costs of treatment if their pre-treatment LDLC < EAS target of 1.8 mmol/L in adults in primary prevention and 1.4 mmol/L in adults in secondary prevention [23].	-2
7. Diagnosed individuals have no benefits and no costs of treatment if their pre-treatment LDLC < 3 mmol/L for primary prevention and < 2 mmol/L for secondary prevention.	-14
8. LDLC burden is not included, and the effect of LDLC on CV risk is obtained from the relationship estimated by the CTTC meta-analysis [16]: rate ratio = 0.79 for major vascular events per 1 mmol/L LDLC reduction.	-14
9. The effect of LDLC reduction on CV event risk is greater that what was estimated in the CTTC relationship (30% vs 21%) [16].	-5
10. The CTTC relationship [16] holds up to a maximum pre-treatment LDLC of 6 mmol/L and beyond this threshold the effect of greater LDLC reductions the effect is the same.	-15
11. FH diagnosis reduces the risk of non-CV death (prior to a 1st CV event) by 1% (hazard ratio = 0.99).	2
12. Individuals who are diagnosed with FH are treated with LLT from 18 years of age.	0
13. Prior FH diagnosis and treatment reduces LDLC after the first non-fatal CV event by 50%, in line with the NICE CG181 [12], while individuals who did not have a prior diagnosis have the base-case risk of death (calculated from the Lewsey equations).	2
14. Prior FH diagnosis and treatment reduces LDLC after the first non-fatal CV event to the EAS target of 1.4 mmol/L. [23], while individuals who did not have a prior diagnosis have the base-case risk of death (calculated from the Lewsey equations).	0
15. In addition to causing earlier onset of cases of diabetes type 2, statins cause additional cases of diabetes, with implications for costs and quality-adjusted life expectancy as per the scenario in the cost-effectiveness analysis informing NICE CG181 [12], updated to 2019 [20,21].	0
Scenarios on CV risk	
16. Individuals are at risk of CV events from age 35, as per Perak et al [15].	3
17. The exponential model informs the risk of CV events.	9
18. The risk of the first CV event after 10 years is based on the risk equations estimated from the CPRD cohort, without the upwards adjustment.	-12
19. The risk of the first CV event is adjusted upwards with the standardised mortality ratio obtained from comparing the Simon Broome cohort with the general population mortality risk, and assuming that this ratio can be applied to the hazard rate [26].	9
20. The probability of death due to the first CV event depends on age: lower for younger ages and	2

Scenario	Change in number of subgroups
larger for older ages, as inferred from the probability of death following acute myocardial infarction in the general population [27].	
21. Doubling the risk of death post-first non-fatal CV event compared to the base-case.	3
22. The hazard rate for death after the first non-fatal CV event at 20-years is generalisable to the entire time horizon.	2
Scenarios on the costs	
23. Individuals are monitored only from 10 years of age.	0
24. Low intensity monitoring: 2 appointments in the first year after treatment initiation, then 0.75 appointments per year if adults or 1 appointment per year if children and adolescents. Children and adolescents who are not treated have 1 appointment (and 1 lipid test) in the year of diagnosis and none thereafter until treatment.	3
25. High intensity monitoring: individuals have 3 appointments (and lipid tests) in the first year after treatment initiation, then 1.2 appointments per year if adults or 2 appointments per year if children and adolescents. Children and adolescents who are not treated have 1 appointment (and 1 lipid test) every year until treatment.	-3
26. 50% of adult individuals who are diagnosed with FH are monitored in primary care.	-6
27. The costs are generalisable from the NICE CG181 [12], updated to 2019 [20,21].	-3
28. Increased costs of care (by 25%) to account for the increased risk of recurrent events compared to the general population.	3
29. We obtain the weights from Ara et al, given that these were used for TA393 [13,30].	1

CG71: Clinical Guideline 71. CG181: Clinical Guideline 181. CPRD: Clinical Practice Research Datalink. CTTC: Cholesterol Treatment Trialists' Collaboration. CV: Cardiovascular. EAS: European Atherosclerosis Society. FH: Familial Hypercholesterolaemia. LDLC: Low Density Lipoprotein Cholesterol. LLT: Lipid Lowering Treatment. NICE: National Institute for Health and Care Excellence. TA393: Technology Appraisal 393.

Expected value of perfect information

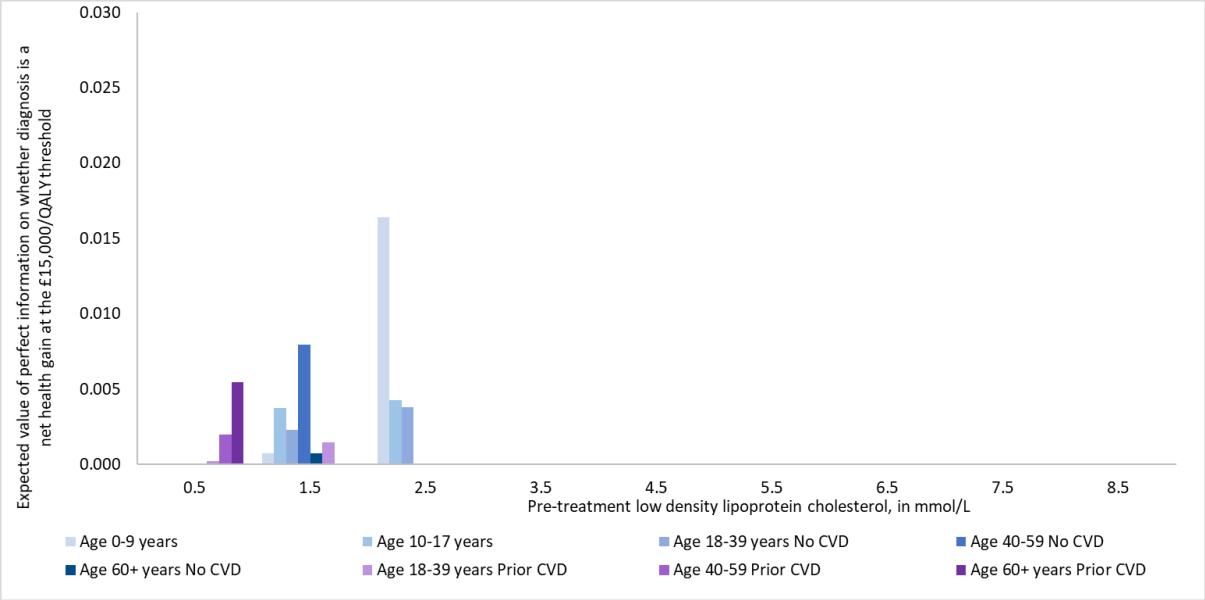


Figure 10A: Expected value of perfect information in males

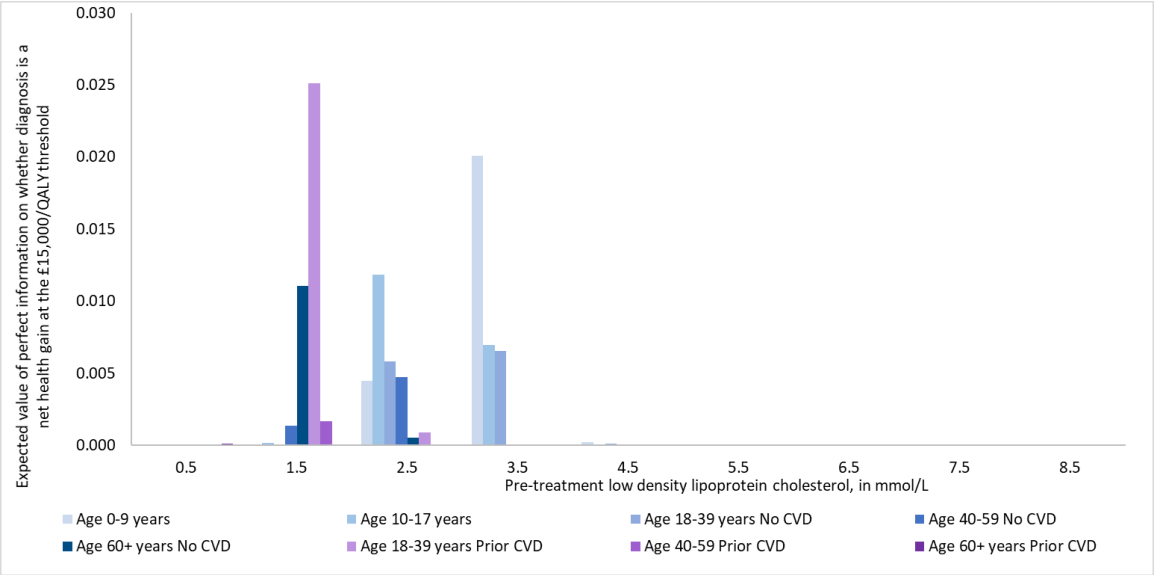


Figure 10B: Expected value of perfect information in females

Figure 10: Expected value of perfect information per individual, at the cost-effectiveness threshold of £15,000/QALY

References

1 Hovland, A. *et al.* Increased risk of heart failure and atrial fibrillation in heterozygous familial hypercholesterolemia. *Atherosclerosis* **266**, 69-73, doi:10.1016/j.atherosclerosis.2017.09.027 (2017).

2 Chacko, L. *et al.* Effects of Percutaneous Coronary Intervention on Death and Myocardial Infarction Stratified by Stable and Unstable Coronary Artery Disease: A Meta-Analysis of Randomized Controlled Trials. *Circ Cardiovasc Qual Outcomes* **13**, e006363, doi:10.1161/CIRCOUTCOMES.119.006363 (2020).

3 Stergiopoulos, K. *et al.* Percutaneous coronary intervention outcomes in patients with stable obstructive coronary artery disease and myocardial ischemia: a collaborative meta-analysis of contemporary randomized clinical trials. *JAMA Intern Med* **174**, 232-240, doi:10.1001/jamainternmed.2013.12855 (2014).

4 Thomas, S., Gokhale, R., Boden, W. E. & Devereaux, P. J. A meta-analysis of randomized controlled trials comparing percutaneous coronary intervention with medical therapy in stable angina pectoris. *Can J Cardiol* **29**, 472-482, doi:10.1016/j.cjca.2012.07.010 (2013).

5 Windecker, S. *et al.* Revascularisation versus medical treatment in patients with stable coronary artery disease: network meta-analysis. *BMJ* **348**, g3859, doi:10.1136/bmj.g3859 (2014).

6 NICE. Clinical guideline 71: identification and management of familial hypercholesterolaemia. (NICE, London, Manchester, 2019).

7 Kazi, D. S. *et al.* Cost-effectiveness of PCSK9 Inhibitor Therapy in Patients With Heterozygous Familial Hypercholesterolemia or Atherosclerotic Cardiovascular Disease. *JAMA* **316**, 743-753, doi:10.1001/jama.2016.11004 (2016).

8 Kerr, M. *et al.* Cost effectiveness of cascade testing for familial hypercholesterolaemia, based on data from familial hypercholesterolaemia services in the UK. *Eur Heart J* **38**, 1832-1839, doi:10.1093/eurheartj/ehx111 (2017).

9 Crosland, P. *et al.* Cost-utility analysis of searching electronic health records and cascade testing to identify and diagnose familial hypercholesterolaemia in England and Wales. *Atherosclerosis* **275**, 80-87, doi:10.1016/j.atherosclerosis.2018.05.021 (2018).

10 Nherera, L. *et al.* Cost-effectiveness analysis of the use of a high-intensity statin compared to a low-intensity statin in the management of patients with familial hypercholesterolaemia. *Curr Med Res Opin* **26**, 529-536, doi:10.1185/03007990903494934 (2010).

11 NICE. Technology appraisal guidance 385 - Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia. (2006).

12 NICE. Clinical guideline 181. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. (2014).

13 NICE. Technology appraisal guidance 393 - Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia. (2016).

14 NICE. Technology appraisal guidance 395 - Ceritinib for previously treated anaplastic lymphoma kinase positive non-small-cell lung cancer. (2016).

15 Perak, A. M. *et al.* Long-Term Risk of Atherosclerotic Cardiovascular Disease in US Adults With the Familial Hypercholesterolemia Phenotype. *Circulation* **134**, 9-19, doi:10.1161/CIRCULATIONAHA.116.022335 (2016).

16 Collaboration, C. T. T. Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. *Lancet* **393**, 407-415, doi:10.1016/S0140-6736(18)31942-1 (2019).

17 Lewsey, J. D. *et al.* A cardiovascular disease policy model that predicts life expectancy taking into account socioeconomic deprivation. *Heart* **101**, 201-208, doi:10.1136/heartjnl-2014-305637 (2015).

18 Office of National Statistics. (ed Office of National Statistics) (2020).

19 NHS Business Services Authority & NHS Prescription Services. (2019).

20 Curtis, L. & Burns, A. *Unit Costs of Health and Social Care 2019*. (Personal Social Services Research Unit, University of Kent, 2019).

21 NHS England and NHS Improvement. (2020).

22 Walker, S. *et al.* Long-term healthcare use and costs in patients with stable coronary artery disease: a population-based cohort using linked health records (CALIBER). *Eur Heart J Qual Care Clin Outcomes* **2**, 125-140, doi:10.1093/ehjqcco/qcw003 (2016).

23 Mach, F. *et al.* 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). *European Heart Journal* **41**, 111-188, doi:10.1093/eurheartj/ehz455 (2019).

24 Bacquer, D. *et al.* Percentage low-density lipoprotein-cholesterol response to a given statin dose is not fixed across the pre-treatment range: Real world evidence from clinical practice: Data from the ESC-EORP EUROASPIRE V Study. *Eur J Prev Cardiol* **27**, 1630-1636, doi:10.1177/2047487319874898 (2020).

25 Ramaswami, U. *et al.* Current management of children and young people with heterozygous familial hypercholesterolaemia - HEART UK statement of care. *Atherosclerosis* **290**, 1-8, doi:10.1016/j.atherosclerosis.2019.09.005 (2019).

26 Humphries, S. E. *et al.* Coronary heart disease mortality in treated familial hypercholesterolaemia: Update of the UK Simon Broome FH register. *Atherosclerosis* **274**, 41-46, doi:10.1016/j.atherosclerosis.2018.04.040 (2018).

27 Asaria, P. *et al.* Acute myocardial infarction hospital admissions and deaths in England: a national follow-back and follow-forward record-linkage study. *Lancet Public Health* **2**, e191-e201, doi:10.1016/S2468-2667(17)30032-4 (2017).

28 Pears, R. *et al.* in *Open Heart* Vol. 1 (2014).

29 Nanchen, D. *et al.* Prognosis of Patients With Familial Hypercholesterolemia After Acute Coronary Syndromes. *Circulation* **134**, 698-709, doi:10.1161/CIRCULATIONAHA.116.023007 (2016).

30 Ara, R. & Brazier, J. E. Populating an economic model with health state utility values: moving toward better practice. *Value Health* **13**, 509-518, doi:10.1111/j.1524-4733.2010.00700.x (2010).

31 Vemer, P., Corro Ramos, I., van Voorn, G. A., Al, M. J. & Feenstra, T. L. AdViSHE: A Validation-Assessment Tool of Health-Economic Models for Decision Makers and Model Users. *Pharmacoeconomics* **34**, 349-361, doi:10.1007/s40273-015-0327-2 (2016).

32 Büyükkaramikli, N. C., Rutten-van Mölken, M. P. M. H., Severens, J. L. & Al, M. TECH-VER: A Verification Checklist to Reduce Errors in Models and Improve Their Credibility. *Pharmacoeconomics* **37**, 1391-1408, doi:10.1007/s40273-019-00844-y (2019).