The University Of Sheffield.

Amendments to methodologies and revised results for the ScHARR economic model - 16th February, 2007

Contents Page

TABLES

FIGURES

Careful attention has been paid to the comments received concerning the ScHARR assessment report 05/22/01 “Ezetimibe for the treatment of hypercholesterolaemia: a systematic review & economic evaluation”. In particular, these led the authors of the report to identify a significant error in the ScHARR model relating to the transition rates used to predict events. In addition, after further discussions with clinical advisors, adjustments have been made to the assumptions used to model changes in health related quality of life associated with events. The ScHARR model has been modified accordingly and a full description of the changes is provided together with results generated from the revised model.

We wish to thank those who responded to our work with constructive criticism, particularly those who were able to offer specific questions and suggestions on technical aspects which have allowed us to improve our analysis and the robustness of the results presented.

A1.0 Transitions

The methodology and data used to model transitions in the recent NICE Statin appraisal has been incorporated into the ScHARR ezetimibe economic model and is described in the following section.

A1.1 Health states modelled

Table A1 lists the health states modelled and a full set of transitions possible. The primary analyses allow one primary event followed by two secondary events. The secondary analyses allow two subsequent secondary events.

Table A1: Health states modelled

Primary events:		Secondary events:	
from	to	from	To
Event free	Stable Angina Unstable Angina Non fatal MI TIA Non fatal stroke Fatal CHD event Fatal CVD event Death other causes	Stable Angina	Post Stable Angina Unstable Angina Non fatal MI Fatal CHD event Death other causes
		Unstable Angina	Post Unstable Angina Non fatal MI Fatal CHD event Non fatal stroke Fatal CVD event Death other causes
		Non fatal MI	Post non fatal MI Non fatal MI Non fatal stroke Fatal CHD event Fatal CVD event Death other causes
		TIA	Post TIA Non fatal MI Non fatal stroke Fatal CHD event Fatal CVD event Death other causes
		Non fatal stroke	Post non fatal stroke Non fatal MI Non fatal stroke Non fatal MI|Stroke Fatal CHD event Fatal CVD event Death other causes
		Non fatal MI|Stroke	Non fatal MI|Stroke Non fatal stroke Fatal CHD event Fatal CVD event Death other causes

A1.2 Data used in the transitions

Primary Incidence Rates / Ratios across health states modelled

Incident rates for primary CHD events are taken from the Bromley Coronary Heart Disease Register,[1] TIA and stroke from the Oxfordshire Community Stroke Project,[2] Bamford.[3]

Table A2: Distribution of patients to primary event health states

Age	Stable Angina	Unstable Angina	MI	Fatal CHD	TIA	Stroke	Fatal CVD	Total event rate per 1,000 per annum#
Male								
45	30.7%	10.7%	29.5%	7.1%	6.0%	12.9%	3.0%	4.2
55	32.8%	7.1%	17.2%	8.6%	8.9%	20.6%	4.8%	13.7
65	21.4%	8.3%	17.3%	9.7%	10.0%	27.0%	6.3%	24.3
75	19.1%	8.1%	16.1%	6.3%	8.0%	34.3%	8.0%	37.5
85	21.4%	9.6%	18.6%	5.5%	1.6%	35.1%	8.2%	42.6
Female								
45	32.5%	11.7%	8.0%	3.7%	16.0%	22.9%	5.4%	1.6
55	34.6%	7.3%	9.2%	3.9%	9.5%	28.8%	6.7%	6.6
65	20.2%	5.2%	12.1%	8.1%	7.3%	38.2%	9.0%	12.4
75	14.9%	3.4%	10.2%	4.3%	9.8%	46.4%	10.9%	23.4
85	13.6%	2.9%	10.0%	3.0%	8.7%	50.1%	11.7%	32.9

The total event rate are for all CVD events per 1,000 population per annum

In the absence of reported UK data for primary CHD events for older age groups, it is assumed that the rates for angina and non fatal MI for the age groups 75-84 years and 85 years plus increase. The rate of increase is based on the ratio of increases reported for the age groups 55-64 and 65-74 years. The rates for fatal CHD events for patients over 74 years were held constant at the reported rate for age 65-74 years. The published rates for first ever stroke by age were assumed to be distributed 81:19 for non-fatal: fatal events, based on the overall published figures from the Oxfordshire study.[2]

Prevalence for secondary evaluations

Published UK prevalence data were used to distribute patients to initial health states for the secondary prevention evaluations. For angina, MI and stroke these were taken from the British Heart Foundation Statistics Database[4] while evidence from Bots *et al*[5] was used to inform prevalence for TIA. It was assumed that the published angina figures included both stable and unstable angina patients and prevalence for these health states were derived using the ratios for stable and unstable angina reported in the incidence data. As TIA prevalence was unavailable for the age group 45-54 this was scaled using the prevalence rates for stroke.

Table A3: Distribution of patients in initial health states for secondary analyses by age and sex

Age	Post Stable Angina	Post Unstable Angina	Post MI	Post TIA	Post Stroke	Total per 1,000#
Male						
45	28.7%	10.0%	37.4%	7.2%	16.6%	7.2
55	37.2%	8.0%	36.2%	4.3%	14.2%	23.2
65	31.2%	12.0%	32.1%	7.5%	17.2%	36.1
75	29.0%	12.4%	30.5%	4.8%	23.3%	44.2
Female						
45	34.1%	11.9%	26.3%	4.6%	23.0%	3.04
55	41.1%	8.9%	21.8%	8.2%	20.0%	11.00
65	33.4%	12.9%	25.7%	4.7%	23.4%	21.40
75	34.3%	14.6%	18.7%	6.9%	25.4%	34.70

#Total is the total number of patients with a history of CVD in a population of 1,000

Secondary event rates

UK specific data is used wherever possible to ensure event rates match the likely distribution in the UK. Two main sources have been used: with the exception of stable angina, for patients with a primary CHD event, the occurrence of further MIs, strokes and vascular deaths are derived from patients on the Nottingham Heart Attack Register (NHAR),[6] while the probabilities of subsequent strokes and vascular deaths for patients with a history of a stroke are derived from patients on the South London Stroke Register (SLSR).[7]

Logistic and multivariate regression analyses were used to estimate the probability of experiencing secondary events within one year of a qualifying primary event. First, logistic regression was used to estimate the probability of experiencing a secondary event of any type i.e. the combined rate of non-fatal MI, non-fatal stroke, and vascular death. Multivariate regression analysis was then used to determine the distribution of secondary events between each type, should an event occur. The results confirm the importance of accounting for age in the model. For patients experiencing an MI the probability of a secondary event within 1 year is strongly correlated with age (mean probability of 14.7% at age 45, and 29.5% at age 85 years). Similarly for patients experiencing a stroke their probability of a secondary event within 1 year increases by age (mean probability of 5.4% at age 45, and 29.8% at age 85 years), while patients with unstable angina have a mean probability of an event of 8.7% at the age of 45 compared to 31.3% at the age of 85 years.

Similar analyses were performed to estimate the probabilities of subsequent events in subsequent years. In the absence of data, these results are used to inform all subsequent

events. This is a conservative approach as the application of these data implies there is no additive effect on fatal or non-fatal event rates from previous events.

TIA transitions are taken from a study by Rothwell *et al.*[8] As this evidence provides a constant rate across all ages (TIA to non fatal stroke = 0.042, non fatal MI = 0.006, fatal CVD = 0.02 and fatal CHD = 0.019 at age 67 years) the data are adjusted using the corresponding changes in incidence rates to derive probabilities by age.

The transitions from stable angina to unstable angina, non fatal MI and fatal CHD are based on RCT data.[9] The trial enrolled 2035 patients from a primary care setting in Sweden between 1985 and 1989. The primary endpoint was the first occurrence of non-fatal or fatal MI or sudden death. Median follow-up time was 50 months. The number of events and thus probability of events at one year are estimated from the number of patients at risk at one year and the ratio of the number of events at trial end. As the results are reported as a constant rate across all ages (stable angina to unstable angina = 0.006, non fatal MI = 0.011, and fatal CHD = 0.007 at age 67 years) the data are combined with the corresponding changes in incidence rates to derive probabilities by age. It is assumed that the probability of a non fatal stroke and fatal CVD events are based on the corresponding transitions for post MI and unstable angina rates respectively.

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

The transitions differ by age and gender and an example is provided in Table A4.

Table A4: Annual transition probabilities for a male cohort starting the model at age 45

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

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

A1.3 Health related quality of life (HRQoL)

Individuals who are diagnosed with CVD or have an event such as a stroke or an MI will have a severe detriment in health related quality of life in the first year after the event. While it seems intuitive that the HRQoL may increase in some individuals post the first year, there is very limited published data which can be used to quantify the changes in HRQoL in subsequent years.

A meta-analysis of quality of life estimates for stroke (Tengs *et al.*) combining 53 quality of life estimates from 20 studies reported utility values of 0.87, 0.68, and 0.52 for mild, moderate and severe stroke respectively. These results give a mean utility of 0.629 when weighted by the proportion (0.19 mild, 0.27 moderate, 0.54 severe) of newly diagnosed patients (n=290,000) experiencing strokes in a UK trial.[10] A Dutch study (n=355) by Exel (2004) reported changes in quality of life between 2 months and 6 months after a stroke using the EQ-5D.[11] The changes in quality of life are different depending on the severity of the stroke. For individuals (n=138) who are independent (Barthel Index 20) utility increases from a mean of 0.76 to 0.81; for individuals (n=155) with a mild or moderate stroke (10<Barthel Index<20) utility decreases from a mean of 0.557 to 0.499; for individuals (n=61) with severe or very severe stroke (Barthel Index < 10) utility increase from a mean of -0.023 to 0.007. The weighted mean value remains unchanged at 0.536 and 0.535 at two and six months respectively. A study by Leeds *et al.* compared long-term changes in HRQoL for individuals discharged to a care home (n=43) as opposed to their own home (n=50) using the EQ-5D.[12] They found that at one year after discharge, HRQoL had increased from mean 0.33 (sd=0.26) to 0.35 (sd=0.2) for those discharged to a care home and had increased from mean 0.46 (sd 0.32) to 0.60 (sd 0.30) for those discharged to their own home. A study (n=98) by Pickard *et al.* reported an increase in mean EQ-5D from 0.31 (sd 0.38) at baseline to 0.62 (sd 0.33) at 6 months post stroke.[13] These figures suggest that there is an initial large reduction in HRQoL and that the long term HRQoL, while substantially lower than before the stroke, increases in the majority of individuals. It has been assumed that HRQoL in subsequent years is 0.629 while the utility in the first year after a stroke is 0.50.

Unstable angina

The results from a randomised controlled trial comparing care in a chest pain clinic observation unit (n=676) with routine care in the emergency department of the Northern General Hospital in Sheffield, UK suggest the mean utility score measured using the EQ-5D at 6 months post diagnosis of unstable angina was 0.77. (Personal communication, Steve Goodacre, Senior Clinical Lecturer in Health Service Research & Emergency Medicine, Medical Care Research Unit, School of Health and Related Research, University of Sheffield, November 2004). Kim *et al.* report changes in HRQoL at 4 months and 12 months in individuals (n=1,810) with unstable angina or non ST-segment elevation myocardial infarction who were randomised to either interventional or a conservative treatment strategy.[14] The mean EQ-5D in both cohorts increased from 0.748 and 0.714 at 4 months to 0.752 and 0.736 at 12 months. Again these results suggest there may be a small increase in HRQoL over time. It has been assumed that 0.80 represents the long term HRQoL associated with unstable angina and this has been decreased to 0.731 during the first year after diagnosis.

MI

The study by Goodacre *et al.* also collected EQ-5D data on individuals who had an MI. The mean value was 0.76.[15] A study (n=222) by Lacey *et al.* reported a change in mean EQ-5D from 0.683 at six weeks post MI to 0.718 at one year post MI.[16] It has been assumed that the mean utility in the first year after an MI is 0.700 based on the Lacey evidence while the mean utility in subsequent years after an MI is increased to 0.8 based on the Goodacre and clinical advice.

Stable angina

There is a dearth of preference-based utility evidence for individuals with stable angina. A recent study by Lenzen *et al.* exploring the HRQoL of patients diagnosed with coronary artery disease reported mean EQ-5D values of 0.85 (0.69-1.00) for individuals eligible for revascularisation (n=3109) and 0.76 (0.62-1.00) for individuals ineligible for revascularisation (n=504).[17] A US study collected quality of life data in 387 patients with multivessel coronary artery disease and angina or documented ischemia using the time trade-off method.[18] They found patients with angina had a mean time trade-off score of 7.03 compared to a mean score of 8.7 in patients without angina. By adjusting the baseline score for individuals without angina to 1, the mean health related quality of life for stable angina is estimated to be 0.808. It has been assumed that patients with angina have a mean utility score of 0.808 during the first year after diagnosis and 0.90 in subsequent years.

TIA

It is assumed that the diagnosis of TIA will not have a lasting impact on HRQoL. A German study by Haacke *et al.* who explored the quality of life in individuals 4 years post diagnosis reported an EQ-5D value of 0.90 for individuals (n=18) with TIA.[19] However, the minimum age of the cohort was 50 years and it is assumed that the reduction from perfect health is more likely to be due to age than TIA. The health-related quality of life for individuals with TIA is assumed to be the same as the population norm (personal communication Dr M Stevenson, Professor P Durrington).

Subsequent major events

No evidence was found which could be used to model the impact on HRQoL for patients who have more than one cardiovascular event. It has been assumed that for second and third events an additional decrement of 10% and 15% will be applied respectively based on clinical advice (personal communication Professor P Durrington).

Table A5: Health state utilities

Health state	1st year	subsequent year	Reference (source)
Stable angina	0.808	0.90	[17,18] clinical input Professor Durrington
Unstable angina	0.731	0.80	[14]clinical input Professor Paul Durrington
MI	0.700	0.80	[20,16] clinical input Professor Paul Durrington
TIA	1.00	1.00	[19] clinical input Professor Paul Durrington
Stroke	0.50	0.629	[10,11,12,13] &clinical input Professor Paul Durrington
2nd major event	10% additional reduction	10% additional reduction	clinical input Professor Paul Durrington
3rd major event	15% additional reduction	15% additional reduction	clinical input Professor Paul Durrington

A1.4 Effectiveness rates and treatment costs used for the treatment scenarios explored

The benefits of treatment regimens modelled are derived from published data on reductions in LDL-c. The effectiveness of ezetimibe monotherapy and ezetimibe in combination with statin therapy are based on meta-analyses (Appendix 1). It is assumed that statin titration of one dose provides an additional reduction of 6% based on meta-analysis of RCT evidence.[21]

The evidence used in the meta-analysis for ezetimibe plus statin therapy is taken from studies which involved a washout period prior to commencing study treatments. As the population considered in the current evaluation are prescribed ezetimibe in addition to ongoing treatment, a sensitivity analysis is conducted using evidence of a meta-analysis of shorter studies where subjects received ezetimibe treatment as an additional treatment to ongoing statin therapy.

Table A6: Treatment regimens compared, annual costs of treatment and effectiveness rates

Treatment regimen	**annual cost**	**% reduction in LDL mean (95% CI)**	**source**
Scenario 1:			
a)Ezetimibe 10mg plus weighted statin (based on prescribing rates)	£493[a]	- 13.94 (-14.90 to -12.98)	meta-analysis
b)Weighted statin titrated by 1 dose	£226	additional 6%	Knopp *et al.*
Scenario 2:			
a)Ezetimibe 10mg monotherapy	£343	-18.56 (-19.68 to -17.44)	meta-analysis
b)no treatment	£0	-	
Scenario 3:			
a)Ezetimibe 10mg plus generic simvastatin (50% Simva 20mg and 50% Simva 40mg)	£386	- 13.94 (-14.90 to -12.98)	meta-analysis
b)Atorvastatin (50% Atorva 20mg and 50% Atorva 40mg)	£344	additional 6%	Knopp *et al.*
Scenario 4:			
a)Ezetimibe 10mg plus weighted statin	£493	13.94% (-14.90 to -12.98)	meta-analysis
b)Weighted statin	£150	-	
Scenario 5:			
a) Ezetimibe 10mg plus rosuvastatin 40mg	£730	- 13.94 (-14.90 to -12.98)	meta-analysis
b) Rosuvastatin 40mg	£387	-	

[a] costs for weighted statin are calculated using prescribing data. The cost of titrated weighted statin is calculated by assuming that all patients on 10mg (20mg, 40mg) will receive 20 (40mg, 80mg) with the exception of patients already on the maximum dose who remain on the same dose.

A2.0 Results generated using the amended transitions and modified HRQoL data

The modifications to the health related quality of life measurements have made a significant difference to the results. The parameters used are based on a mixture of published data supported by clinical advice hence this increases the uncertainty surrounding the values used. Additional univariate sensitivity analyses have been modelled to demonstrate the impact on the results when varying the values used.

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

The results generated for treatment scenario 1 using different time horizons are shown in Table A7. The ICERs decrease as the time horizon increases as would be expected. When examining the results for secondary prevention cohorts, the ICERs for the full lifetime horizons are of a similar magnitude ranging from £38k to £48k per QALY. When looking at the costs and benefits accrued over 20 years, the ICERs for the secondary cohorts range from £47k to per QALY for males aged 65 years, to £87k per QALY for females aged 45 years.

When examining the results for primary prevention cohorts, the ICERs for the full lifetime horizon increase by age with the younger cohorts having similar results. The lifetime horizon ICERs range from £40k per QALY for males aged 45 years to £72k per QALY for females aged 75 years. The larger ICERs for the older cohorts is to be expected as there is less time for older cohorts to accrue costs and benefits from events saved.

If the results are compared using the shorter time horizons, the ICERs for the older cohorts (age 75 years) are lower at 5 years than those for the other cohorts, reflecting the higher risk of the older cohort and thus the increase in number of events avoided when using a shorter time period.

Table A7: Scenario 1, discounted ICERs (£,000) using different time horizons and a baseline LDL-c of 3.5 mmol/L

	Primary Prevention			Secondary Prevention		
Horizon:	5 yr	20 yr	life	5 yr	20 yr	life
Age			Male			
45	£477.5	£83.3	£39.8	£453.1	£80.0	£40.4
55	£433.2	£69.3	£43.2	£329.2	£55.6	£37.9
65	£322.4	£57.7	£47.9	£213.6	£47.1	£41.5
75	£283.1	£68.8	£66.7	£154.6	£49.0	£48.2
			Female			
45	£611.2	£103.0	£45.6	£489.1	£87.2	£41.8
55	£485.9	£75.2	£46.2	£349.2	£56.8	£38.3
65	£339.4	£61.9	£51.6	£219.1	£47.9	£42.1
75	£307.0	£73.9	£71.7	£148.5	£47.6	£46.8

The incremental discounted costs (Table A8) increase as the time horizon increases as would be expected as the cost offsets due to events avoided accrue over a longer period. The costs offsets for the life time horizons decrease as age increases, as events avoided in the older cohorts have less time to accrue benefits than those avoided in the younger cohorts. The incremental costs are of a similar magnitude when comparing primary and secondary cohorts of the same age.

Table A8: Scenario 1, discounted incremental costs (£,000) using different time horizons and a baseline LDL-c of 3.5 mmol/L

	Primary			Secondary		
Age	5 yr	20 yr	life	5 yr	20 yr	life
			Male			
45	£1,145	£3,379	£4,499	£1,211	£3,515	£4,563
55	£1,135	£3,148	£3,752	£1,190	£3,165	£3,678
65	£1,106	£2,700	£2,901	£1,148	£2,651	£2,804
75	£1,052	£2,060	£2,082	£1,075	£1,970	£1,984
			Female			
45	£1,149	£3,415	£4,630	£1,216	£3,571	£4,738
55	£1,138	£3,223	£3,877	£1,198	£3,299	£3,883
65	£1,113	£2,762	£2,973	£1,162	£2,757	£2,923
75	£1,047	£2,042	£2,064	£1,074	£1,991	£2,006

The incremental QALYs (Table A9) increase as the time horizon increases as would be expected. Looking at the incremental QALYs accrued over a lifetime, the total incremental QALYs decrease steeply as age increases. This is because the younger cohorts have a longer opportunity to save additional events and an event saved at the age of 45 years accrues benefits over a longer period than one saved at the age of 75 years. The incremental QALYs

for the 5 year horizons increase by age for the secondary analyses reflecting the increased risk for older cohorts while those for the primary cohorts do not increase as sharply reflecting the similar starting risks of the cohorts modelled.

For the primary analyses, the results for the 5 year time horizons are of a similar magnitude. The differences are mainly due to the distribution across event type which differs by age and gender, and the small increase by age in initial primary risk modelled. As in the results for the secondary analyses, the incremental QALYs decrease as the age of the cohort increases, again reflecting the difference in time to accrue benefits in the older cohorts.

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

Table A9: Scenario 1, discounted incremental QALYs for a cohort of 1,000 patients using different time horizons and a baseline LDL-c of 3.5 mmol/L

	Primary			Secondary		
Lifetime	5 yr	20 yr	life	5 yr	20 yr	life
Age			Male			
45	2.4	40.6	113.2	2.7	44.0	113.1
55	2.6	45.4	86.9	3.6	56.9	97.0
65	3.4	46.8	60.6	5.4	56.2	67.6
75	3.7	29.9	31.2	7.0	40.2	41.2
			Female			
45	1.9	33.2	101.5	2.5	40.9	113.2
55	2.3	42.9	83.9	3.4	58.1	101.5
65	3.3	44.6	57.6	5.3	57.5	69.5
75	3.4	27.6	28.8	7.2	41.9	42.9

When varying the baseline LDL-c, the results (Table A10) are more cost effective for cohorts with higher baseline LDL-c levels, as the percentage reduction in LDL-c and thus the number of events avoided increases. When using a 20 year time horizon, the discounted ICERs for cohorts with no history of CVD range from £50k per QALY for males aged 65 years with a baseline LDL-c of 4.0 mmol/L to £120k per QALY for females aged 45 years with a baseline LDL-c of 3.0 mmol/L. The results for the secondary cohorts range from £41k per QALY for males aged 65 years with a baseline LDL-c of 4.0 mmol/L, to £102k per QALY for females aged 45 years with a baseline LDL-c 3.0 mmol/L.

When looking at the lifetime horizons, the results for the cohorts with no history of CVD range from £34k per QALY for males aged 45 years with a baseline LDL-c of 4.0 mmol/L to £84k per QALY for females aged 75 years with a baseline LDL-c of 3.0 mmol/L. The lifetime results for cohorts with a history of CVD are of a similar magnitude, and range from £33k to £56k per QALY.

Table A10: Scenario 1, discounted 20 year ICERs (£,000) when varying the baseline LDL-c value

20 year horizon						
Age	Primary prevention			Secondary prevention		
Male						
	3	3.5	4	3	3.5	4
45	£97.5	£83.3	£72.6	£93.5	£80.0	£69.8
55	£81.2	£69.3	£60.4	£65.1	£55.6	£48.6
65	£67.6	£57.7	£50.2	£55.1	£47.1	£41.2
75	£80.5	£68.8	£60.0	£57.2	£49.0	£42.9
Female						
45	£120.6	£103.0	£89.7	£102.0	£87.2	£76.1
55	£88.1	£75.2	£65.5	£66.3	£56.8	£49.6
65	£72.6	£61.9	£53.9	£56.0	£47.9	£41.9
75	£86.5	£73.9	£64.4	£55.5	£47.6	£41.6
Lifetime horizon						
Age	Primary prevention			Secondary prevention		
Male						
	3	3.5	4	3	3.5	4
45	£46.6	£39.8	£34.6	£47.2	£40.4	£35.2
55	£50.5	£43.2	£37.6	£44.3	£37.9	£33.2
65	£56.1	£47.9	£41.7	£48.4	£41.5	£36.2
75	£78.1	£66.7	£58.2	£56.2	£48.2	£42.2
Female						
45	£53.5	£45.6	£39.7	£48.9	£41.8	£36.6
55	£54.1	£46.2	£40.2	£44.6	£38.3	£33.5
65	£60.5	£51.6	£44.9	£49.1	£42.1	£36.8
75	£84.0	£71.7	£62.5	£54.6	£46.8	£40.9

Results for Scenario 2: ezetimibe monotherapy versus no treatment

The ICERs for Scenario 2 (Table A13) decrease as the time horizon increases as would be expected. Looking at the results for the 20 year horizon, the ICERs for the primary cohorts range from £34k per QALY for males aged 65 years to £60k per QALY for females aged 45 years. With the exception of the younger cohorts (aged 45 years) the 20 year ICERs for the

secondary cohorts are in the region of £35k (range £31k to £38k) per QALY. When using the lifetime horizon, the results for the primary cohorts are of a similar magnitude for cohorts under the age of 75 years (range £24k to £30k per QALY), while the ICERs for cohorts aged 75 years are higher at approximately £40k per QALY.

For the secondary prevention analyses, the results when using a 20 year time horizon are of a similar magnitude (£32k to £38k) with the exception of the younger age cohorts (aged 45 years) which are approximately £53k per QALY. When using a lifetime horizon, the majority of ICERs are below £30k (range £25k to £33.8k) per QALY.

Table A11: Scenario 2, discounted ICERs (£,000) using different time horizons and a baseline LDL-c of 3.5 mmol/L

Age	Primary			Secondary		
	5 year	20 year	Lifetime	5 year	20 year	Lifetime
Male						
45	£277.7	£48.3	£23.8	£275.2	£50.8	£27.3
55	£251.9	£40.4	£25.6	£203.2	£36.1	£25.4
65	£186.9	£33.7	£28.2	£136.1	£31.4	£27.9
75	£164.4	£40.5	£39.3	£105.6	£34.3	£33.8
Female						
45	£356.1	£59.8	£27.4	£301.7	£56.5	£28.9
55	£282.6	£44.0	£27.5	£220.5	£37.7	£26.1
65	£196.8	£36.3	£30.4	£142.7	£32.6	£28.8
75	£178.4	£43.7	£42.4	£102.3	£33.6	£33.1

When varying the baseline LDL-c, looking at the 20 years ICERs the results range from £27k per QALY for males with a history of CVD (secondary analyses) aged 65 years with a baseline LDL-c of 4.0 mmol/L to £70k per QALY for males aged 45 years with no history of CVD (primary analyses) with a baseline LDL-c of 3.0 mmol/L.

Looking at the results when accruing costs and benefits over a lifetime, all ICERs for the secondary prevention analyses are below £40k (range £22k to £39.5k) per QALY. The results for the cohorts with no history of CVD range from £21k per QALY for males aged 45 years with a baseline LDL-c of 4mmol/L to £50k per QALY for females aged 75 years with a baseline LDL-c of 3.0 mmol/L.

Table A12: Scenario 2, discounted ICERs (£,000) when varying the baseline LDL-c value.

20 year time horizon						
Age	Primary			Secondary		
	baseline LDL-c (mmol/L)					
	3	3.5	4	3	3.5	4
	Male					
45	£56.8	£48.3	£41.9	£59.7	£50.8	£44.2
55	£47.6	£40.4	£35.0	£42.4	£36.1	£31.4
65	£39.7	£33.7	£29.2	£36.9	£31.4	£27.3
75	£47.7	£40.5	£35.1	£40.2	£34.3	£29.9
	Female					
45	£70.4	£59.8	£51.9	£66.3	£56.5	£49.2
55	£51.9	£44.0	£38.1	£44.2	£37.7	£32.8
65	£42.8	£36.3	£31.3	£38.2	£32.6	£28.3
75	£51.5	£43.7	£37.8	£39.4	£33.6	£29.2

Lifetime horizon

Age	Primary			Secondary		
	Male					
	3	3.5	4	3	3.5	4
45	£28.0	£23.8	£20.6	£32.1	£27.3	£23.8
55	£30.2	£25.6	£22.2	£29.7	£25.4	£22.1
65	£33.2	£28.2	£24.4	£32.7	£27.9	£24.3
75	£46.3	£39.3	£34.1	£39.5	£33.8	£29.4
	Female					
45	£32.3	£27.4	£23.7	£33.9	£28.9	£25.2
55	£32.5	£27.5	£23.8	£30.6	£26.1	£22.7
65	£35.9	£30.4	£26.3	£33.7	£28.8	£25.1
75	£50.1	£42.4	£36.7	£38.8	£33.1	£28.8

This scenario is particularly informative for individuals who cannot tolerate statins. It is possible that their baseline LDL-c could be well above the 4.0 mmol/L value modelled. Further results were generated using higher baseline LDL-c levels. Figure 1 shows male age 45 year secondary results.

Plotting the lifetime ICERs against the baseline LDL-c (Figures 1 and 2) it is clear that for individuals with baseline LDL-c greater than 5.0 (5.5) mmol/L, all results are below a threshold of £30k (£25k) per QALY.

Figure 1: Plotting the lifetime discounted ICERs for males against baseline LDL-c for Scenario 2 (ezetimibe versus no treatment)

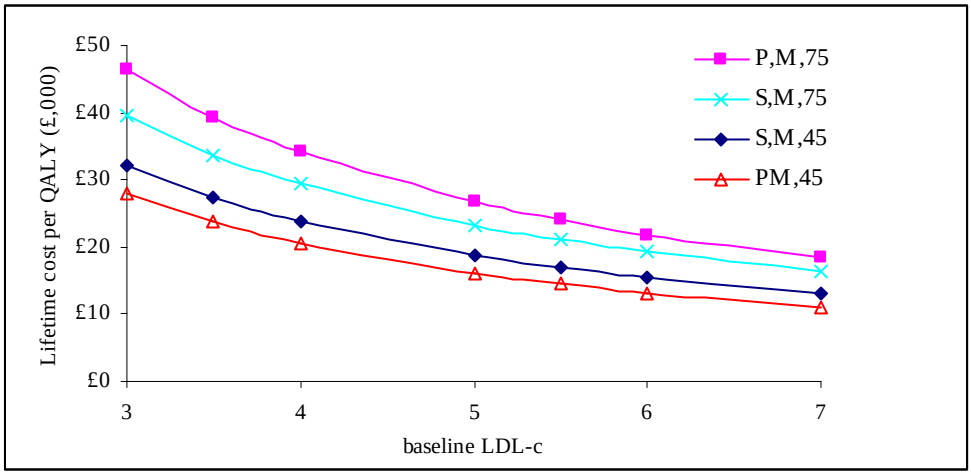
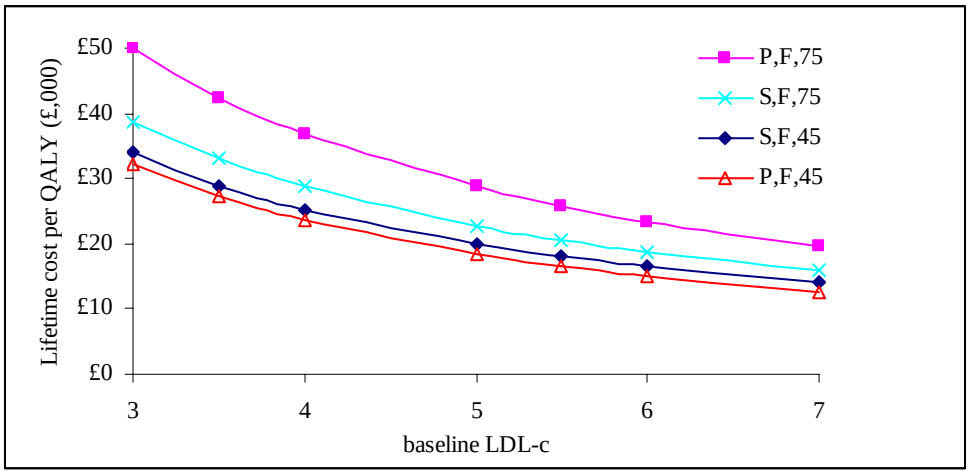


Figure 2: Plotting the lifetime discounted ICERs for females against baseline LDL-c for Scenario 2 (ezetimibe versus no treatment)



Univariate sensitivity analyses for Scenario 2: A series of sensitivity analyses (Table A15 and A16) were performed to explore the impact on the results of changing values used to represent the key parameters. As with Scenario 1, exploring the costs and benefits associated with only CHD events (i.e. setting the relative risk for stroke and TIA to 1) has a substantial impact on the ICERs. Again this analysis has a larger impact on the primary prevention results than on the secondary prevention results with ICERs increasing by 23% at age 45 years to 67% at age 75 years for the primary cohorts and increasing by approximately 10-15% for the secondary cohorts.

The results are sensitive to the changes in values used for the HRQoL. In particular when using a baseline utility of 1 as opposed to the utility adjusted by age, the ICERs are all reduced. The results decrease by approximately 18% for cohorts aged 45 years to

approximately 30% for cohorts aged 75 years. The difference is to be expected as by increasing the baseline utility to 1, the analyses for the older cohorts gain more in terms of quality of life measures than when using the utility adjusted by age.

The results are not sensitive to the time lag for applying the relative risk of treatment effects. When looking at the ICERs for CHD events only (i.e. no relative risk applied to the non fatal or TIA event rates) the ICERs increase as would be expected as the potential to save benefits and costs is reduced. This sensitivity analysis has a larger impact on the results for the primary cohorts than the secondary cohorts. The 20 year horizon primary ICERs increase by 23% at the age of 45 years and increase by 67% at the age of 75 years. The impact on the secondary cohorts is smaller with results increasing by approximately 12%. Increases of a similar magnitude are seen in the lifetime ICERs. Again, the large difference in the impact on the secondary and primary results is due to the difference in QoL gains from saving a primary stroke compared with saving a secondary stroke event due to the baseline HRQoL modelled for the different cohorts.

Table A13: Scenario 2, univariate discounted ICERs (£,000) for males with a baseline LDL-c of 3.5 mmol/L using a 20 year horizon

Value		Primary Prevention				Secondary Prevention			
	Age	45	55	65	75	45	55	65	75
Scenario 2		£48.3	£40.4	£33.7	£40.5	£50.8	£36.1	£31.4	£34.3
Discount rates for costs and utilities									
0%		£41.5	£34.2	£28.6	£34.9	£43.8	£30.7	£27.1	£30.2
Time lag for effectiveness of treatment									
0		£43.8	£36.6	£30.0	£34.4	£46.4	£32.8	£27.7	£28.8
2 yr		£53.7	£44.9	£38.2	£48.6	£56.4	£40.1	£36.0	£41.8
Health state costs									
Plus 20%		£47.7	£39.8	£33.1	£39.9	£50.4	£35.8	£31.2	£34.0
Minus 20%		£48.9	£41.0	£34.3	£41.2	£51.3	£36.4	£31.7	£34.5
Health related quality of life (QoL) utilities									
Plus 10%		£58.9	£46.3	£36.9	£43.6	£46.9	£33.1	£28.9	£31.4
Minus 10%		£40.9	£35.8	£31.0	£37.8	£55.5	£39.8	£34.4	£37.8
Constant utility by age		£39.4	£31.2	£24.7	£28.3	£41.5	£28.0	£23.2	£24.1
Constant utility by age plus 10% on health state utilities		£48.0	£35.8	£27.0	£30.5	£38.2	£25.6	£21.3	£22.1
Constant utility by age minus 10% on health state utilities		£33.4	£27.7	£22.8	£26.5	£45.3	£30.8	£25.4	£26.6
Relative risk on events corresponding to reduction in LDL-c									
	LCI	£39.4	£32.5	£26.8	£32.2	£40.9	£29.0	£25.2	£27.6
	UCI	£62.4	£52.9	£44.6	£53.9	£65.1	£46.2	£40.4	£44.0
Effectiveness of ezetimibe treatment									
	LCI	£45.4	£38.0	£31.6	£38.1	£47.8	£34.0	£29.6	£32.3
	UCI	£51.6	£43.2	£36.0	£43.3	£54.2	£38.5	£33.5	£36.6
No relative risk on stroke or transient ischaemic attack (TIA)									
		£59.6	£56.1	£51.4	£67.6	£56.3	£39.6	£35.9	£39.5
Baseline LDL-c (mmol/L)									
	3.0	£56.8	£47.6	£39.7	£47.7	£59.7	£42.4	£36.9	£40.2
	4.0	£41.9	£35.0	£29.2	£35.1	£44.2	£31.4	£27.3	£29.9
Using effectiveness rates from meta-analysis of 6 week ezetimibe studies									
	6wk data	£48.3	£40.4	£33.7	£40.5	£50.8	£36.1	£31.4	£34.3

Table A14: Scenario 2, univariate ICERs (£,000) for males with baseline LDL-c of 3.5 mmol/L using a lifetime horizon

	Value	Primary Prevention				Secondary Prevention			
Age		45	55	65	75	45	55	65	75
Scenario 2		£23.8	£25.6	£28.2	£39.3	£27.3	£25.4	£27.9	£33.8
Discount rates for costs and utilities									
0%		£16.6	£19.1	£22.6	£33.5	£19.6	£19.5	£23.1	£29.5
Time lag for effectiveness of treatment									
0		£22.6	£24.0	£25.5	£33.5	£26.1	£23.7	£25.0	£28.4
2 yr		£25.1	£27.4	£31.3	£46.9	£28.8	£27.2	£31.4	£41.0
Health state costs									
Plus 20%		£23.4	£25.2	£27.7	£38.7	£27.2	£25.2	£27.7	£33.5
Minus 20%		£24.1	£26.0	£28.7	£40.0	£27.5	£25.5	£28.1	£34.0
Health related quality of life (QoL) utilities									
Plus 10%		£26.2	£27.8	£30.3	£42.2	£25.1	£23.2	£25.6	£30.9
Minus 10%		£21.8	£23.7	£26.3	£36.8	£30.0	£28.0	£30.6	£37.2
Constant utility by age		£18.2	£19.0	£20.3	£27.4	£21.1	£19.0	£20.3	£23.7
Constant utility by age plus 10% on health state utilities		£20.0	£20.6	£21.8	£29.4	£19.4	£17.4	£18.7	£21.7
Constant utility by age minus 10% on health state utilities		£16.8	£17.7	£19.0	£25.7	£23.2	£21.0	£22.3	£26.1
Relative risk on events corresponding to reduction in LDL-c									
LCI		£19.2	£20.5	£22.4	£31.3	£22.0	£20.4	£22.4	£27.2
UCI		£31.0	£33.7	£37.3	£52.3	£35.0	£32.4	£35.8	£43.3
Effectiveness of ezetimibe treatment									
LCI		£22.3	£24.0	£26.4	£37.0	£25.7	£23.9	£26.2	£31.8
UCI		£25.4	£27.4	£30.1	£42.0	£29.2	£27.0	£29.8	£36.0
No relative risk on stroke or transient ischaemic attack (TIA)									
		£31.1	£36.7	£43.4	£65.6	£30.2	£27.9	£31.9	£38.9
Baseline LDL-c (mmol/L)									
3.0		£28.0	£30.2	£33.2	£46.3	£32.1	£29.7	£32.7	£39.5
4.0		£20.6	£22.2	£24.4	£34.1	£23.8	£22.1	£24.3	£29.4
Using effectiveness rates from meta-analysis of 6 week ezetimibe studies									
6wk data		£23.8	£25.6	£28.2	£39.3	£27.3	£25.4	£27.9	£33.8

Scenario 3: Ezetimibe plus generic simvastatin versus a more potent dose of atorvastatin

The results when using different time horizons for the treatment scenario 3 are shown in Table A15. The ICERs suggest that when comparing Ezetimibe plus generic simvastatin with a more potent dose of atorvastatin, all results are well below £15k per QALY for both the 20 years and lifetime horizons.

Table A15: Scenario 3: discounted ICERs (£,000) using different time horizons and a baseline LDL-c of 3.5 mmol/L done

Discounted ICERs						
Age	5 yr	20 yr	life	5 yr	20 yr	life
Male						
45	£40.6	£6.3	£3.4	£62.9	£11.0	£6.2
55	£36.6	£5.1	£3.5	£45.2	£7.8	£5.9
65	£25.6	£4.1	£3.6	£27.9	£6.9	£6.4
75	£21.9	£5.2	£5.1	£19.7	£7.6	£7.5
Female						
45	£53.3	£7.5	£3.7	£69.0	£12.1	£6.6
55	£40.7	£5.1	£3.6	£48.1	£8.0	£6.0
65	£26.2	£4.2	£3.8	£28.9	£7.2	£6.7
75	£22.8	£5.3	£5.2	£18.5	£7.3	£7.2

When varying the baseline LDL-c (Table A16), all the ICERs remain below £15k per QALY irrespective of time horizon (20 year or lifetime), age, gender or history of CVD.

Table A16: Scenario 3: discounted ICERs (£,000) when varying the baseline LDL-c value

20 year time horizon						
Age	Primary Prevention			Secondary Prevention		
	Male					
	3	3.5	4	3	3.5	4
45	£7.8	£6.3	£5.1	£13.1	£11.0	£9.4
55	£6.4	£5.1	£4.1	£9.3	£7.8	£6.8
65	£5.2	£4.1	£3.3	£8.1	£6.9	£6.0
75	£6.5	£5.2	£4.2	£8.8	£7.6	£6.6
	Female					
45	£9.4	£7.5	£6.1	£14.4	£12.1	£10.4
55	£6.6	£5.1	£4.1	£9.5	£8.0	£6.9
65	£5.3	£4.2	£3.3	£8.5	£7.2	£6.3
75	£6.7	£5.3	£4.3	£8.5	£7.3	£6.4

Lifetime horizon

Age	Primary			Secondary		
	Male					
	3	3.5	4	3	3.5	4
45	£4.1	£3.4	£2.8	£7.3	£6.2	£5.4
55	£4.3	£3.5	£2.9	£6.9	£5.9	£5.2
65	£4.6	£3.6	£3.0	£7.5	£6.4	£5.6
75	£6.4	£5.1	£4.2	£8.7	£7.5	£6.5
	Female					
45	£4.6	£3.7	£3.0	£7.7	£6.6	£5.8
55	£4.5	£3.6	£2.9	£7.0	£6.0	£5.3
65	£4.8	£3.8	£3.0	£7.7	£6.7	£5.8
75	£6.6	£5.2	£4.2	£8.5	£7.2	£6.3

ADDITIONAL TREATMENT regimens REQUESTED:

In addition to the treatment regimens presented above, the following analyses have been requested:

- Ezetimibe plus average weighted statin versus average weighted statin (Scenario 4)
- Ezetimibe plus atorvastatin versus the same dose of atorvastatin
- Ezetimibe plus simvastatin versus the same dose of simvastatin

Clinical advice was sought and the most useful comparison doses were suggested to be atorvastatin 40mg and atorvastatin 80mg. It was also suggested that simvastatin 40mg and simvastatin 80mg may be useful comparators although if a patient fails to achieve a satisfactory reduction on simvastatin 40mg a switch to atorvastatin and then titration through the doses was thought to be a more likely alternative to adding ezetimibe onto simvastatin. Simvastatin 80mg is not used widely due to the flat response and increase in adverse events. However, as the guideline development group on lipids is recommending simvastatin 80mg

for both secondary and primary prevention, and pravastatin 40mg for primary prevention, these would also be relevant regimens. It was also suggested that for patients who fail to achieve reasonable reductions on atorvastatin, the more likely alternative would be a switch to rosuvastatin.

If ezetimibe is added onto statin *x* (any dose or cost) and compared with the same statin *x* (of equal dose and cost), the cost of statin treatment in each arm will cancel. The impact of adding ezetimibe onto the statin will be the same for each regimen, due to lack of evidence on any differences, consequently the results will be the same irrespective of the statin in the regimen. Any differences in the ICERs generated will be due to rounding errors and will be minimal.

Scenario 5, which compares the treatment regimen ezetimibe plus rosuvastatin 40mg versus rosuvastatin 40mg, are presented to demonstrate the cost-effectiveness ratio of ezetimibe plus a statin versus a statin of the same dose.

Scenario 4: Ezetimibe plus average weighted statin vs average weighted statin

When comparing the treatment regimen, ezetimibe 10mg plus the weighted average statin versus the weighted average statin of the same doses (Table A17), the results are slightly higher than those for scenario 1 which compares ezetimibe plus weighted statin dose versus weighted statin dose titrated by one dose. The results for the lifetime horizon range from £30k per QALY for males aged 45 years with no history of CVD to £55k per QALY for females aged 75 years with no history of CVD.

Table A17: Scenario 4: discounted ICERs (£,000) using different time horizons and a baseline LDL-c of 3.5 mmol/L

Age	Primary			Secondary		
	5 year	20 year	Lifetime	5 year	20 year	Lifetime
Male						
45	£352.5	£61.9	£30.6	£350.7	£65.1	£35.1
55	£319.9	£51.9	£33.0	£259.1	£46.3	£32.6
65	£237.9	£43.4	£36.3	£174.1	£40.4	£35.8
75	£209.5	£52.1	£50.6	£135.3	£44.0	£43.3
Female						
45	£451.7	£76.6	£35.3	£384.1	£72.3	£37.1
55	£359.0	£56.6	£35.6	£281.1	£48.3	£33.5
65	£250.7	£46.8	£39.3	£182.5	£41.8	£37.0
75	£227.7	£56.2	£54.7	£131.2	£43.1	£42.4

When varying the baseline LDL-c level modelled, the results are slightly higher than those for Scenario 1, and range from £28k per QALY for males aged 55 years with a history of CVD and a baseline LDL-c of 4.0 mmol/L to £50k per QALY for females aged 75 years with no history of CVD and a baseline LDL-c of 3 mmol/L.

Table A18: Scenario 4: discounted ICERs (£,000) when varying the baseline LDL-c value

Age	Primary			Secondary		
20 year time horizon						
baseline LDL-c (mmol/L)						
	3	3.5	4	3	3.5	4
Male						
45	£72.6	£61.9	£53.8	£76.3	£65.1	£56.7
55	£60.9	£51.9	£45.1	£54.3	£46.3	£40.4
65	£51.1	£43.4	£37.7	£47.3	£40.4	£35.2
75	£61.1	£52.1	£45.3	£51.4	£44.0	£38.4
Female						
45	£90.0	£76.6	£66.6	£84.7	£72.3	£63.0
55	£66.5	£56.6	£49.1	£56.6	£48.3	£42.1
65	£55.1	£46.8	£40.6	£48.9	£41.8	£36.4
75	£66.1	£56.2	£48.8	£50.4	£43.1	£37.6
lifetime horizon						
Male						
	3	3.5	4	3	3.5	4
45	£36.0	£30.6	£26.6	£41.1	£35.1	£30.6
55	£38.7	£33.0	£28.7	£38.1	£32.6	£28.4
65	£42.7	£36.3	£31.6	£41.9	£35.8	£31.3
75	£59.4	£50.6	£43.9	£50.6	£43.3	£37.8
Female						
45	£41.5	£35.3	£30.7	£43.4	£37.1	£32.4
55	£41.8	£35.6	£30.8	£39.2	£33.5	£29.2
65	£46.3	£39.3	£34.1	£43.2	£37.0	£32.3
75	£64.3	£54.7	£47.5	£49.7	£42.4	£37.0

Scenario 5: Ezetimibe plus Rosuvastatin 40mg versus Rosuvastatin 40mg

As expected the results for Scenario 5 are the same as those for Scenario 4 and range from £31k per QALY for males aged 45 years with no history of CVD to £55k per QALY for females aged 75 years with no history of CVD. The lifetime ICERs for the secondary cohorts again range from £33k to £44k with the majority under £38k per QALY.

Table A19: Scenario 5: discounted ICERs (£,000) using different time horizons and a baseline LDL-c of 3.5 mmol/L

Age	Primary			Secondary		
	5 year	20 year	Lifetime	5 year	20 year	Lifetime
Male						
45	£352.5	£62.0	£30.8	£350.8	£65.3	£35.4
55	£319.9	£52.0	£33.2	£259.3	£46.6	£32.9
65	£238.0	£43.6	£36.6	£174.2	£40.7	£36.2
75	£209.6	£52.3	£50.8	£135.5	£44.3	£43.6
Female						
45	£451.7	£76.7	£35.5	£384.2	£72.5	£37.4
55	£359.1	£56.7	£35.8	£281.2	£48.6	£33.8
65	£250.8	£47.0	£39.6	£182.6	£42.1	£37.3
75	£227.8	£56.5	£54.9	£131.4	£43.5	£42.8

The results presented in Table A19 above can be used to illustrate the cost-effectiveness of ezetimibe plus a statin compared with the same statin.

A2.1 Summary of key results

A summary of the key results is shown in Table A20. When comparing adding ezetimibe onto ongoing statin treatment with the alternative of switching to a more potent statin using the rule of 6%, the lifetime ICERs range from £2.8 (Scenario 3: adding ezetimibe onto ongoing generic simvastatin versus the same dose of the more potent atorvastatin) to £84k per QALY (Scenario 1: adding ezetimibe onto an ongoing statin weighted by prescribing data compared with weighted statin titrated for one dose). The ICERs when using a shorter time horizon are higher and range from under £15k per QALY for Scenario 3 to over £100k per QALY for Scenario 1. Based on the evidence available, when comparing the costs and benefits associated with adding ezetimibe onto ongoing statin compared with a titration to either a higher dose or a more potent statin, the ICERs will be governed by the difference in the cost of the treatment regimens compared.

When comparing the costs and benefits of adding ezetimibe onto ongoing statin treatment compared with maintaining statin treatment at the current dose (Scenario 5), the lifetime ICERs range from £27k per QALY to £64k per QALY for the primary cohorts and from £28k to £50k per QALY for the secondary cohorts. Based on the evidence available, these results are representative of the cost-effectiveness of any statin co-administered with ezetimibe when compared with the same statin at the same dose.

The results for Scenario 2 (Ezetimibe monotherapy versus no treatment) range from £20k per QALY to £50k per QALY when looking at the costs and benefits accrued over a lifetime and

from £27k to £70k per QALY when looking at the costs and benefits accrued over a 20 year horizon.

Table A20: Summary of Key Results, Discounted ICERs (£,000)using LDL-c of 3.0, 3.5 and 4.0 mmol/L

		20 yrs horizon		Lifetime horizon	
		Primary	Secondary	Primary	Secondary
Scenario 1	M	£50.2-£97.5	£41.2-£93.5	£34.6-£78.1	£33.2-£56.2
	F	£53.9-£121	£41.6-£102	£39.7-£84.0	£33.5-£54.6
Scenario 2	M	£29.2-£56.8	£27.3-£59.7	£20.6-£46.3	£22.1-£39.5
	F	£31.3-£70.4	£28.3-£66.3	£23.7-£50.1	£22.7-£38.8
Scenario 3	M	£3.3-£7.8	£6.0-£13.1	£2.8-£6.4	£5.2-£8.7
	F	£3.3-£9.4	£6.3-£14.4	£2.9-£6.6	£5.3-£8.5
Scenario 4	M	£37.7-£72.6	£35.2-£76.3	£26.6-£59.4	£28.4-£50.6
	F	£40.6-£90.0	£36.4-£84.7	£30.7-£64.3	£29.2-£49.7
Scenario 5	M	£37.7-£72.6	£35.2-£76.3	£26.6-£59.4	£28.4-£50.6
	F	£40.6-£90.0	£36.4-£84.7	£30.7-£64.3	£29.2-£49.7

A3.0 Discussion of results and limitations

While there is a wide range in the estimated ICERs, the results suggest that ezetimibe could be a cost effective treatment for some individuals. In particular, when extrapolating the results to patients with higher baseline LDL-c levels (Figure 1 and Figure 2), and comparing ezetimibe treatment versus no treatment, for individuals with a baseline LDL-c of greater than 5.5 mmol/L all results are below £25k per QALY.

When comparing ezetimibe co-administered with a statin versus the same statin, the majority of results are below £15k per QALY. However, when comparing ezetimibe plus a statin with switching to a more potent statin, the results are much higher.

The results presented should be treated with caution as there are several key areas of uncertainty. The model extrapolates very short-term changes in surrogate outcomes into potential reductions in CV events using a link which is based on an association with statin monotherapy. However, when applying the CTTC data to estimate the relative risk for events, care has been taken to be conservative. We have incorporated a time delay in effectiveness of 1 year, have used the reduced 1 year rates as opposed to the larger 5 year values, and have assumed there is no benefit in terms of reductions in stroke deaths (as the confidence interval crosses zero). It is thought that a conservative approach is required due to the length of extrapolation and the need to translate surrogate changes into events.

A4.0 Conclusions

When comparing the costs and benefits associated with ezetimibe plus a statin versus the same statin, the majority of results are greater than £30k per QALY. When comparing ezetimibe co-administered with a statin versus switching to a more potent statin, further research is required to establish differences in effectiveness rates as the results are currently governed by the statin cost. However, the results suggest that ezetimibe monotherapy compared to no treatment is a cost effective alternative for individuals with a high (>5.5 mmol/L) baseline LDL-c value.

APPENDIX 1

Figure 3: 12 week meta-analysis

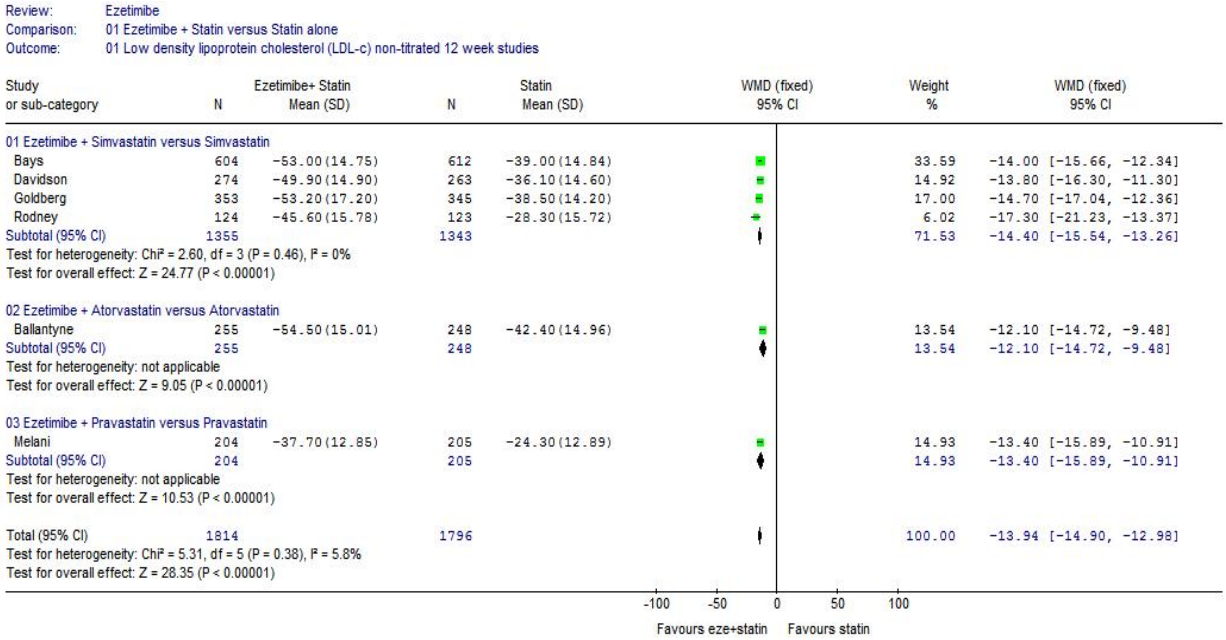


Figure 4: 6 week meta analysis

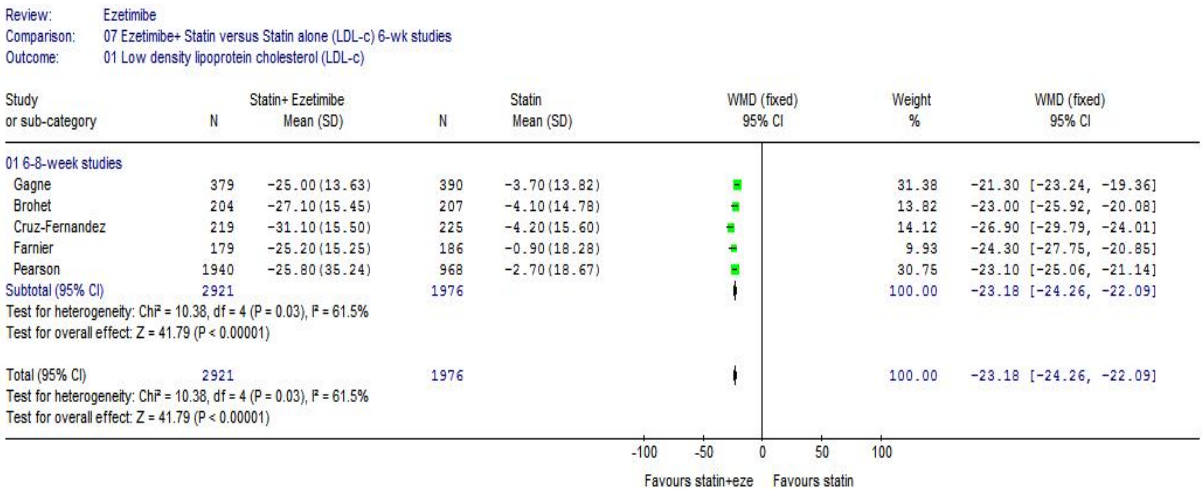


Figure 5: Changes in plasma lipid/lipoprotein concentrations (mmol/L) in HeFH vs. non-HeFH groups *(Obtained by personal communication from Stein et al. 2004[117])*

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

*A full detail of the titration process of this trial is reported in Appendix 9

Additional Results Tables

Table A21: Scenario 2, univariate ICERs (£,000) for females with baseline LDL-c of 3.5 mmol/L using a 20 year horizon

	Value	Primary Prevention				Secondary Prevention			
Age		45	55	65	75	45	55	65	75
Scenario 2		£59.8	£44.0	£36.3	£43.7	£56.5	£37.7	£32.6	£33.6
Discount rates for costs and utilities									
	0%	£51.2	£37.2	£30.9	£37.6	£48.8	£32.1	£28.2	£29.6
Time lag for effectiveness of treatment									
	0	£54.2	£40.0	£32.2	£36.9	£51.5	£34.3	£28.8	£28.1
	2 yr	£66.5	£48.8	£41.2	£52.5	£62.9	£41.7	£37.2	£41.1
Health state costs									
	Plus 20%	£59.0	£43.3	£35.6	£42.9	£56.1	£37.4	£32.3	£33.3
	Minus 20%	£60.6	£44.7	£37.0	£44.5	£56.9	£38.0	£32.8	£33.8
Health related quality of life (QoL) utilities									
	Plus 10%	£74.5	£51.3	£39.7	£46.8	£51.8	£34.7	£29.8	£30.8
	Minus 10%	£50.0	£38.5	£33.4	£41.0	£62.1	£41.3	£35.8	£36.9
	Constant utility by age	£48.7	£34.0	£26.6	£30.6	£46.1	£29.1	£24.0	£23.6
	Constant utility by age plus 10% on health state utilities	£60.6	£39.5	£29.1	£32.7	£42.3	£26.8	£22.0	£21.7
	Constant utility by age minus 10% on health state utilities	£40.8	£29.8	£24.5	£28.7	£50.7	£31.9	£26.4	£26.0
Relative risk on events corresponding to reduction in LDL-c									
	LCI	£48.1	£35.0	£28.4	£34.1	£45.6	£30.4	£26.2	£27.1
	UCI	£79.0	£58.6	£48.9	£59.6	£72.5	£48.4	£41.7	£43.2
Effectiveness of ezetimibe treatment									
	LCI	£56.2	£41.3	£34.0	£41.0	£53.2	£35.5	£30.6	£31.6
	UCI	£63.9	£47.0	£38.8	£46.7	£60.3	£40.2	£34.7	£35.8
No relative risk on stroke or transient ischaemic attack (TIA)									
		£94.2	£73.6	£67.1	£99.0	£64.6	£43.0	£36.8	£39.4
Baseline LDL-c (mmol/L)									
	3.0	£70.4	£51.9	£42.8	£51.5	£66.3	£44.2	£38.2	£39.4
	4.0	£51.9	£38.1	£31.3	£37.8	£49.2	£32.8	£28.3	£29.2

Table A22: Scenario 2, univariate lifetime ICERs (£,000) for females with baseline LDL-c of 3.5 mmol/L

	Value	Primary Prevention				Secondary Prevention			
Age		45	55	65	75	45	55	65	75
Scenario 2 basecase		£27.4	£27.5	£30.4	£42.4	£28.9	£26.1	£28.8	£33.1
Discount rates for costs and utilities									
	0%	£18.8	£20.6	£24.6	£36.1	£20.6	£20.1	£23.9	£28.9
Time lag for effectiveness of treatment									
	0	£26.1	£25.8	£27.5	£36.0	£27.6	£24.5	£25.9	£27.8
	2 yr	£28.8	£29.4	£33.9	£50.7	£30.5	£27.9	£32.4	£40.3
Health state costs									
	Plus 20%	£27.0	£27.1	£29.9	£41.7	£28.8	£26.0	£28.6	£32.8
	Minus 20%	£27.8	£28.0	£31.0	£43.2	£29.1	£26.2	£29.0	£33.3
Health related quality of life (QoL) utilities									
Plus 10%		£30.4	£30.2	£32.8	£45.4	£26.5	£24.0	£26.4	£30.3
Minus 10%		£24.9	£25.3	£28.4	£39.9	£31.9	£28.6	£31.7	£36.3
Constant utility by age		£20.9	£20.5	£22.0	£29.6	£22.3	£19.5	£21.0	£23.2
Constant utility by age plus 10% on health state utilities		£23.1	£22.4	£23.6	£31.6	£20.4	£17.9	£19.2	£21.3
Constant utility by age minus 10% on health state utilities		£19.1	£18.9	£20.6	£27.9	£24.5	£21.5	£23.1	£25.5
Relative risk on events corresponding to reduction in LDL-c									
	LCI	£21.8	£21.8	£23.8	£33.1	£23.3	£21.1	£23.3	£26.7
	UCI	£36.4	£36.8	£41.1	£57.9	£37.0	£33.4	£36.9	£42.5
Effectiveness of ezetimibe treatment									
	LCI	£25.7	£25.8	£28.6	£39.9	£27.2	£24.6	£27.1	£31.1
	UCI	£29.3	£29.4	£32.6	£45.4	£30.9	£27.8	£30.7	£35.3
No relative risk on stroke or transient ischaemic attack (TIA)									
		£44.5	£47.2	£57.2	£96.3	£32.6	£29.7	£32.6	£38.8
Baseline LDL-c (mmol/L)									
	3.0	£32.3	£32.5	£35.9	£50.1	£33.9	£30.6	£33.7	£38.8
	4.0	£23.7	£23.8	£26.3	£36.7	£25.2	£22.7	£25.1	£28.8

Table A23: Scenario 1, discounted costs (£,000) when varying the baseline LDL-c value

20 year horizon						
Age	Primary			Secondary		
	Male					
	3	3.5	4	3	3.5	4
45	£3,395	£3,379	£3,363	£3,524	£3,515	£3,506
55	£3,164	£3,148	£3,132	£3,170	£3,165	£3,160
65	£2,715	£2,700	£2,685	£2,653	£2,651	£2,649
75	£2,070	£2,060	£2,050	£1,969	£1,970	£1,972
	Female					
45	£3,433	£3,415	£3,397	£3,579	£3,571	£3,563
55	£3,243	£3,223	£3,204	£3,305	£3,299	£3,294
65	£2,779	£2,762	£2,745	£2,757	£2,757	£2,757
75	£2,053	£2,042	£2,031	£1,990	£1,991	£1,992

Lifetime horizon

Age	Primary			Secondary		
	Male					
	3	3.5	4	3	3.5	4
45	£4,516	£4,499	£4,483	£4,559	£4,563	£4,567
55	£3,767	£3,752	£3,738	£3,673	£3,678	£3,683
65	£2,917	£2,901	£2,887	£2,802	£2,804	£2,806
75	£2,092	£2,082	£2,072	£1,982	£1,984	£1,986
	Female					
45	£4,651	£4,630	£4,609	£4,731	£4,738	£4,744
55	£3,895	£3,877	£3,855	£3,877	£3,883	£3,888
65	£2,989	£2,973	£2,957	£2,918	£2,923	£2,927
75	£2,075	£2,064	£2,053	£2,004	£2,006	£2,007

Table A24: Scenario 1, discounted QALYs when varying the baseline LDL-c value

20 year horizon						
Age	Primary			Secondary		
	Male					
	3	3.5	4	3	3.5	4
45	34.8	40.6	46.3	37.7	44.0	50.3
55	39.0	45.4	51.8	48.7	56.9	65.0
65	40.2	46.8	53.4	48.2	56.2	64.3
75	25.7	29.9	34.2	34.4	40.2	46.0
	Female					
45	28.5	33.2	37.9	35.1	40.9	46.8
55	36.8	42.9	48.9	49.8	58.1	66.4
65	38.3	44.6	50.9	49.3	57.5	65.8
75	23.7	27.6	31.6	35.9	41.9	47.9

Lifetime horizon

Age	Primary			Secondary		
	Male					
	3	3.5	4	3	3.5	4
45	96.9	113.2	129.4	96.7	113.1	129.6
55	74.5	86.9	99.4	82.9	97.0	111.1
65	52.0	60.6	69.2	57.9	67.6	77.4
75	26.8	31.2	35.6	35.2	41.2	47.1

Table A25: Scenario 2, discounted costs (£,000) using different time horizons

	Primary			Secondary		
Age	5 yr	20 yr	life	5 yr	20 yr	life
	Male					
45	£1,553	£4,501	£5,946	£1,613	£4,654	£6,041
55	£1,538	£4,169	£4,943	£1,582	£4,181	£4,862
65	£1,491	£3,549	£3,808	£1,517	£3,487	£3,690
75	£1,410	£2,712	£2,741	£1,413	£2,587	£2,606
	Female					
45	£1,562	£4,542	£6,087	£1,622	£4,732	£6,273
55	£1,541	£4,251	£5,081	£1,594	£4,354	£5,123
65	£1,497	£3,618	£3,887	£1,536	£3,629	£3,848
75	£1,401	£2,679	£2,707	£1,409	£2,608	£2,628

Table A26: Scenario 2, discounted QALYs using different time horizons

	Primary			Secondary		
Age	5 yr	20 yr	life	5 yr	20 yr	life
Male						
45	5.6	93.2	250.1	5.9	91.6	220.9
55	6.1	103.2	193.1	7.8	115.8	191.7
65	8.0	105.3	135.2	11.1	111.0	132.3
75	8.6	66.9	69.7	13.4	75.5	77.2
Female						
45	4.4	75.9	222.2	5.4	83.7	216.8
55	5.5	96.6	184.5	7.2	115.5	196.3
65	7.6	99.8	127.7	10.8	111.4	133.6
75	7.8	61.3	63.8	13.8	77.7	79.5

Table A27: Scenario 2, discounted costs (£,000) when varying the baseline LDL-c value

20 year horizon						
Age	Primary			Secondary		
Male						
	4	3.5	3	4	3.5	3
45	£4,462	£4,501	£4,540	£4,629	£4,654	£4,678
55	£4,127	£4,169	£4,211	£4,162	£4,181	£4,201
65	£3,508	£3,549	£3,590	£3,471	£3,487	£3,502
75	£2,684	£2,712	£2,741	£2,579	£2,587	£2,595
Female						
45	£4,500	£4,542	£4,585	£4,709	£4,732	£4,755
55	£4,201	£4,251	£4,300	£4,333	£4,354	£4,375
65	£3,572	£3,618	£3,665	£3,615	£3,629	£3,641
75	£2,647	£2,679	£2,710	£2,598	£2,608	£2,618
Lifetime horizon						
Age	Primary			Secondary		
Male						
	4	3.5	3	4	3.5	3
45	£5,891	£5,946	£5,997	£6,030	£6,041	£6,051
55	£4,895	£4,943	£4,990	£4,854	£4,862	£4,869
65	£3,766	£3,808	£3,850	£3,679	£3,690	£3,700
75	£2,713	£2,741	£2,769	£2,598	£2,606	£2,613
Female						
45	£6,023	£6,087	£6,151	£6,264	£6,273	£6,281
55	£5,023	£5,081	£5,138	£5,115	£5,123	£5,132
65	£3,839	£3,887	£3,934	£3,840	£3,848	£3,855
75	£2,675	£2,707	£2,738	£2,619	£2,628	£2,637

Table A28: Scenario 2, discounted QALYs when varying the baseline LDL-c value

Age	Primary			Secondary		
Male						
	3	3.5	4	3	3.5	4
45	106.4	93.2	79.9	104.7	91.6	78.4
55	117.8	103.2	88.5	132.5	115.8	99.1
65	120.2	105.3	90.3	127.0	111.0	94.9
75	76.4	66.9	57.4	86.4	75.5	64.6
Female						
45	86.7	75.9	65.1	95.7	83.7	71.7
55	110.3	96.6	82.9	132.1	115.5	98.9
65	113.9	99.8	85.6	127.5	111.4	95.4
75	70.0	61.3	52.6	88.9	77.7	66.5
Lifetime horizon						
Age	Primary			Secondary		
Male						
	3	3.5	4	3	3.5	4
45	286.1	250.1	214.2	253.4	220.9	188.7
55	220.8	193.1	165.5	219.8	191.7	163.8
65	154.5	135.2	115.9	151.5	132.3	113.1
75	79.5	69.7	59.8	88.4	77.2	66.1
Female						
45	254.0	222.2	190.4	248.5	216.8	185.2
55	210.9	184.5	158.1	224.9	196.3	167.8
65	145.9	127.7	109.5	153.1	133.6	114.2
75	72.8	63.8	54.7	91.0	79.5	68.0

Table A29: Scenario 3, discounted costs (£,000) using different time horizons

	Primary			Secondary		
Age	5 yr	20 yr	life	5 yr	20 yr	life
Male						
45	£97	£255	£382	£168	£482	£703
55	£96	£230	£305	£163	£446	£572
65	£88	£193	£221	£150	£388	£431
75	£81	£156	£160	£137	£304	£308
Female						
45	£100	£250	£375	£172	£496	£746
55	£95	£221	£302	£165	£467	£613
65	£86	£186	£217	£153	£415	£462
75	£78	£147	£151	£134	£306	£310

Table A30: Scenario 3, discounted QALYs using different time horizons

	Primary			Secondary		
Age	5 yr	20 yr	life	5 yr	20 yr	life
Male						
45	2.4	40.6	113.2	2.7	44.0	113.1
55	2.6	45.4	86.9	3.6	56.9	97.0
65	3.4	46.8	60.6	5.4	56.2	67.6
75	3.7	29.9	31.2	7.0	40.2	41.2
Female						
45	1.9	33.2	101.5	2.5	40.9	113.2
55	2.3	42.9	83.9	3.4	58.1	101.5
65	3.3	44.6	57.6	5.3	57.5	69.5
75	3.4	27.6	28.8	7.2	41.9	42.9

Table A31: Scenario 3, discounted costs (£,000) when varying the baseline LDL-c value

20 year horizon						
Age	Primary			Secondary		
	Male					
	3	3.5	4	3	3.5	4
45	£272	£255	£238	£492	£482	£471
55	£248	£230	£213	£454	£446	£439
65	£209	£193	£176	£392	£388	£384
75	£167	£156	£145	£304	£304	£303
	Female					
45	£268	£250	£231	£506	£496	£487
55	£241	£221	£200	£474	£467	£459
65	£205	£186	£167	£417	£415	£413
75	£159	£147	£135	£306	£306	£305
Lifetime horizon						
Age	Primary			Secondary		
				Male		
	3	3.5	4	3	3.5	4
45	£402	£382	£362	£703	£703	£703
55	£323	£305	£289	£571	£572	£573
65	£239	£221	£204	£431	£431	£430
75	£171	£160	£148	£308	£308	£308
	Female					
45	£399	£375	£350	£743	£746	£748
55	£324	£302	£278	£610	£613	£614
65	£235	£217	£199	£460	£462	£464
75	£163	£151	£138	£310	£310	£310

Table A32: Scenario 3, discounted QALYs when varying the baseline LDL-c value

20 year horizon						
Age	Primary			Secondary		
	Male					
	3	3.5	4	3	3.5	4
45	34.8	40.6	46.3	37.7	44.0	50.3
55	39.0	45.4	51.8	48.7	56.9	65.0
65	40.2	46.8	53.4	48.2	56.2	64.3
75	25.7	29.9	34.2	34.4	40.2	46.0
	Female					
45	28.5	33.2	37.9	35.1	40.9	46.8
55	36.8	42.9	48.9	49.8	58.1	66.4
65	38.3	44.6	50.9	49.3	57.5	65.8
75	23.7	27.6	31.6	35.9	41.9	47.9
Lifetime horizon						
Age	Primary			Secondary		
	Male					
	3	3.5	4	3	3.5	4
45	96.9	113.2	129.4	96.7	113.1	129.6
55	74.5	86.9	99.4	82.9	97.0	111.1
65	52.0	60.6	69.2	57.9	67.6	77.4
75	26.8	31.2	35.6	35.2	41.2	47.1
	Female					
45	87.0	101.5	115.9	96.8	113.2	129.7
55	72.0	83.9	95.9	86.8	101.5	116.2
65	49.4	57.6	65.8	59.4	69.5	79.5
75	24.7	28.8	32.9	36.7	42.9	49.0

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