Individual participant trial data and cost-effectiveness in a heterogeneous population

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Abstract

Aims and data: Cost-effectiveness analyses based on clinical trials often report a single cost-effectiveness estimate and ignore variation across study participants. Cost-effectiveness decision models frequently explicitly model heterogeneity, but often based solely on published summary data and modelling assumptions. In this paper individual participant data (IPD) from the 20536 patient Heart Protection Study are employed to demonstrate the benefits of IPD when evaluating cost-effectiveness in people at different vascular disease risk and age.

Methods: The IPD were used to develop and validate a decision analytic model. A series of risk and cost equations estimate disease progression and healthcare costs with and without the intervention. Cost-effectiveness is evaluated for each trial participant and summarized across subcategories. Parameter uncertainty is evaluated through bootstrapping.

Results: IPD permits more accurate model development, for example capturing the complex relationship between non-fatal events and subsequent survival (i.e. a heart attack or stroke increases the hazard of a subsequent such event more than 3-fold in the first year (hazard ratio 3.2 (95% CI 2.9 to 3.5)), and about 2-fold in the second year (2.0 (1.7 to 2.3))). The cost-effectiveness model also leads to more efficient estimates, narrowing the confidence intervals around incremental costs, major vascular events avoided and life years gained at five years by about 30% to 40% compared to censoring adjusted estimates during trial. Validation in subcategories of participant and evaluation of parameter uncertainty by preserving the interdependence between the different elements of the model are also illustrated.

Paper presented at the Health Economics' Study Group Meeting,
Brunel University, 5-7 September 2007

Conclusions: IPD informs the heterogeneity and offers substantial advantages in validating cost-effectiveness models.

I. Introduction

Decision analytic cost-effectiveness modelling to synthesise all available evidence is the recommended analytical framework in technology assessment for decision making in the UK National Health Service (Claxton et al. 2005;National Institute for Clinical Excellence 2004;Sculpher et al. 2006). These models are usually based on review of the published evidence to inform the structure of the model and the model parameters (Cooper et al. 2005;Philips et al. 2004). The need to appropriately synthesise evidence from different studies and study designs and the need to correctly incorporate the correlations between the model parameters have been discussed (Fryback, Chinnis, & Ulvila 2001) and Bayesian approaches are proposed to facilitate the evidence synthesis (Ades 2003;Ades, Claxton, & Sculpher 2006;Ades & Cliffe 2002;Ades & Lu 2003;Caldwell, Ades, & Higgins 2005;Lu & Ades 2004;Welton & Ades 2005). Within the current framework the use of individual participant data for the development and validation of decision analytic models is limited.

In this paper we discuss the value of individual participant trial data for the evaluation of cost-effectiveness, using the example of a cardiovascular disease preventive intervention across a heterogeneous population. A decision analytic cost-effectiveness model is developed to extrapolate survival and healthcare costs beyond the duration of the study. The individual participant data informs the structure and parameters of the cardiovascular disease model and allows for its internal validation. Furthermore, a comparison of the short term cost-effectiveness estimates within the duration of the study with estimates from the decision model is used to evaluate the impact of modelling on the uncertainty of cost-effectiveness components.

We illustrate the issues using data from the Heart Protection Study (HPS), a large streamlined randomised controlled trial of cholesterol lowering with simvastatin versus placebo in 20,536 patients at an increased risk of cardiovascular disease. The study

effectiveness and cost-effectiveness results are reported elsewhere (Heart Protection Study Collaborative Group 2002;Heart Protection Study Collaborative Group 2005;Heart Protection Study Collaborative Group 2006) and here we focus on our methods of developing and validating the cost-effectiveness analysis of lifetime 40mg simvatatin daily based on the individual participant data from the study. The estimated life years gained, hospital costs saved and cost-effectiveness are reported within quintiles of study participants defined by their estimated five year risk of a major vascular event[1]- ranging from 12% to 42% (Heart Protection Study Collaborative Group 2005)- to account for the impact of patient heterogeneity, further subdivided into four age groups (40 to 49, 50 to 59, 60 to 69, and above 70 years) to allow for the additional (to vascular disease risk) impact of age on lifetime cost-effectiveness[2] (Jonsson 2001;Russell & Sisk 2000).

II. Methods

II.1 Markov decision analytic cardiovascular disease model and patient heterogeneity

The aim of the cost-effectiveness model is to estimate the occurrence of cardiovascular events and death, life expectancy and healthcare costs with and without the use of 40mg simvastatin daily. Cardiovascular epidemiology has shown that cardiovascular risk is multifactorial, with factors such as age, gender, lipid levels, blood pressure, smoking status and prior disease being the main determinants of future disease events. We develop a decision analytic Markov model based on an integrated system of parametric equations informed by the individual participant data from the HPS, and use it to estimate the absolute risk of vascular events and death during each subsequent year.

Cardiovascular event risk equations

Annual risks of occurrence of three main adverse events reported in the trial- "vascular death" (VD, defined as coronary death or fatal stroke), "nonfatal major vascular event"

[1] Major vascular event is defined as heart attack, stroke or arterial revascularisation procedure.
[2] "From a cost-effectiveness viewpoint, treatment recommendations should be based on absolute coronary risk since benefits are related to reduction in absolute risk. However, because prevention of coronary events will have different consequences for younger than older people, and for men than women, sex and age should be taken into account separately, even if they are implicitly included in the assessment of absolute risk" (Jonsson 2001).

(NFMVE, defined as nonfatal myocardial infarction, stroke, or arterial revascularisation), and "other vascular event" (OVE, defined as admission for angina, heart failure, or other vascular problems)- are estimated as functions of baseline risk factors, allocation to simvastatin, current age and within study experience of vascular events.

Continuous time parametric survival models estimated the risk of three nested categories of events: i) vascular death, ii) NFMVE or vascular death, and iii), any vascular event. The experience of the event of interest within a year (first occurrence if more than one event of interest was experienced within the year) was the endpoint and the standard errors for the estimates were adjusted for the presence of clustering at individual level (i.e. more than one endpoint could have been experienced by an individuals in different years within the trial). Weibull parametric survival models were employed, but where the ancillary parameter indicated that there was no evidence of a time dependent hazard, the model was reduced to an exponential model. Given the large sample size, risk factors with a p-value of less than 0.01 were considered statistically significant and retained within the models.

Separate statin treatment effects were fitted in the three equations (for VD, NFMVE or VD, OVE or NFMVE or VD), but the same effect was modelled for the risk of first within trial and subsequent events (i.e. the relative risk reduction was assumed to be identical, independently of whether the event is the first or subsequent event for an individual within the study).

The experience of vascular events within the trial increases the hazard of subsequent vascular events with a more recent and more serious history being more important. Therefore, preliminary analyses based on the HPS data informed the development of a hierarchy (in decreasing order) of six mutually exclusive event history variables that was employed: (1) NFMVE in previous year; (2) OVE only in previous year; (3) NFMVE in year before previous; (4) OVE only in year before previous; (5) earlier within trial NFMVE history; and (6) earlier within trial OVE only history. These event history variables together with participant’s current age entered the models as annually updated time-dependent covariates.

Non vascular mortality

The fourth event of the model, the mortality rate for non-vascular causes, is evaluated based on a Gompertz survival model for the nonvascular deaths observed within the HPS with age, gender and smoking status as explanatory variables. This approach aims to closely model the experience of trial participants for the purpose of within trial model validation, but when the model is used for lifetime cost-effectiveness analysis nonvascular death rates based on official life table data are used. **Figure 1** presents the structure of the Markov model with the vascular events history states that trigger different probabilities of transitions to new cardiovascular events or death.

Effects of treatment in presence of non-compliance with allocated intervention

In the HPS, a proportion of participants allocated to simvastatin discontinued taking the statin tablets (18% by study end), and a proportion of those allocated to placebo started taking non-study statin prescribed by their general practitioners (32% by study end) (Heart Protection Study Collaborative Group 2002). This 'drop out' from treatment among those allocated simvastatin and 'drop in' to treatment among those allocated placebo have reduced the observed LDL cholesterol difference in the trial relative to perfect adherence to the study protocol. In this situation of non-compliance with study statin and contamination with non-study statin it is obvious that the intention to treat relative risk reported by the primary analysis is underestimating the statin effectiveness of actually taking a statin. We have used the individual participant data and developed a method of analysis that respects the randomisation and is similar to the method suggested by Cuzick et al. (Cuzick, Edwards, & Segnan 1997) to estimate the full effect of actually taking statin as compared to not taking statin. The LDL cholesterol difference between the trial arms, measured in random samples of about 10% of trial participants annually and in all participants at about 4.6 years of follow-up, was adjusted for the proportion of participants in each group that were taking statin, in order to estimate the full treatment effect that corresponds to a 1 mmol/L reduction in LDL cholesterol. Thus, if $s(t)$ is the proportion taking statin in the simvastatin arm, and $p(t)$ the proportion taking statin in the placebo arm of the trial, the observed LDL cholesterol difference at time t is expected to be $\Delta LDL(t) = \big(s(t) - p(t)\big) \times \Delta LDL(t)_{S40}$, where

$\Delta LDL(t)_{S40}$ is the LDL cholesterol reduction achieved by full compliance with 40mg simvastatin daily and is estimated by

$$\Delta LDL(t)_{S40} = \frac{\Delta LDL(t)}{s(t) - p(t)}.$$

Therefore, by adjusting the allocation to simvastatin by

$$s(t) \times \Delta LDL(t)_{S40} = \frac{s(t) \times \Delta LDL(t)}{s(t) - p(t)}$$

and the allocation to placebo by

$$p(t) \times \Delta LDL(t)_{S40} = \frac{p(t) \times \Delta LDL(t)}{s(t) - p(t)}$$

treatment effects on event rates corresponding to reduction of LDL cholesterol by 1mmol/L are estimated. **Figure 2** presents a schematic of the impact of non-compliance and contamination on the LDL cholesterol difference between trial arms.

Second, although the plasma LDL cholesterol response to statin is quick, the effect of lower LDL cholesterol on vascular risk may emerge more slowly. Effects corresponding to LDL cholesterol difference, averaged across different time periods (from immediate to two-year average) were considered at the stage of model validation. The average LDL cholesterol difference over the previous 18 months provided a good fit to the observed effect on major vascular events during the study and was employed in the model.

Health care costs in the Markov model

Each observed hospital episode within the HPS was mapped to one of 40 hospital specialties, and the most recently available national average cost per inpatient day for these specialties from UK Trust Financial Returns was applied to generate the cost per hospitalisation episode (Heart Protection Study Collaborative Group 2005). Annual hospitalisation costs (vascular and non-vascular related) were evaluated for each trial participant. A linear regression model then evaluated the annual hospitalisation costs with age, gender, baseline prior vascular disease or diabetes, other risk factors measured at baseline, vascular or non-vascular death, NFMVE or nonfatal OVE in the current

year, and history of vascular event (within-trial experience of NFMVE or OVE in previous years) as explanatory variables. The estimates of the coefficients were adjusted for clustering by participant to account for the fact that trial participants provide resource use, and therefore cost data, for all years of their participation in the study. The hospitalisation costs for each year within the cost-effectiveness model were then evaluated based on the regression model and the participants' characteristics at baseline, current age and the vascular events and death simulated in the model.

The statin treatment cost is added for each year within the model when the intervention has been taken.

Uncertainty in the model

The decision analytic model is fully determined by the event risk equations and the estimated annual hospitalisation costs. Parameter uncertainty is investigated based on a nonparametric bootstrap approach (Efron & Tibshirani 1993) that involves resampling (with replacement) from the original dataset, then refitting all risk and cost equations on the resampled data. 1000 samples from the original data of 20536 participants were used to evaluate the vascular events and costs equations. The outcomes for all trial participants were evaluated based on the decision model and each of the parameter sets and summarised across the risk quintiles (and age if relevant) and the 95% confidence intervals were summarised based on the percentile method.

II.2 Internal validation of the model using the HPS population

We tested the consistency of the predicted annual event rates of modelled vascular events against the observed event rates after adjusting for the administrative censoring in the last year of the study.(Bang & Tsiatis 2000) Furthermore, we have explored the consistency of the main treatment effect by examining differences in rates of major vascular events between the placebo- and simvastatin-allocated participants during the 5 year duration of the study among all participants as well as among participants in different quintiles of vascular disease risk. The Markov model was adapted for the pattern of statin use and the LDL cholesterol difference observed between trial arms in the HPS. Treatment effects, determined by average LDL cholesterol difference between study arms over time periods ranging from current to 2 years, were employed to guide the choice of a model that fits well the temporal pattern of treatment effect observed in

the study. The parameterization of the decision model with respect to the pattern of emerging statin effect was decided upon within the process of internal validation.

II.3 Components of cost-effectiveness: decision model versus trial data

Decision analytic models are the primary tool to evaluate the value of further information based on the parameter uncertainty in model estimates and a given decision rule. It is rarely acknowledged that value of information analyses are driven by the model and its representation of the uncertainty. In order to address this limitation we compare measures of uncertainty in observed mean differences of major vascular event rates, vascular death rates, life expectancy and cost of hospitalisations between the arms of the trial overall and within quintiles of vascular disease risk with the corresponding uncertainties evaluated by the decision model. Confidence intervals and coefficients of variation are compared. As the patient heterogeneity is identical in both data-driven and model based analyses, any differences are expected to be driven primarily by the modelling assumptions.

III. Results

III.1 Model parameterisation

Event risk equations

During the HPS there were 1718 vascular deaths, 5755 years with MVE or VD (4780 first within the trial and 975 subsequent) and 11420 years with OVE, MVE or VD (7732 first and 3688 subsequent). The hazard ratios (95% CI) of the covariates included in the event risk equations are shown in **Table 1**. The estimated hazard ratios of the event history variables show that the impact of a nonfatal vascular event is largest shortly after the event, and decreases in time. The estimated effects for an event history more than two year previously were consistent with the estimated size of the effect of similar disease history at randomisation. This suggests that it is appropriate to separately model the impact within the first two years post nonfatal vascular event (**Figure 1** and **Table 1**). Modelling age as a time dependent variable within the equations leads to the reduction of the Weibull parametric survival models to exponential (shape parameter

consistent with 1) for the two combined vascular endpoints, but the vascular death equation remained with a strong positive shape parameter.

A Gompertz survival model for the risk of nonvascular death in the HPS was fitted (data not shown). However, as expected the estimated nonvascular mortality within the trial differed from that of the general populations, presumably due to the exclusion of patients with serious comorbidities from the trial (consistent with the trial inclusion criteria).

Annual hospitalisation costs

During the follow-up of the HPS, trial participants contributed 111,822 years of data, of which 21% including registered hospitalisations (i.e. with any hospitalisation costs). A number of regression models (linear regression model (GEE); two-part model with first part logistic model and second part GLM model with log link and gamma distribution; and a two-part model with first part logistic model and second part GLM model with identity link and gamma distribution) were compared. These models had similar mean squared errors but the model employing gamma link consistently overestimated annual costs for those individuals with multiple conditions. Subsequently, given the large sample, and the lack of influence from the type of statistical model it was decided that a linear regression model would be used to model the annual hospitalisation costs. **Table 3** reports the coefficients and standard errors for this model. "Background" annual hospitalisation costs that depends on age, gender, and the presence of prior vascular disease or diabetes at study initiation is evaluated. In addition, an experience of a non-fatal major vascular event adds £6067, other vascular event adds £2975, vascular death adds £2272 and non-vascular death adds £3744 to the annual cost in the year of the event. Finally, for each year following a vascular event in which no further vascular event or death has occurred additional £187 are added to the annual hospital costs.

It is important to note that a single vascular event history state is modelled in the annual hospitalization cost equation compared to the six states used in the Markov model. This is because the hospitalisation costs related to history of vascular event were similar for major and other vascular events, as well as for different time periods following a vascular event, and therefore the model of annual costs was simplified.

III.2 Internal validation of the model and the treatment effects of 40 mg simvastatin daily

Figure 3 illustrates the difference in the event rate if current or a 2-year average LDL cholesterol difference between trial arms is used instead of the averaged over previous 18-months. The adjustments based on the current LDL difference or 2-year average difference fail to outline the pattern of the effect as observed in the study. Similarly, adjustments based on 6 and 12-monthly averaging of LDL did not outperform the 18-monthly adjustment (data not shown). The predicted simvastatin effect based on 18-monthly LDL impact on the annual rates of first, subsequent and both first and subsequent nonfatal MVEs or vascular deaths within the study period shows good correspondence with the observed within trial rate difference. **Figure 3** also shows that the impact of the intervention seems to be underestimated in the case of first event and overestimated in the case of subsequent events. Although a stronger treatment effect was estimated on first event compared to subsequent events (data not shown), the difference was not statistically significant and could not justify separate modelling of first and subsequent events, given that most of the HPS participants had some prior disease history before entry into the study. **Table 1** reports the estimated treatment effect of the model based on effectiveness driven by previous 18-monthly average LDL cholesterol difference between trial arms. 1 mmol/l reduction in LDL was associated with 23% reduction in the hazard of major vascular event or vascular death, 18% reduction in the hazard of vascular death and 16% reduction in the hazard of any vascular event. Therefore, the estimated full impact of a 1.5 mmol/l reduction in LDL with 40mg simvastatin in this population on the hazard[3] of NFMVE or vascular death is 32%, on vascular death 25% and on any vascular event 24%. **Table 3** presents the differences between the study arms in the rates of vascular deaths and mean costs of hospitalisations observed in the study (95% CI) and predicted by the model (95% CI) within the quintiles of vascular disease risk for the duration of the study.

[3] The formula that provides the hazard ratio on event of a reduction in LDL-C of 1.5mmol/L is $\ln(HR\_1.5mmol/L) = \exp(1.5 \times \ln(HR\_1mmol/L))$

III.3 Parameter uncertainty: decision model versus trial data

Parameter uncertainty in components of cost-effectiveness evaluated based on the decision model was consistently lower than in analyses directly based on the trial data with reported narrower confidence intervals and smaller coefficients of variation. **Table 4** reports the proportional reduction in the width of confidence intervals and the proportional reductions in the coefficient of variation for the mean differences in major vascular events, in vascular deaths, in life expectancy, and in the costs of hospitalisation for the study overall as well as within the vascular risk quintiles over the 5 year duration of the study. This apparent gain in precision was substantially larger across the subgroups compared to the overall study results and in the cost outcome compared with the events. The latter is likely to be due to the fact that the costs in the model were predominantly driven by the events, which is expected to introduce more structure in the costs and results into gains in precision. Analyses within the first four years of the study showed similar results (data not shown), suggesting that this observation is independent of the adjustment for administrative censoring in data driven analyses.

IV. Discussion

Developing a decision model based on individual participant data

In this paper a Markov decision model of cardiovascular disease, developed based on a large streamlined clinical trial, was used to illustrate three areas in which integrated individual patient data can improve the analytical framework of cost-effectiveness analyses. Firstly, the data could be used to explore the structure of the model (e.g. test modelling assumptions) and to directly evaluate and propagate the impact of patient heterogeneity on outcomes. For example, we have modelled MVEs and OVEs over time, in contrast with other economic analyses that model separately MI, stroke, angina, TIA and revascularisations (Ward et al. 2005). HPS has reported similar relative impact of the intervention on different endpoints and during different time periods from randomisation (Heart Protection Study Collaborative Group 2002). Given the substantial epidemiological evidence that similar risk factors are responsible for the increased risk of different cardiovascular events, the model was developed around the main trial endpoints (major vascular events and vascular deaths). Both first and

subsequent events during the study were used within the estimation of the model parameters, and were subsequently predicted by the model. Parametric survival models were used to extrapolate the event risks beyond the trial follow-up, and time dependent covariates were employed to update the disease risk for the current age and history of vascular events. The impacts of nonfatal vascular events on subsequent disease risk together with the effects of simvastatin treatment were shown to be the main determinants of treatment benefit. One of the main advantages of the individual participant data is the ability to jointly estimate the model parameters and evaluate and propagate the overall uncertainty in parameter estimates. In decision analytic models it is likely that model parameters are correlated, which has particularly strong implications for value of information analyses. Recently, a number of publications have recommended the use of a Bayesian modelling framework to overcome the limitations of ignoring pieces of evidence or the correlation between modelling parameters. In this paper we suggest better use of individual participant data to inform different sources of uncertainty in a more data driven approach. Future research should address approaches to synthesise individual patient and summary data in order to relax the current limitation of basing the analysis on a single, albeit large source of evidence.

Another aspect of the analysis in which the use of individual participant data was indispensable was the estimation of treatment effects in the presence of non-compliance with allocated intervention. We have used an intention-to-treat based approach in which patients were analysed in the arm to which they were randomised, but in which the achieved difference in LDL cholesterol due to study and non-study statin use between trial arms is allowed to drive the effects on subsequent vascular events. We have further explored the dependence of treatment effects not only on current level of LDL cholesterol but its history as well. By doing so, we have suggested that the average LDL cholesterol over the previous 18 months is a better predictor of the effect on vascular events for the intervention studied.

Internal model validation and individual participant data

The second aspect of use of individual participant data is for validation of cost-effectiveness models. The scope for validation of decision analytic models developed through synthesis based on published summary data is very limited, and it has been shown that in current cost-effectiveness studies model validation is largely ignored or is

extremely rare (Cooper, Coyle, Abrams, Mugford, & Sutton 2005). Individual participant data is indispensable for the validation of various outcomes of the model in terms of event rates, survival and costs with and without allocation to the intervention of interest. We have illustrated model validation for different model endpoints and across different time periods in the study. In the presence of heterogeneity across the population the validation should attempt to confirm the performance at the level of heterogeneity at which the results will be reported and used for decision making, which we have illustrated with the internal validation within the quintiles of vascular disease risk in the Heart Protection Study. Nevertheless, internal validation is only the first step: external validation based on further data is highly desirable and is the subject of further research.

Model driven parameter uncertainty

It has been increasingly recognised that the structure of the model could have a serious impact on the cost-effectiveness results and research is being developed to account for the structural uncertainty (Bojke et al. 2006). Although this research is in its infancy and the implications are not well understood, cost-effectiveness models are being increasingly used for decision making and researchers are urged to perform series of value of information analyses driven by their models in order to inform further research priorities.

In the current paper a decision analytic cost-effectiveness model is presented, extensively based on individual participant data from a single large randomised controlled trial. We have used the opportunity to evaluate how the estimates of uncertainty evaluated by the model compare with corresponding uncertainty fully based on the trial data. Our results suggest that modelling per se is likely to lead to seemingly more efficient estimates for the various components of cost-effectiveness which could have important impact on the value of information analyses based on the model. These effects were even more pronounced for the results within quintiles of vascular disease risk which would suggest that using models to evaluate cost-effectiveness across heterogeneous populations is likely to lead to even more structure driven results. Previous analyses suggest that in this application the use of a similar relative treatment effects across different patient populations is likely to be the main, although not sole source of this gain in precision (Heart Protection Study Collaborative Group 2005).

Clearly, the assumptions being made while developing a decision model are likely to impact on the uncertainty and ultimately on the value of information analyses. The direction and strength of impact is likely to differ in various contexts but in general, all else equal, the reduction in uncertainty in the components of cost-effectiveness could lead to lower value of further research.

V. Conclusions

In this paper we have shown that integrated individual participant data is important for the development and validation of decision analytic cost-effectiveness models. In particular, in the context of heterogeneity in cost-effectiveness driven by individual patient characteristics, models based on such data are likely to outperform their counterparts extensively based on summary data by allowing testing of main modelling assumptions and more specific and extensive validation of model performance. We have also shown that the process of modelling is likely to have an important impact on the parameter uncertainty of the estimates and that, compared to data-driven analyses, models lead to apparent gain in precision. This effect should be acknowledged not only with respect to model estimates but also with respect to further value of information analyses, particularly when these are used for setting priorities for further research.

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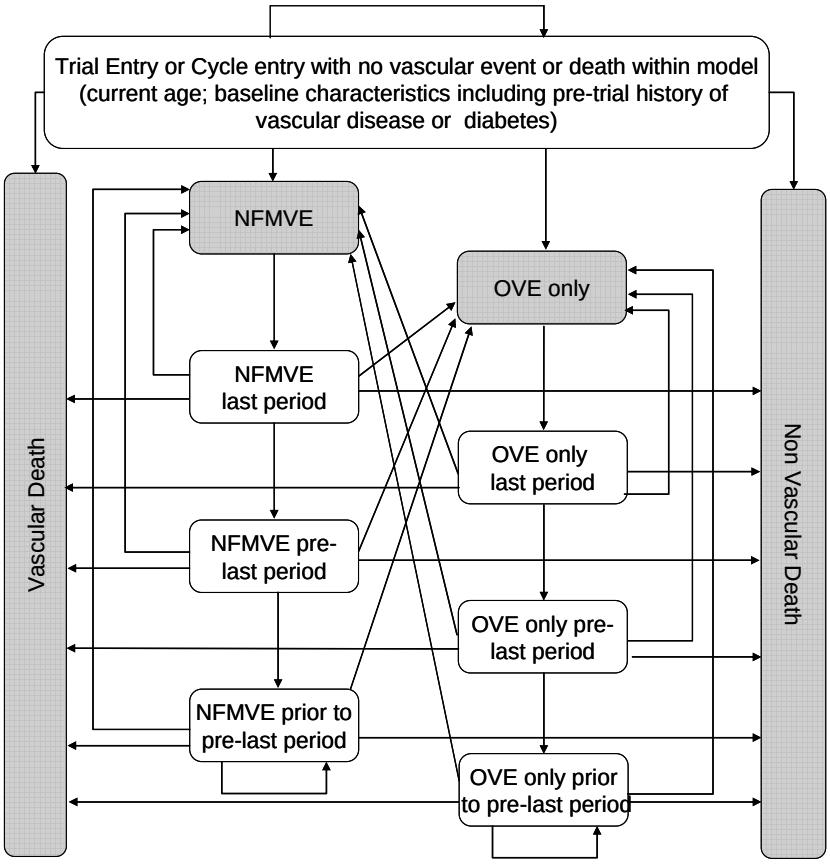
Figure 1 HPS decision analytic Markov model



MVE- major vascular event; OVE- other vascular event (see text for description)
Note: This figure represents a scheme of modelled events; additional states are employed in the model to capture the history of vascular events.

Figure 2 Schematic of impact of compliance with study protocol

on the LDL-C difference between trial arms

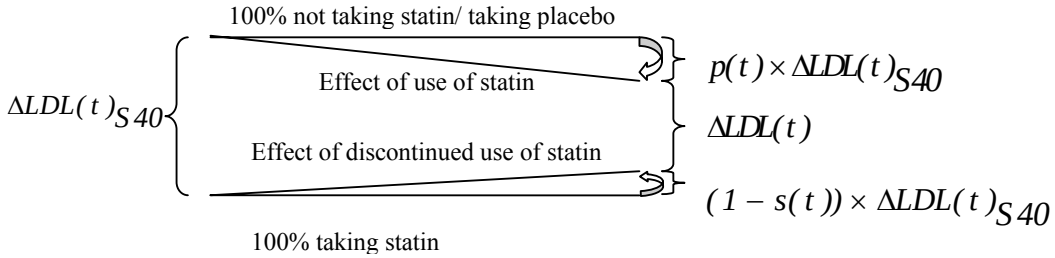


Table 1 Hazard ratios (95% CI) for the risk of annual vascular endpoints derived from the HPS

Endpoint	VD	NFMVE or VD	OVE, NFMVE or VD
Functional form	Weibull	Exponential	Exponential
Parameters	Hazard ratio (95% CI)	Hazard ratio (95% CI)	Hazard ratio (95% CI)
Treatment effect (1mmol LDL difference)	0.82 (0.74 , 0.91)	0.77 (0.74 , 0.82)	0.84 (0.81 , 0.87)
Current Age	1.06 (1.05 , 1.07)	1.02 (1.02 , 1.02)	1.01 (1.01 , 1.02)
Sex (male)	1.41 (1.23 , 1.61)	1.37 (1.27 , 1.48)	1.06 (1.01 , 1.12)
HDL (per 0.3mmol/l)		0.92 (0.90 , 0.95)	0.95 (0.93 , 0.97)
LDL-C (per 0.8mmol/l)	1.07 (1.02 , 1.12)	1.08 (1.05 , 1.11)	1.04 (1.02 , 1.06)
Ex-smoker		1.12 (1.04 , 1.20)	1.09 (1.04 , 1.15)
Current smoker	1.47 (1.28 , 1.68)	1.48 (1.35 , 1.62)	1.27 (1.19 , 1.35)
Treatment for hypertension	1.19 (1.08 , 1.31)	1.15 (1.09 , 1.22)	1.11 (1.07 , 1.15)
Creatinine (per 20μmmol/l)	1.29 (1.23 , 1.35)	1.11 (1.08 , 1.14)	1.11 (1.09 , 1.13)
Baseline disease history			
History of MI	1.57 (1.42 , 1.73)	1.33 (1.24 , 1.42)	1.77 (1.68 , 1.87)
History of CHD but not MI		1.14 (1.06 , 1.24)	1.54 (1.46 , 1.63)
History of one of PVD/CVD/Diabetes	1.52 (1.36 , 1.70)	1.44 (1.35 , 1.54)	1.31 (1.25 , 1.37)
History of >1 of PVD/CVD/Diabetes	2.44 (2.13 , 2.79)	2.33 (2.16 , 2.52)	1.89 (1.78 , 1.99)
Hierarchy of vascular event history within the model			
NFMVE in previous year	2.58 (2.16 , 3.08)	3.22 (2.94 , 3.54)	2.94 (2.74 , 3.16)
OVE in previous year	2.28 (1.94 , 2.68)	2.83 (2.59 , 3.09)	3.54 (3.33 , 3.76)
NFMVE in year before previous		1.98 (1.71 , 2.30)	1.76 (1.57 , 1.97)
NFMVE history more than 1 year old*	1.34 (1.07 , 1.67)		
OVE in year before previous	2.06 (1.64 , 2.57)	1.79 (1.55 , 2.06)	2.32 (2.12 , 2.54)
Earlier NFMVE history within trial		1.66 (1.41 , 1.95)	1.52 (1.34 , 1.71)
Earlier OVE history within trial	1.56 (1.18 , 2.06)	1.32 (1.10 , 1.57)	1.67 (1.49 , 1.87)
Shape parameter	1.10 (1.04 , 1.16)		

Notes: Blank places correspond to risk factor not significant at 1% level.

*In the vascular death risk equation "NFMVE history in year before previous" was combined with "Earlier NFMVE history within trial".

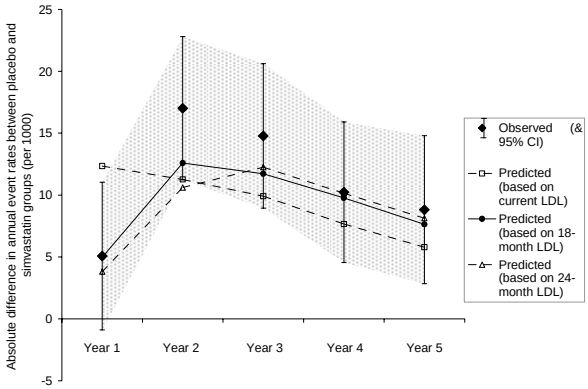
Table 2 Impact of baseline disease history and within trial events on annual hospitalisation costs (£), estimated from the hospitalisation costs and events, observed within the HPS

Covariate	Cost (SE)
Event status within the study	
Died, vascular	2,272 (130)
Died, non-vascular	3,744 (171)
Survived, MVE	6,067 (123)
Survived, OVE, no MVE	2,975 (71)
Survived, no vascular event in current year but vascular event in previous year	187 (20)
Disease before entry into the study	
History of one of PVD/CVD/Diabetes	42 (17)
History of more than one of PVD/CVD/Diabetes	161 (32)
Per a year of age	11 (1)
Female	77 (20)
Constant (i.e. cost for male at age 64 with none of the above events and baseline disease)	281 (20)

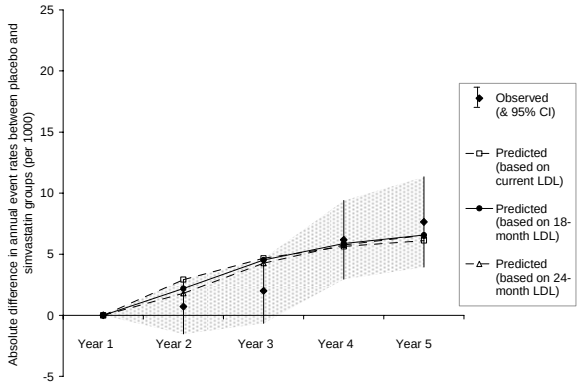
Figure 3 Observed (95%CI) within the study and predicted by the model

difference in the annual rates of nonfatal MVE or vascular death

(a) First nonfatal MVE or vascular death



(b) Subsequent nonfatal MVE or vascular death



(c) First and subsequent nonfatal MVE or vascular death

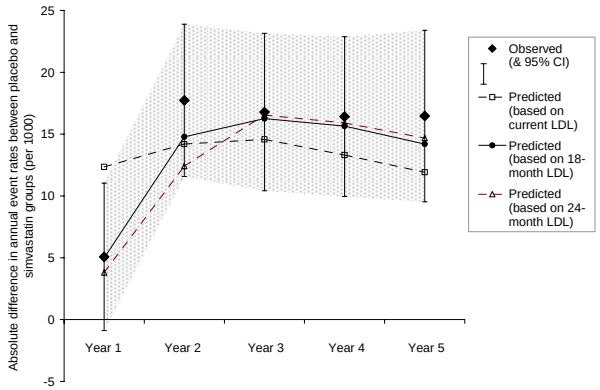


Figure 4 Observed (95%CI) within the study and predicted by the model difference in the annual rates of all nonfatal MVE or vascular death in quintiles of vascular disease risk

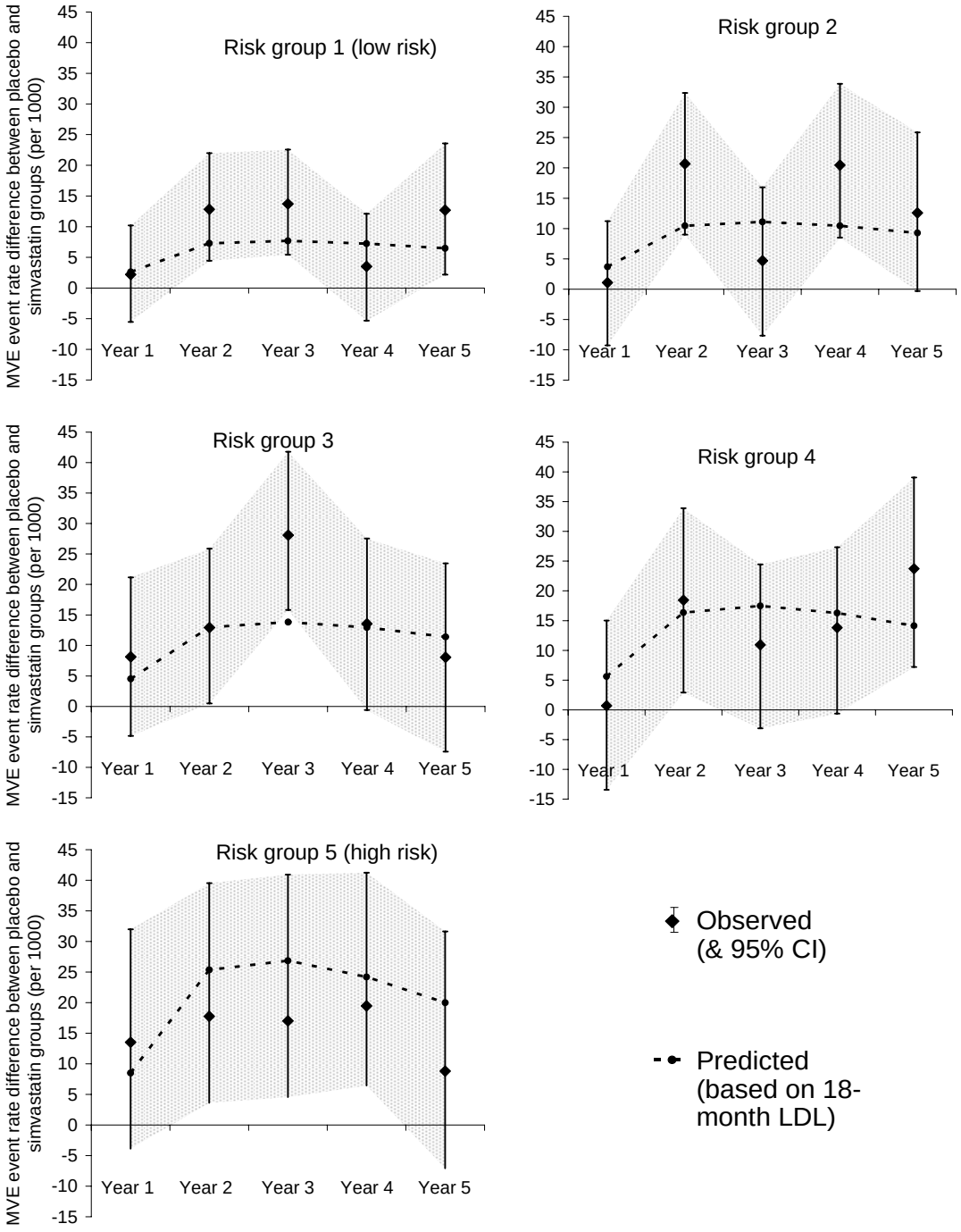


Table 3 Comparison of treatment effects on vascular deaths and hospitalisation costs within 5 years across the vascular risk quintiles

Quintile of vascular risk	Observed during HPS*	Modelled
Vascular deaths avoided per 1000 participants		
1 (low risk)	0.3 (-7.4; 7.9)	4.9 (2.6; 7.2)
2	7.3 (-2.4; 17.7)	8.2 (4.4; 11.9)
3	16.9 (3.3; 29.8)	11.6 (6.4; 16.7)
4	22.1 (6.6; 38.2)	16.3 (9.2; 23.4)
5 (high risk)	21.9 (2.2; 45.5)	28.2 (16.5; 40.7)
All participants	13.7 (7.4; 20.7)	13.8 (7.9; 19.9)
Costs of hospitalisations avoided per person		
1 (low risk)	383 (83; 713)	238 (189; 289)
2	406 (49; 744)	306 (245; 372)
3	85 (-290; 440)	353 (280; 428)
4	199 (-155; 563)	415 (326; 506)
5 (high risk)	878 (389; 1356)	535 (403; 668)
All participants	389(217; 565)	370 (291; 451)

*adjusted for administrative censoring in year five

Table 4 Proportional reduction in 95% confidence intervals (95% CI) and coefficient of variations (CoV): a comparison of parameter uncertainty evaluated based on a decision model and parameter uncertainty evaluated from the data within 5 years

	Component of cost-effectiveness: ΔMVEVD		ΔVD		ΔLY		ΔHC	
	Reduction in 95% CI (%)	Reduction in CoV (%)	Reduction in 95% CI (%)	Reduction in CoV (%)	Reduction in 95% CI (%)	Reduction in CoV (%)	Reduction in 95% CI (%)	Reduction in CoV (%)
1 (low risk)	71%	58%	75%	78%	81%	86%	87%	67%
2	71%	61%	69%	68%	76%	84%	86%	77%
3	66%	56%	66%	55%	72%	68%	83%	98%
4	62%	63%	60%	50%	69%	60%	80%	75%
5 (high risk)	55%	59%	50%	65%	55%	46%	75%	52%
All patients	21%	13%	20%	21%	33%	25%	61%	43%

ΔMVEVD=major vascular events & vascular deaths avoided, ΔVD=vascular deaths avoided, ΔLY=life years gained, ΔHC=hospital costs saved