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Intensive versus standard dose statin therapy: the costs and benefits for patients with acute coronary syndrome

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ABSTRACT

Introduction: Recent NICE guidance in England and Wales states that statin therapy for secondary CVD should "*usually be initiated with a drug with a low acquisition cost (taking into account required daily dose and product price per dose)"*. Intensive dose statin therapy is more costly than standard dose, but offers additional benefits and may potentially be more cost effective for a sub-group of high risk patients.

Objective: To determine if the strategy of treating ACS patients with intensive dose statin compared with standard dose statin can be considered to be cost effective and to what extent these results are influenced by the age of the patient at start of treatment.

Methods: A Markov model was used to explore the costs and health outcomes associated with a lifetime of intensive dose (represented by 80mg atorvastatin) versus standard dose (represented by 20mg simvastatin) treatment for patients with acute coronary syndrome. Health states included unstable angina, MI, stroke, fatal CHD, fatal stroke, or non vascular death. The benefits associated with statin treatment were modelled by applying the relative risks from a meta-analysis of 4 large RCTs reporting clinical endpoints. Costs and utilities assigned to health states were derived from a review of published evidence.

Results: Treatment with intensive dose statin therapy offers additional benefits over standard dose therapy. The cost offsets through avoided events are less than the associated treatment costs and result in a cost per QALY of around £24,000 for patients with ACS starting treatment at 60 years of age and falling to around £14,000 for patients starting treatment at 70 years. The key driver of cost effectiveness is the relative risk for mortality.

Conclusions: This analysis suggests that intensive statin regimens (represented by atorvastatin 80mg /day) are cost effective compared with standard statin regimens (represented by simvastatin 20mg /day) for patients with ACS over the age of 60 years. A recent registry study report a mean age of 70 years for ACS patients admitted to UK hospitals and hence this comparison applies to the great majority of ACS patients.

Key words: Statins; intensive dose therapy; cost effectiveness; acute coronary syndrome

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INTRODUCTION

Cardiovascular disease (CVD) remains one of the major causes of premature death in the United Kingdom, accounting for 35% of premature deaths in men and 27% in women. It is also a significant cause of morbidity. Statins have been shown to reduce the risk of cardiovascular events.[1] Current NICE guidance in the UK recommends that patients with established coronary heart disease (CHD) should receive statins and statin therapy is also recommended as part of the management strategy for the primary prevention of CVD for adults who have a 20% or greater 10-year risk of developing CVD.[2] Over 5 million people, around 14% of adults in England, meet these eligibility criteria. Statins currently account for 19 per cent of the total primary care drugs bill{2007 17952 /id} and this proportion is likely to grow as a result of more aggressive lipid lowering strategies resulting from the anticipated changes to both the GMS contract and the QOF, and a shift towards payment by result.[4] Statin prescribing, at over £700 million per annum in 2004, represented the largest drug cost to the NHS.[5,6] Increasing adherence to guidelines over time will continue to put upward pressure on prescribing budgets. The relevance of cost effective prescribing of statins to the NHS is clear.

Current NICE guidance states that *"therapy should usually be initiated with a drug with a low acquisition cost (taking into account required daily dose and product price per dose)"*.[2] Five statins currently have a UK marketing authorisation: atorvastatin, fluvastatin, pravastatin, rosuvastatin and simvastatin, with simvastatin and atorvastatin currently dominating the UK market. Two of the five (simvastatin and pravastatin) have become available as generics, experiencing significant price reductions as a result. Perhaps not surprisingly, there has been a trend towards generic prescribing. It has been reported that switching from atorvastatin (10 to 20mg /day) to simvastatin (20 to 40mg /day) saves around £1000 per patient over five years,

freeing up much needed resources for other uses.[6] Figures reported by the Department of Health 'Better Care, better value' indicators, indicate that the NHS could save at least £85m a year on drug acquisition costs through more efficient prescribing of statins.[7] These savings are based on every PCT prescribing generic statins in 69 per cent of cases, the level achieved by the top quarter of Trusts. Importantly, this takes no account of the possible differences in individual patient and drug profiles and therefore the magnitude of secondary costs following subsequent events.

Recent draft guidance from NICE on lipid modification recommends that treatment for patients with established CVD "*…should be initiated with simvastatin 40mg per day*." Although they do not provide a target for total or LDL cholesterol it is recommended that "statins should be up-titrate….. *"statins should be up-titrated if the patient does not reach a total cholesterol of 4 mmol/l or LDL cholesterol 2mmol/l on the initial dose*."[2] This is in contrast to recent guidelines for management of patients with acute coronary syndrome issues by the European Society of Cardiology,[8] American Heart Association and American College of Cardiology,[9] which both advise that an optimal LDL cholesterol target of below 1.81 mmol/L (<70mg/dl) be adopted. These levels of cholesterol have only been achieved by a majority of patients in trials that have assessed intensive statin regimens, namely simvastatin or atorvastatin 80mg /day.

Some Trusts in the UK have taken the decision to suspend prescribing of intensive dose statins, such as 40 – 80mg /day of atorvastatin, for patients with ACS and switch to prescribing of 40mg /day of simvastatin.[10] Dose for dose, atorvastatin is more potent than simvastatin and an audit of the effect of this change in one hospital suggested that switching to the less efficacious statin may impact adversely on patient morbidity and mortality for this patient group.[10] This audit raised questions about the level of additional benefit achieved by more intensive statin regimens and whether or not there is a group of high risk patients for whom the use of more intensive therapy for patients – in line with current clinical guidelines - is likely to be cost effective.

Four trials to date have presented clinical endpoint evidence for intensive versus standard dose statins on an intention-to-treat basis.[11,12,13,14] The clinical setting and baseline risks of the populations varied - two trials were undertaken in patients after an acute coronary syndrome (ACS) event and two in populations with stable coronary artery disease (CAD). Three of the studies used 80 mg /day atorvastatin as the intensive statin regimen and one used a target dose of 80 mg /day of simvastatin (A-to-Z). Standard statin regimens in these trials were simvastatin 20mg /day,[11,12] atorvastatin 10mg /day,[13] and pravastatin 40 mg /day.[14] Prescribing data for statins in England suggest that simvastatin 80mg /day is rarely used. (Prescription Cost Analysis 2005)

In this paper we use this clinical evidence base to consider whether or not the strategy of treating ACS patients with intensive dose statin (represented by 80 mg /day atorvastatin) compared with standard dose statin (represented by 20mg /day simvastatin) can be considered to be cost effective and to what extent these results are influenced by the age of the patient at start of treatment.

METHODS

Model Design

An existing Markov model constructed to evaluate the cost effectiveness of statin treatment versus no treatment was modified to compare intensive dose (80mg /day atorvastatin) with standard dose (20mg /day simvastatin) statin therapy for patients with existing cardiovascular disease.[15] Markov models are particularly useful for cardiovascular interventions as the disease involves events that can occur more that once, a risk that increases over time and probabilities of subsequent events that change depending on the time since a previous event.[16]

The model replicates a hypothetical cohort moving between a finite number of mutually exclusive health states. The current model consists of the following health states (Figure 1): new unstable angina, new MI, new stroke, post unstable angina, post MI, post stroke, fatal CHD, fatal stroke, or non vascular death. Patients enter the model after experiencing a qualifying event: new unstable angina, new acute myocardial infarction or new non fatal stroke. Patients move between health states annually until they have reached 100 years of age or die. The transitions to subsequent events are higher in the first year after a new event than in subsequent years reflecting the increased risk during the initial period. If an individual in a "new event" health state does not experience a subsequent event in the first year they move to the corresponding "post event" health state. Markov models do not retain a memory of patients' previous events thus transitions are conditional on current health state and age only. Consequently we do not model transitions to health states with lower health state costs and higher quality of life (for example moving to unstable angina from stroke). An exception is patients with a history of a stroke may experience an MI. This is modelled using an additional health state (MI given stroke) where utilities, costs and future transitions are adjusted to reflect the history of stroke. The proportion of patients in each of the health states is governed by age-dependent time-variant transition matrices which describe the annual probability of either moving to an alternative health state or remaining in the same health state. Interim life tables adjusted for CV mortalities published by the UK Government Actuary Department were used to account for the proportion of patients dying from other causes.

INSERT FIGURE 1: Patient pathway in Markov Model

Event Rates

The baseline transition rates (Table 1) for patients who receive no treatment are taken from the statin HTA model.[15] These are derived from logistic and multinomial regressions using patient level data from the South London Stroke Registry and the Nottingham Heart Attack Register.[17,18]

INSERT TABLE 1: Examples of transitions for patients receiving no treatment[15]

Effectiveness Rates

The relative risks from a meta-analysis of placebo controlled statin RCTs are used to represent the effectiveness of standard statin therapy versus no treatment. Of the 25 studies (n=35,721 for statin; n=35,432 for placebo) included in the meta-analyses used in the current evaluation, three of the four fluvastatin studies (FLARE, FLORIDA, LIPS) used the maximum dose of 80 mg /day while the LiSA study increased the starting dose of 40 mg /day to 80 mg /day 6 weeks after randomisation if the decrease in LDL-c was less than 30%. Two of the four pravastatin studies used the maximum dose of 40 mg /day. In the remaining two (PLAC II and PMSG), the dose could be increased to 40 mg /day in participants whose LDL-c levels had not responded to the starting dose of 20 mg /day. Two of the six simvastatin studies (Aronow 2003, HPS) used 40 mg /day throughout while the MAAS study used a 20 mg /day dose throughout. The remaining three (4S, CIS, SCAT) used a starting dose of 20 mg /day which could be increased to 40 mg /day if this was necessary to achieve an adequate reduction in LDL-c. By contrast, the atorvastatin studies generally used doses well below the maximum dose of 80 mg /day: the ASCOT-LLA and CARDS studies used a fixed dose of 10 mg /day. Only the small DALI (n=145 on atorvastatin) and Mohler (n=240 on atorvastatin) studies used an 80 mg /day dose: each had two treatment arms, one on a fixed dose of 10 mg /day and the other on 80 mg /day. Assuming that atorvastatin 10mg /day, fluvastatin 80mg /day, pravastatin 40mg /day and simvastatin 20/40mg /day provide similar benefits, the results can be used to represent the effectiveness achieved through standard statin treatment compared with no treatment. Excluded from this meta-analysis are more recent

placebo controlled trials with rosuvastatin 10 mg /day including the CORONA trial.{NEJM 2007}

The clinical benefit of intensive dose versus standard dose statin therapy is obtained from publications of event rates in four clinical trials[14,12,13,11] and one previous economic evaluation.[19] The Pravastatin or Atorvastatin Evaluation and Infection Therapy[14] study compared atorvastatin 80 mg /day with pravastatin 40mg /day. The Aggrastat to Zocor[12] study compared simvastatin with a target dose of 80mg /day with simvastatin 20mg /day. The Treating to New Targets[13] study compared atorvastatin 80mg /day with atorvastatin 10mg /day. The Incremental Decreases in End Points Through Aggressive Lipid Lowering[11] study compared atorvastatin 80mg /day with simvastatin 20mg /day. For the purpose of this analysis we assume that the intensive dose statin treatment arms are represented by atorvastatin 80mg /day and that the standard dose control arms are represented by simvastatin 20mg /day.[20]

Due to differences in patients' baseline characteristics the four statin head to head studies are categorised as: ACS trials;[14,12] and stable CAD trials.[13,11] Relative risks and corresponding 95% confidence intervals for hospitalization for unstable angina, non fatal MI, non fatal stroke, fatal coronary heart disease, and all cause mortality are estimated using random effects models. These outcomes are chosen as they are reported in the majority of the four studies and most closely reflect the definitions used in the original meta-analysis of standard statin therapy and the health states in the existing model. For the stable CAD studies, we assume that the combined fatal and non fatal stroke events can be used to represent rates for non fatal stroke.

Applying Relative Risks in the model

The model is constructed with three distinct pathways: no treatment, standard dose statin and intensive dose statin. Initial distribution across qualifying events and transitions to events in the no treatment arm are taken from the NICE statin model.[15] Transitions to events in the standard dose arm are derived by applying the relative risk (RR) (Table 2) from the standard dose meta-analyses to the no treatment arm transitions.[15] Transitions to events in the intensive dose arm are derived by applying the RR (Table 2) from our meta-analyses to the standard dose transitions. The RR from the two ACS studies are applied to transitions from new event health states while the RR from the two stable CAD studies are applied to transitions from post event health states. This infers that the underlying disease for patients who do not have an event in the previous 12 months stabilises somewhat. This assumption is tested in univariate sensitivity analyses by varying the evidence source for the RRs applied during the first and subsequent years.

Cost input parameters

The cost of treatment and costs associated with the different health states modelled (Table 2) are obtained from a variety of UK specific sources (£ sterling, 2006).[15] Statin treatment is costed annually assuming simvastatin 20mg /day for standard dose and atorvastatin 80mg/day for intensive dose, using prices listed in the British National Formulary.[21] In the base case we assume 100% compliance for treatment costs as the RRs are estimated on an intention to treat basis.

Costs for health states are based on the evidence used in the original statin economic evaluation. Costs for MI and fatal CHD are taken from the GP IIb/IIIa analysis by Palmer *et al.*[22] Costs for stroke are taken from Chambers *et al.* weighted by the distribution of disabling and independent events.[23] Follow on costs for post CHD event states are based on clinical input.

We assume no additional monitoring costs for the intensive dose treatment in the base case. A sensitivity analysis is performed where costs are included to account for two additional GP visits and phlebotomy tests in the first year and one visit and test in subsequent years. The model estimates costs from a UK NHS perspective as per recommendations hence only direct costs are included.[24] In accordance with UK guidance, costs and benefits are discounted at 3.5% per annum.[24]

INSERT TABLE 2: Relative risks, utilities and costs used in the model

Utility input parameters

The model assesses cost effectiveness in terms of the incremental cost per quality adjusted life year (QALY) gained. Utility values are taken from UK based studies using the UK preference-based weights for the EQ-5D where possible as advocated in the NICE reference case.[24] It is assumed that patients in post event health states will incur an increase in quality of life in comparison to values modelled for the new event health states. Quality of life is adjusted for age based on the UK general population estimates.[25] All health state values are correlated for the probabilistic analyses and univariate sensitivity analyses are conducted to explore the impact of varying the individual parameters.

Analyses

The basecase is derived using 10,000 MonteCarlo simulations where the parameters are sampled simultaneously. The impact of varying key parameters within their specified ranges is examined by holding the parameter value constant and sampling from all other parameters distributions simultaneously, again using 10,000 MonteCarlo simulations. The variables include: health state costs (+/- 50%), treatment and monitoring costs, utility estimates, and the relative risks for the individual outcomes. Results are also presented for different ages (50 and 70 years), and for

females. In addition, the model is run using different RRs for fatal CHD and fatal stroke as opposed to the all cause mortality RR used in the basecase.

RESULTS

Average base case estimate

The clinical and cost outcomes for a cohort of 1,000 patients are presented in Table 3. During the first five years of treatment, standard dose statin therapy results in the avoidance of an average of 71 vascular events (47 non fatal MIs, 9 non fatal strokes and 15 vascular deaths) compared with no treatment providing an average of 911 additional life years or 547 additional QALYs. Over the full life time horizon, patients receiving standard dose statin treatment experience an average of 118 fewer vascular events that those receiving no treatment accruing an additional 547 QALYs. The cost offsets through events avoided (£404,478) are greater than the associated treatment costs (£328,848). Standard dose statins are associated with greater health benefits and lower costs than no treatment.

INSERT TABLE 3: Clinical outcomes and costs for a cohort of 1,000 males aged 60 years

During the first five years of treatment, intensive dose statin therapy results in the avoidance of approximately 30 vascular events (14 non fatal MIs, 4 non fatal strokes and 11 vascular deaths) compared with standard dose treatment. These provide an average additional 53 life years or 35 QALYs. Over the full life time horizon, patients receiving intensive dose statins are estimated to experience 71 fewer vascular events than those receiving standard dose statins. Avoiding these events accrues an additional 276 life years or 172 QALYs. With a total incremental cost of £4.1m, the cost per life year gained for intensive dose statin treatment compared with standard dose statin treatment is estimated to be £14,844 and the cost per QALY gained is estimated to be £23,779.

With a mean cost per QALY of £23,779 (Jackknife CI: £23,454 - £24,100), Figure 2 shows that for a decision threshold of £20,000 (£30,000) per QALY, intensive dose statin therapy is cost effective in approximately 43% (68%) of cases compared with standard dose therapy. It should be noted that the CEAC never reaches one. This tells us that on currently available evidence intensive dose statin may reduce the benefits compared with standard dose statin.

INSERT FIGURE 2: Cost effectiveness acceptability curve for intensive dose versus standard dose statin treatment

Deterministic sensitivity analyses

The results of the deterministic sensitivity analyses undertaken to investigate the stability of the base case estimates are presented in Table 4. When comparing standard dose statin therapy (simvastatin 20mg /day) with no treatment, the model is robust to variations in all the input parameters. When comparing intensive dose with standard dose statin treatment, the model is robust to variations in a wide range of input parameters (Table 4 and Figure 3). The results demonstrate that treatment with intensive dose statin is a cost effective alternative for older aged cohorts. The ICER decreases as the starting age increases (analysis 16) reflecting the greater potential for avoiding events associated with the higher baseline risk in the older age groups.

INSERT TABLE 4: Results for one-way sensitivity analyses

The key driver of cost effectiveness of intensive versus standard dose statins are the RRs applied for all cause mortality (range £11,034 (CI: £11,008; £11,060) per QALY to dominated). If the RR for fatal CHD and fatal stroke are applied separately (analysis 8) as opposed to the all cause mortality RR the average ICER is estimated to be £19,474 (CI: £19,312; £19,637). Varying the

quality of life detriment associated with events by plus or minus 15% (analyses 10:11) produces ICERs ranging from £20,800 to £28,492. The results are not substantially affected when varying health state costs (analyses 2:4), costs associated with monitoring for intensive dose regimens (analysis 5), the relative risks for standard dose treatment (analyses 9:10) or changes in the relative risks for non fatal events for the intensive dose treatment (not shown).

INSERT FIGURE 3: Tornado diagram showing robustness to changes in key parameters

The price difference between the two therapies impacts on the cost effectiveness results. The base case assumes the standard dose is simvastatin 20mg /day at an annual cost of £24.25 per annum. If the cost for standard dose treatment is increased to £44.32 per annum (equivalent to simvastatin 40mg /day), the ICER decreases to £22,657. However this does not taken into account any difference in efficacy between the two doses of simvastatin. The costs for atorvastatin 40mg /day and 80mg /day are currently equal at £367.74. If it is assumed that this cost is reduced to £294.19 per annum (analysis 6) the ICER reduces to £18,606.

DISCUSSION

We have shown that standard dose statins compared with no treatment for high risk patients with acute coronary syndrome are highly cost effective. Treatment with intensive dose statin (represented by atorvastatin 80mg /day) offers additional benefits over standard dose (represented by simvastatin 20mg /day), but these additional benefits are smaller in magnitude than the benefits achieved when from moving from no statin to standard dose statins. In addition the cost offsets through avoided events when comparing intensive and standard dose statin regimens are

less than the associated treatment costs and result in a cost per QALY of around £24,000 for cohorts starting treatment at 60 years of age. The incremental cost effectiveness ratio (ICER) decreases as the age of the cohort increases; for patients commencing treatment at the age of 70 years the ICER is estimated to be around £14,000. This reflects the greater potential for avoiding events associated with the higher baseline risk in the older age groups and also the rise in the proportion of fatal to non-fatal events as age increases. If the price difference between atorvastatin and simvastatin diminishes significantly when generic atorvastatin becomes available in 2011, this would undoubtedly make the case for intensive dose therapy more robust.

The key drivers of cost effectiveness of intensive versus standard dose statins are the relative risk for mortality and, to a lesser extent, the cohort starting age and assumptions on utility. The results are particularly sensitive to uncertainty relating to the size of treatment effects on mortality in the first year. Previous meta-analyses have considered the impact of intensive dose statins on mortality. A meta-analysis of the four trials included within our analysis reported a trend toward decreasing cardiovascular mortality and, to a lesser extent, all-cause mortality but identified that it was underpowered to detect statistical differences with regard to these outcomes (Cannon et al 2006). A recent meta-analysis by Afilalo provides supporting evidence for the role of intensive dose statins in reducing mortality. The analysis concluded that in patients with recent ACS intensive statin therapy reduced all-cause mortality from 4.6% to 3.5% over 2.0 years (OR 0.75, 95% CI 0.61 to 0.93).[26] However, in patients with stable CHD, intensive statin therapy had no effect on all-cause mortality over 4.7 years (OR 0.99, 95% CI 0.89 to 1.11). In contrast MACE, defined as cardiovascular death or ACS or stroke, was comparably reduced in patients with recent ACS (OR 0.86, 95% CI 0.73 to 1.01) and stable CHD (OR 0.82, 95% CI 0.75 to 1.01).[26]

The clinical evidence underlying the analysis is based on four trials which vary in terms of design and population studied. Two of the trials that used simvastatin 20mg /day as the standard statin

regimen (A to Z, IDEAL) showed no significant difference in their primary composite endpoints as compared to intensive statin regimens of simvastatin 80mg /day and atorvastatin 80mg /day. One of these was conducted in the context of ACS (A to Z) and the other in the context of CAD (IDEAL). Conversely the two trials that used pravastatin 40mg /day and atorvastatin 10mg /day as the standard statin regimen (PROVE-IT & TNT) showed a significant difference in their primary composite endpoints as compared to intensive statin regimens of atorvastatin 80mg /day. Again, one of these was conducted in the acute context of ACS (PROVE-IT) and the other in the stable context of CAD (TNT). This raises a question as to whether simvastatin 20mg /day might be a more effective standard statin regimen than pravastatin 40mg /day or atorvastatin 10mg /day. However, as each of these regimens achieved a similar mean LDL cholesterol of approximately 100 mg/dl (2.6 mmol/L) during the conduct of these studies,[26] the most likely explanation for this observation is the effects of chance and also other trial specific differences in individual trial design and conduct.

Two published studies of the long term cost effectiveness of intensive dose statins have been identified.[19,27] Chan et al considered the lifetime cost effectiveness of intensive-dose statin therapy in high risk patients aged 60 years with coronary artery disease. A Markov model was used, taking clinical effectiveness from the same four trials as our analysis. They concluded that intensive-dose statin is potentially highly cost-effective for patients aged 60 years with ACS, but less so for patients with CAD. Chan et al did not present results for different age groups. In ACS the high dose strategy resulted in a gain of 0.35 QALYs per patient over a life time. The majority of these benefits accrued through the reduction in all cause mortality in the first two years of therapy. Our results suggest that few QALYs are gained, but this is due in part to the assumption that patients remain in the ACS state for one year rather than two. Even based on our more conservative assumptions the use of high dose statins remains cost effectiveness.

Lindgren et al evaluated the long term cost–effectiveness of intensive dose atorvastatin when compared with generic simvastatin for secondary prevention in four Scandinavian countries, based on the IDEAL trial.[27] Both direct and indirect costs were included in the analysis. Cost effectiveness varied between 35 210 Euros (£26, 240 at £:EURO exchange rate of 1:1.3419[28]) in Norway and 62 639 Euros (£46, 680 at £:Euro exchange rate of 1 : 1.13419[28]) in Finland, due to differences in price of the two drugs between countries. The price difference between the therapies was identified as one of the key drivers of the cost-effectiveness of high-dose atorvastatin. The inclusion of indirect costs makes it difficult to compare the results directly and given the potential uncertainties relating to the estimation of indirect costs[29] it would be useful to be able to compare the results based on direct costs only.

Our study has several limitations. The model does not include health states for hospital interventions (PCI, CABG) due to the absence of reliable data describing event rates in the UK. However the impact is likely to be small given that the cost of non-fatal MI in the first year, taken from Palmer et al, does include the cost of revascularisation for a proportion of patients.[22] The stable CAD studies reported only combined fatal and non fatal stroke events and we assumed that these are representative of rates for non fatal stroke. The model does not take into account the cost or utility impact of adverse events. Minor adverse events are likely to have limited resource and cost implications in terms of related medications and hospitalizations and therefore their omission is expected to have a limited impact on the ICER. Significant adverse events are rare, but are more likely with higher doses.[30] Severe adverse events are assumed to lead to treatment discontinuation, exposing patients to placebo level of risks and are therefore taken into account by the intention-to–treat analysis. Patient adherence to treatment with statins is, however, a broader issue. It has been reported that only half the patients at highest risk after myocardial infarction continue to take their statins at 2 years,[31] suggesting that not all the potential benefits for this group of patients are being realised.

Our base case analysis assumes that the relative risks derived from the two ACS studies are representative of the benefits in the first year after an event; the relative risks derived from the two CAD studies are assumed to be representative of the benefits in subsequent years. To test this assumption in sensitivity analysis the relative risks from the ACS studies were applied to all transitions. This increases the benefits over time and reduces the cost per QALY to £7,059.

This analysis was undertaken using simvastatin 20mg /day as the standard dose statin, based on the available evidence with three of the four trials using simvastatin 20mg /day or pravastatin 40mg /day as standard therapy. The use of simvastatin 40mg /day rather than 20mg /day would cost over 80% more, but produce only 6% more LDL cholesterol lowering and would therefore be expected to impact only slightly on the benefits offered by intensive dose therapy. However the clinical evidence is not currently available to assess the value of simvastatin 40mg /day following ACS and hence to directly compare these options. In addition, drug interactions for simvastatin 40 mg /day are likely to be a more significant issue. Screening data on 5,000 contemporary UK ACS cases from the recent SPACE ROCKET trial show that there are specific contraindications to simvastatin 40mg /day in 55% of patients due to interacting drug treatments; renal impairment; excess alcohol consumption / liver impairment or other general statin contraindication (Bailey et al. SPACE ROCKET screening registry - Personal Communication).

In conclusion this analysis suggests that intensive statin regimens (represented by atorvastatin 80mg /day) are cost effective compared with standard statin regimens (represented by simvastatin 20mg /day) for patients with ACS over the age of 60 years. Recent registry studies report a mean age of 72 years for ACS patients admitted to UK hospitals[32,33] and hence this comparison applies to the great majority of ACS patients. Further research on the evidence of intensive dose statins on mortality for this patient group is required.

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Table 1: Examples of transitions for patients receiving no treatment {Ward 2007}

Markov model health state	Non fatal MI	Non fatal Stroke	Fatal CHD	Fatal Stroke	Any event
Age 55 years					
New UA (1st year after event)	4.97%	-	5.55%	0.25%	10.77%
Post UA (> 1st year after event)	3.48%		1.00%	0.04%	4.52%
New MI (1st year after event)	11.52%	0.32%	3.19%	0.14%	15.18%
Post MI (> 1st year after event)	1.79%	0.10%	0.91%	0.04%	2.84%
New Stroke (1st year after event)	0.31%	4.59%	1.11%	1.11%	7.12%
Post Stroke (> 1st year after event)	0.31%	1.86%	0.49%	0.49%	3.14%
Age 65 years					
New UA (1st year after event)	4.88%		10.31%	0.46%	15.65%
Post UA (> 1st year after event)	6.32%		1.19%	0.05%	7.57%
New MI (1st year after event)	10.19%	0.68%	5.99%	0.27%	17.12%
Post MI (> 1st year after event)	1.85%	0.22%	1.52%	0.07%	3.65%
New Stroke (1st year after event)	0.55%	4.81%	2.60%	2.60%	10.56%
Post Stroke (> 1st year after event)	0.55%	2.23%	1.04%	1.04%	4.87%
Age 75 years					
New UA (1st year after event)	4.66%		16.71%	0.74%	22.11%
Post UA (> 1st year after event)	11.22%		1.39%	0.06%	12.67%
New MI (1st year after event)	8.74%	1.41%	10.88%	0.48%	21.51%
Post MI (> 1st year after event)	1.78%	0.47%	2.35%	0.10%	4.71%
New Stroke (1st year after event)	0.80%	4.83%	5.86%	5.86%	17.35%
Post Stroke (> 1st year after event)	0.80%	2.46%	2.06%	2.06%	7.37%

UA=unstable angina; MI=myocardial infarction, Str=stroke

Table 2: Relative risks, utilities and costs used in the model

Parameter	Mean	Lower limit	Upper limit	Source (ref)
RR: standard dose versus placebo				
non fatal MI	0.70	0.63	0.77	{Ward 2007}
non fatal Stroke	0.75	0.63	0.90	
fatal CHD	0.77	0.72	0.83	
fatal CVD (non CHD)				
all cause mortality	0.84	0.78	0.90	
RR ACS: intensive dose versus standard dose				
non fatal MI	0.92	0.78	1.07	{PROVE-IT
non fatal Stroke [a]	0.89	0.61	1.31	A to Z}
fatal CHD	0.78	0.45	1.34	
fatal CVD (non CHD)				
all cause mortality	0.76	0.62	0.94	
RR CAD: intensive dose versus standard dose				
non fatal MI	0.81	0.73	0.91	{TNT and
non fatal Stroke [a]	0.82	0.70	0.96	IDEAL}
fatal CHD	0.90	0.73	1.11	
fatal CVD (non CHD)				
all cause mortality	0.99	0.89	1.10	
Annual treatment costs				
Standard dose (20mg simvastatin)	£24.25			{BNF}
High dose (80mg atorvastatin)	£367.74			
Monitoring for intensive dose (yr1)	£58.88			{PSSRU & Netten}
Monitoring for intensive dose (yr2+)	£29.44			
Annual health state costs [b]				
New unstable angina	£477	£358	£596	{Ward 2007}
Post unstable angina	£201	£151	£251	
New MI	£4,934	£3,701	£6,168	
Post MI	£201	£151	£251	
Fatal CHD	£1,261	£946	£1,576	
New stroke	£8,070	£6,053	£10,088	
Post stroke	£2,169	£1,627	£2,711	
Fatal stroke	£7,425	£5,569	£9,281	
Utilities				
UA first year	0.77	0.65	0.89	{Ward 2007}
UA subsequent year	0.72	0.85	0.97	assumed
MI first year	0.65	0.76	0.87	{Ward 2007}
MI subsequent year	0.71	0.84	0.96	assumed
Stroke first year	0.53	0.63	0.72	{Ward 2007}
Stroke subsequent year	0.59	0.69	0.80	assumed
Age related utility				(Kind 1998)
Constant	1.06	0.03		
Beta	0.00	0.00		

[a] assumed same as "all stroke". [b] inflated to 2006; RR=relative risk; MI=myocardial infarction; CHD=coronary heart disease; ACS=acute coronary syndrome; CAD=coronary artery disease; UA=unstable angina

Table 3: Clinical outcomes and costs: Average values for a cohort of 1,000 males aged 60 years (using 10,000 MonteCarlo simulations)

	No treatment	Standard dose statin	High dose statin
Clinical outcomes			
Initial 5 year period			
Number of MIs	154	107	93
Number of Strokes	41	30	26
Number of fatal CHD	90	75	65
Number of fatal stroke	16	13	12
Total number of events	300	225	195
Discounted life years	3,759	3,827	3,880
Discounted QALYs	2,387	2,434	2,469
Lifetime model			
Number of MIs	323	258	222
Number of Strokes	143	120	100
Number of fatal CHD	363	340	327
Number of fatal stroke	90	85	82
Total number of events	920	802	731
Discounted life years	11,130	12,041	12,317
Discounted QALYs	6,815	7,362	7,534
Cost outcomes (discounted) (£,000)			
Total costs (5 year)	£3,691	£3,527	£4,787
Total cost (lifetime)	£10,617	£10,902	£15,000
Cost effectiveness (lifetime horizon)		Standard vs No treatment	High dose vs Standard
Incremental life years		911	276
Incremental QALYs		547	172
Incremental costs		£285,617	£4,098,141
Incremental cost per life year gained		£312	£14,844
Incremental cost per QALY		£520	£23,779

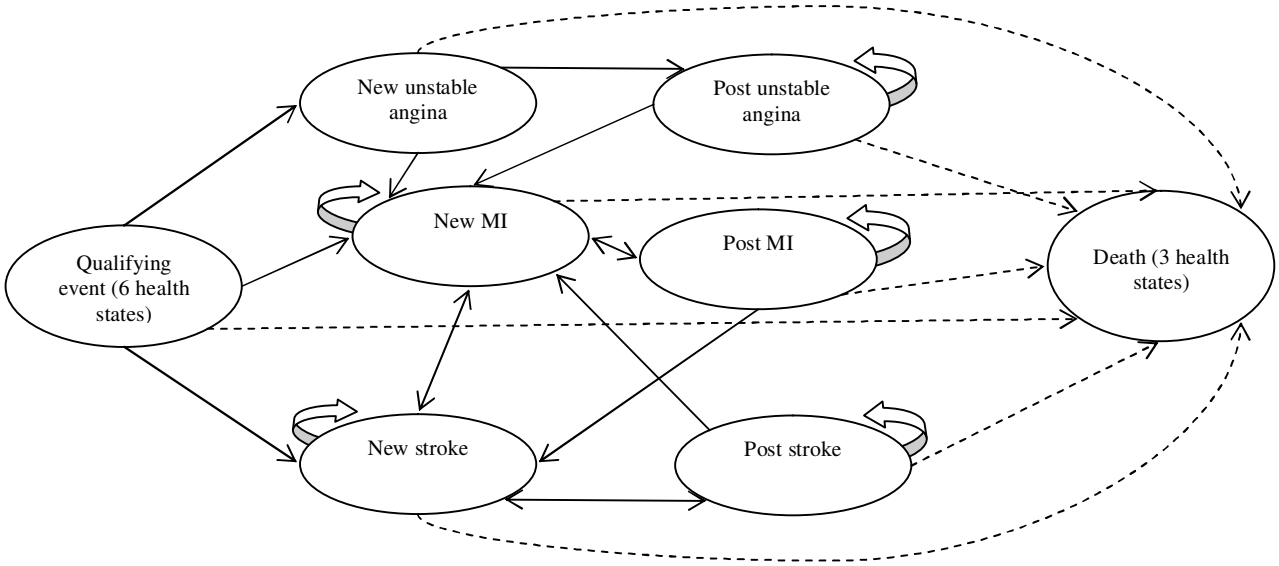
MI= myocardial infarction; CHD=coronary heart disease; DoC= death through other causes; QALY=quality adjusted life years.

Table 4: Results for deterministic sensitivity analyses (basecase: male age 60 years, lifetime horizon).

		Standard versus No treatment			High dose versus Standard		
No.	Analysis	Cost	QALY	ICER	Cost	QALY	ICER
0	**Base case**	**£285**	**545**	**£520**	**£4,098**	**172**	**£23,779**
	Discount rates for costs and QALYs						
1	No discount	£791	996	£794	£5,914	279	£21,169
	Health State (HS) & monitoring costs						
2	HS costs: plus 50%	£273	547	£498	£4,027	172	£23,429
3	HS costs: minus 50%	£286	547	£523	£4,162	169	£24,620
4	Addition of monitoring cost for intensive dose	£280	548	£510	£4,455	171	£26,086
	Treatment costs						
5	Increase cost of standard dose: to equivalent of simvastatin 40mg=£44.32 pa	£523	546	£958	£3,583	170	£22,657
6	Decrease cost of intensive dose (to 80%): atorvastatin 80mg = £294.19 pa		no change		£3,192	172	£18,606
	Health related quality of life						
6	HS utilities: plus 15% - lower detriment	£279	629	£443	£4,092	197	£20,800
7	HS utilities: minus 15% - higher detriment	£279	465	£601	£4,091	144	£28,492
	Effectiveness data						
8	Separate RR for Fatal CHD and Fatal Stroke (with RR for non CVD death = 1)	£157	507	£309	£4,165	214	£19,474
	Using 95% CI for standard dose RR, holding intensive dose RR at mean values						
9	All Cause Mortality: LCI = 0.78	£564	751	£751	£4,193	165	£25,374
10	All Cause Mortality: UCI = 0.90	£8.9	352	£25	£3,990	173	£23,129
	Using 95% CI for CAD RR, holding standard dose and ACS RR at mean values						
11	All Cause Mortality: UCI =1.10		No change		£3,590	-80	-£44,650 (Dd)
12	All Cause Mortality: LCI =0.89		No change		£4,587	416	£11,034
	Using 95% CI for ACS RR, holding standard dose and CAD RR at mean values						
13	All Cause Mortality: UCI =0.94		No change		£3,996	111	£36,089
14	All Cause Mortality: LCI = 0.62		No change		£4,212	243	£17,367
	Cohort characteristics						
15	Male, starting age 50 years	£238	526	£453	£5,196	137	£37,822
16	Male, starting age 70 years	£371	514	£721	£297	209	£14,205
17	Female, starting age 60 years	£538	537	£1,001	£4,411	174	£25,298

ACS=acute coronary syndrome; RR=relative risk; CAD=coronary artery disease; UCI=upper confidence interval; LCI=lower confidence interval; MI=myocardial infarction; CHD = coronary heart disease. Pa = per annum
Ds= Dominates - strategy is more effective and costs less
Dd=Dominated - strategy is less effective and more expensive

Figure 1: Patient pathway in Markov Model



The qualifying event includes 6 health states (new UA, new MI, new Stroke, post UA, post MI, post Stroke). The absorbing health state, death, includes 3 health states (fatal CHD, fatal Stroke, death through other causes). Transitions from new event health states use first year event rates while transitions from post event health states use subsequent year event rates.

Figure 2: Cost effectiveness acceptability curve for intensive dose versus standard dose statin treatment

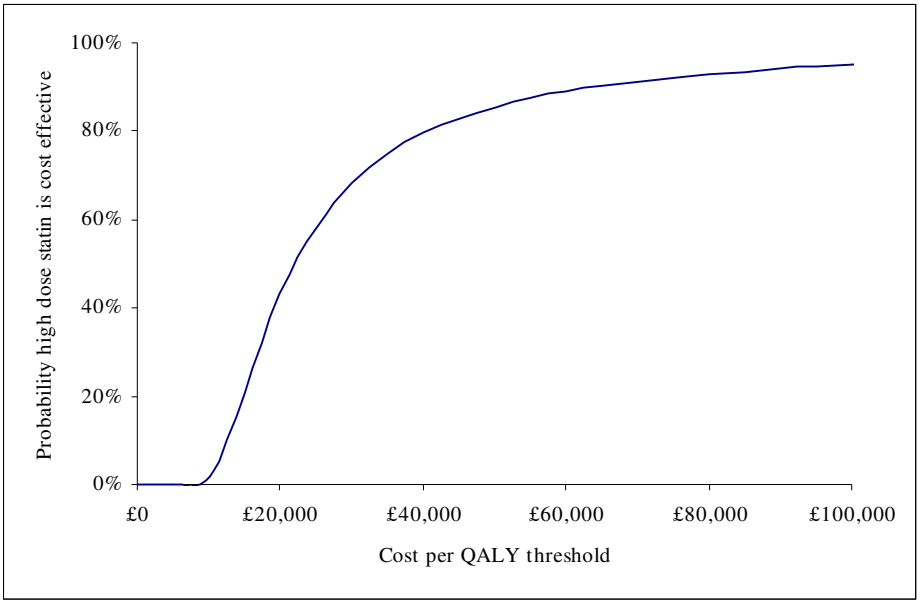


Figure CEAC for basecase

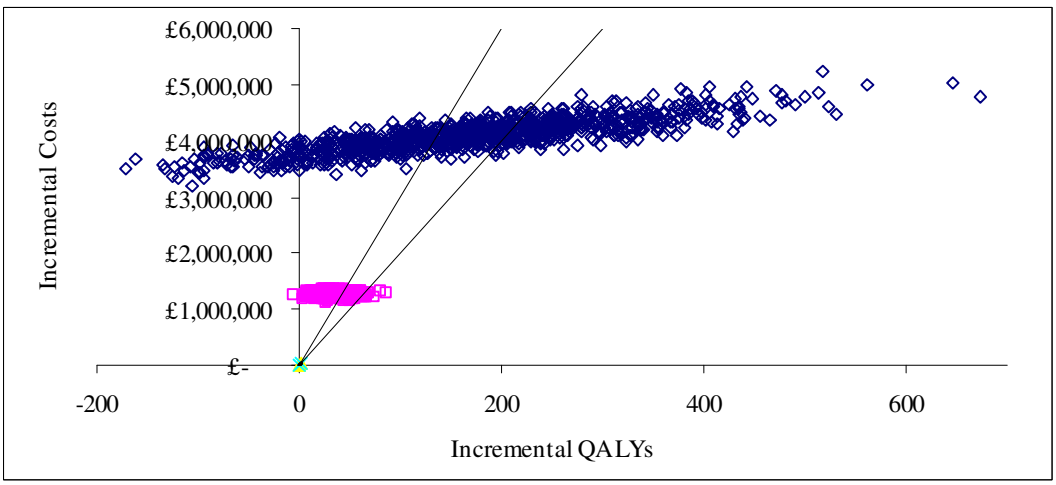
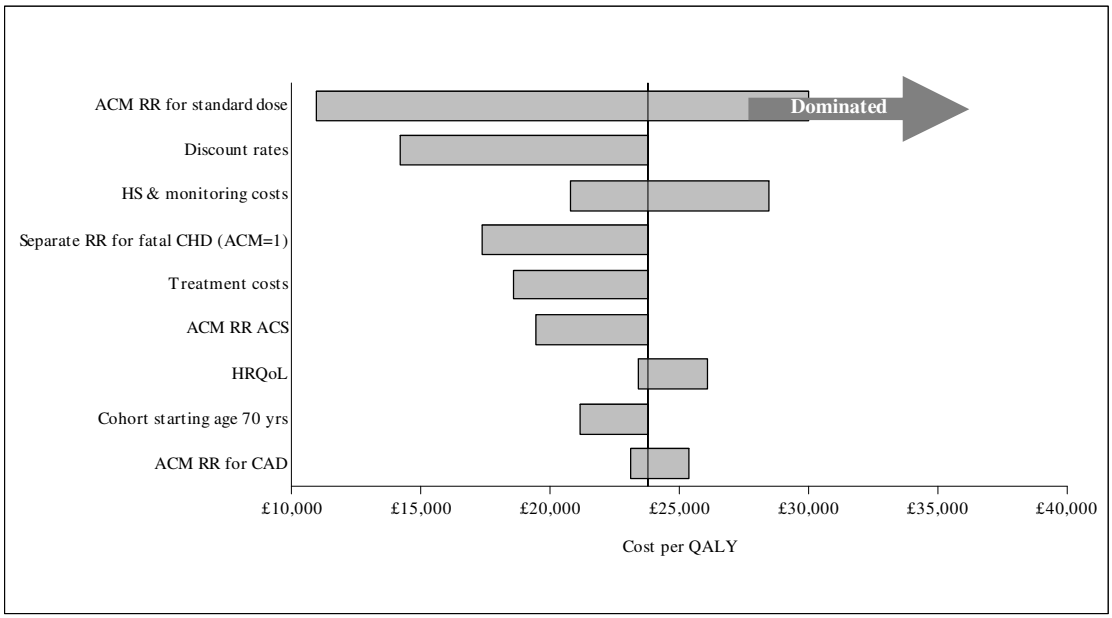


Figure 3: Tornado diagram showing robustness to changes in key parameters



The variables that have the most influence on the cost per QALY estimated by the model have the widest bars at the top of the tornado diagram. RR = relative risk; ACM = all cause mortality, ACS = acute coronary syndrome, CAD = coronary arterial disease HRQoL = health related quality of life; HS = health state.