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DOI:
10.1016/j.jval.2017.03.003

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of primary care interventions for the management of hypertension

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Key words: decision-analytic modelling, modelling, structural uncertainty, hypertension, cardiovascular disease

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Contributors: MCP undertook the review and analyses and wrote the first draft. All authors edited and refined the manuscript and approved the final version.

Competing interests: None declared. The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Health Economics Unit or the University of Birmingham. No funding was received for this manuscript.

Funding sources: No financial support was received for this research.

Abstract

Background: Management of hypertension can lead to significant reductions in blood pressure, thereby reducing the risk of cardiovascular disease (CVD). Modelling the course of CVD is not without complications, and uncertainty surrounding the structure of a model will almost always arise once a choice of a model structure is defined.

Objective: To provide a practical illustration of the impact on the results of cost-effectiveness of changing or adapting model structures in a previously published cost utility analysis of a primary care intervention for the management of hypertension (TASMIN-SR).

Methods: Case study assessing structural uncertainty arising from model structure and from the exclusion of secondary events. Four alternative model structures were implemented. Long-term cost-effectiveness was estimated and the results compared to those from the TASMIN-SR model.

Results: The main cost-effectiveness results obtained in the TASMIN-SR study did not change with the implementation of alternative model structures. Choice of model type was limited to a cohort Markov model and, due to lack of epidemiological data, only Model 4 captured structural uncertainty arising from the exclusion of secondary events in the case study model.

Conclusion: The results of this study indicate that main conclusions drawn from the TASMIN-SR model of cost-effectiveness were robust to changes in model structure and the inclusion of secondary events. Even though one of the models produced results that were different to those of TASMIN-SR, the fact that the main conclusions were identical suggests that a more parsimonious model may have sufficed.

Words: 243

Introduction

High blood pressure (hypertension, defined as blood pressure (BP) persistently (140/90mmHg) is one of the most important but preventable causes of premature morbidity and mortality in the UK and worldwide (1-3). Hypertension is a major risk factor for ischaemic and haemorrhagic stroke, myocardial infarction (MI), heart failure (HF), chronic kidney disease (CKD), cognitive decline and premature death. It has been estimated that in England, a 2 mmHg reduction in average systolic BP for 40-69 year olds could save 1,500-2,000 lives per year (4). One of the most common interventions in primary care is the management of hypertension. Self-management of hypertension, in which individuals monitor their own BP and adjust their own medication, has been shown to lead to significantly lower BP in hypertension, including individuals with higher cardiovascular risk (5-7).

Economic evaluations can be undertaken alongside randomised controlled trials (RCTs) where costs and health outcomes are measured. The primary outcome of RCTs in hypertension is often a change in BP. However, a change in BP corresponds to an intermediate outcome, where the final outcome of interest in this case is the risk of CVD. As RCTs rarely follow patients over the long-term decision-analytic modelling (DAM) provides a vehicle to extrapolate the impact of a change in BP on the risk of CVD events in the long-term. Modelling the course of CVD can be challenging requiring CVD risk factors (smoking, cholesterol, and diabetes), interactions among the risk factors, adverse events and the resulting health states (e.g. stroke sequelae and angina) to be considered.

The TASMIN-SR (6) trial aimed to determine the effect of self-monitoring with self-titration (self-management) of antihypertensive medication on systolic BP among hypertensive patients with suboptimal BP control and pre-existing CVD, diabetes mellitus and CKD compared to usual care. An economic evaluation was undertaken to assess the cost-effectiveness of the self-management intervention compared with usual care (7). The main results indicated that self-management of BP in high risk patients with poorly controlled hypertension not only reduced BP compared to usual care, but also represented a cost-effective use of healthcare resources.

The aim of this study is to assess structural uncertainty in the TASMIN-SR model-based cost-effectiveness analysis (7) and to provide practical illustration of the impact, on results of cost-effectiveness, of changing or adapting model structures in a model-based economic evaluation on the primary prevention of CVD.

Structural uncertainty

We consider structural uncertainty as uncertainty associated with all aspects of model structure, i.e., health states and relationships between health states. This is in contrast to parameter uncertainty, which is very much focused on the parameters used in a model and their uncertainty. Structural uncertainty reflects the extent to which a given model differs from the real system it is intended to reflect (8, 9), and will almost always arise once a choice of model structure or choice of relationships between inputs and outputs is defined within the model development process (10).

Differences in model structure are dependent on the importance given to various aspects of the process being modelled, allowing in some instances for model simplifications. In some cases, these originate when data are not available, although their inclusion could potentially still be relevant for the analysis.

The nature of models being a simplification of reality means that many assumptions need to be adopted during the model building process (10-12). This can potentially lead to a wide variation in model predictions with potential impact on funding decisions (13).

Various alternative statistical methods have been proposed to address the impact of structural uncertainty on the results of cost-effectiveness (8, 10, 13-23) whilst some other authors have provided examples on how to implement some of these methods in different clinical areas (24-26). However, it has been recognised that methods for quantifying structural uncertainty are less well described if compared to methods for characterising parametric or methodological uncertainty (8, 10, 13, 16). A main challenge in addressing structural uncertainty is posed by the many issues that have been identified as 'structural uncertainty' making it a complex task (which may not even be cost-effective) to address properly (27).

Previous studies (16, 28-30) indicate that even though elements pertaining to structural uncertainty are occasionally considered, the assessment of structural uncertainty is not common practice and most modelling tends to omit testing for structural uncertainty. However, it is essential to assess the extent to which model predictions are influenced by such choices made within the model development process (28).

Challenges posed by the assessment of structural uncertainty might be overcome if additional research is undertaken on an experimental basis. Case studies aimed at measuring the impact of changing or adapting chosen model structures on previous results of cost-effectiveness could provide insightful evidence of how

much results would be altered when alternative model structures are implemented. This would also provide evidence of what other elements, besides model structure, may be critical in affecting results of cost-effectiveness

Methods

Taking the TASMIN-SR model as the case study, the research methods of this study are outlined as follows: i) description of the TASMIN-SR model; ii) alternative model structures to TASMIN-SR; iii) definition and implementation of changes to the structure of the TASMIN-SR model; iv) inclusion of secondary events in the TASMIN-SR model; and v) identification of alternative model inputs; and results.

i) Description of the TASMIN-SR model

A detailed description of the original Markov model can be found elsewhere (7). Briefly, the economic evaluation consisted of a model-based cost-utility analysis to assess the long-term cost-effectiveness of the self-management intervention in a 'high risk' patient population compared with usual care, using a Markov model to extrapolate the results of the TASMIN-SR trial (6) given in terms of BP to the long-term risk of cardiovascular endpoints. The study considered a cohort of 70 year old patients (39% female) with sub-optimal hypertension (BP>= 130/80 mmHg at baseline), combined with a history of stroke, diabetes, CHD, and CKD. The model was run over a lifetime time horizon using a six-month time cycle, with results presented from a UK National Health Service (NHS) and Personal Social Services (PSS) perspective.

The structure of the TASMIN-SR model is shown in Figure 1. Patients start in an initial 'HR' or high risk health state representing individuals with hypertension and a history of stroke, CHD, diabetes and CKD. The model simulates the lifetime of these patients until any of three possible events occur (stroke, myocardial infarction (MI) and unstable angina (UA)) or the patient dies from other causes. Individuals that survive an acute phase in any of the health states progress into a post event or chronic phase for that condition until death, with no recurrences of cardiovascular events being possible. A lower quality of life was permanently applied until death in all chronic health states.

The CVD history of patients entering the model was informed by the TASMIN-SR (6) trial data. Transition probabilities of suffering a stroke, MI, or UA were obtained from the literature for each of the high risk conditions. Age-related risk reductions from treatment for MI, UA, and stroke were estimated using trial based systolic BP reductions at 6 and 12 months (Appendix 1 Table 1). Resource use and costs were obtained from trial data and published studies (Appendix 1 Table 2).

ii) Alternative model structures

Structural uncertainty was addressed here by assessing issues such as the adequacy of the type of model used (Markov), the structure of the model (health states and transition probabilities) that translates into plausible alternative model structures, and data availability to inform input parameters, for example the risk of secondary events.

A systematic review was used to inform plausible alternative model structures (30). The review identified model-based studies of interventions aimed at lowering the BP of patients with hypertension and at risk of CVD, where the management of hypertension was part of a primary prevention strategy (30). The aim of the review was to assess compliance of model-based economic evaluations to DAM guidelines (30). The review identified 13 model-based economic evaluations from the literature that were used to inform the changes implemented to the TASMIN-SR model (30). Information on the inclusion or exclusion of potentially relevant comparators, type of model used, health states included, recurrence of events, choice of covariate effects used in the transition probabilities, and the inclusion or exclusion of any other assumption(s) pertaining to structural uncertainty were extracted (Appendix 1 Table 3).

All 13 included studies used Markov models but only two justified their use. Kourlaba (31) justified the use of a Markov model in their own study by saying that it is ‘a conventional model that describes restricted transition probabilities between important health states’ (p.87). Kaambwa (5) indicated that ‘the Markov model overcame limitations associated with within-trial analyses’ (p.1527). In the TASMIN-SR (7) study, it was stated that ‘arguably, a more complex model such as individual patient level simulation could be more appropriate’ (p.9) by incorporating patients' histories more efficiently. The use of Markov models can overcome limitations associated with within-trial analyses, specifically by allowing the modelling of effects and costs of long-term events and the assessment of the long term cost-effectiveness beyond the trial period (32). Even though

individual patient level simulation models have long been praised for their flexibility and ability to record patient attributes (33), because cardiovascular diseases are chronic with recurring events and often result in health states with persistently reduced quality of life, the use of a Markov model is often preferred as a more parsimonious approach (34, 35).

The complexity of the model structures used varied, and this was due to the different approaches to the inclusion of the acute or post-event health states modelled. Model structures were most frequently a reflection of the course and history of CVD events or disease progression. The most common initial state was disease-free and the most common acute states modelled were stroke and MI followed by angina, heart failure and CVD. Few studies modelled only a single health state to describe an acute cardiovascular event (36-38). Some studies modelled additional states such as congestive HF (39), coronary artery disease (40), renal failure (41) or peripheral artery disease (42). Absorbing states consisted of death and non-CVD death. Some authors acknowledged they had excluded states (40, 41) or combinations of health states (HF and stroke) (43) due to data limitations. Compared to the TASMIN-SR model, the review identified a variety of model structures ranging from a simplistic (single CVD morbidity) (37, 38, 44) to more complex approaches (four states including stroke, MI, HF, angina) (39, 42, 43).

The risk of secondary events was modelled in seven (36-40, 42, 43) of the studies reviewed. It could be argued that some of these studies adopted assumptions which would add extra uncertainty to the results. These included assuming that the risk of secondary events was equal to the risk of a first non-fatal event (38), assuming that the patient with a second event will be in a health state worse than the state prior to the event (43), or using expert opinion to inform risks of secondary events (37). Lack of epidemiological data was acknowledged as the main reason for the exclusion of secondary events by some authors (5, 44). The TASMIN-SR model assumed no recurrence of CV events due to the unavailability of data describing secondary events for a high risk population. The choice of modelling approach should be considered as part of the investigation into the impact of structural uncertainty. However in this study, based on the findings of this review, only the Markov model structure was considered.

iii) Definition and implementation of changes to the structure of the TASMIN-SR model

Alternative Markov model structures were primarily identified based on the findings of the systematic review. Validation of the adequacy of this type of model over competing structures such as decision trees, DES or individual sampling model was checked using a framework to select an appropriate model type (34). The validation check indicated that Markov was just the right type of model, considering that estimating interactions between individuals was not necessary whilst modelling health states was important (patient pathways would not be adequately represented by probability trees) and we did not require an excessive number of states (excluding the option of individual sampling model).

Alternative model structures were labelled Model 1 through Model 3 and were developed by varying the number of the health states used from a simplistic structure to one of increased complexity (Figure 2).

Model 1 uses a simplified approximation of the TASMIN-SR model structure. It was informed by the study of Stevanovic (38) and consists of a single CVD state with progression to a chronic state (Figure 2). Following NICE Statin guidelines (45) it was assumed that CVD is a combined state consisting of CHD (MI and UA) and stroke. Assumptions were adopted to estimate transition probabilities, utilities, and costs due to lack of data in the literature to inform a single CVD health state (Table 1). Parameters for the CVD state correspond to a weighted average of input parameters used in the case study model for the states stroke, MI and UA (Table 1).

Model 2 applied the assumption that if the costs and utilities for two health states are the same, then it may not be necessary to distinguish between those two states to estimate lifetime costs and effectiveness (Figure 2) (20). In the TASMIN-SR model, treatment effects and the long-term costs and utilities for states MI and UA were assumed to be the same due to lack of data on UA (Table 1). Under these circumstances, it may not be necessary to include a state UA. Model 2 reflects a restricted version of the TASMIN-SR model consisting of two health states Stroke and MI. The review identified studies using a model structure consisting of two states, named stroke and a MI (31, 46) or stroke and CHD (47). We implemented Model 2 consisting of health states stroke and MI with progression to a chronic phase for individuals who survive (Figure 2 and Table 1).

Model 3 adopted an expanded structure that was informed by the structure of the most complex models (39, 42, 43), using an increased number of health states (Table 1). In Model 3, high risk patients can move to one of a number of primary CVD events, MI, stroke, HF, UA and transient ischemic attack (TIA) or dead from CVD or other causes. Individuals that survive an acute CVD phase naturally progress to a chronic phase where quality of life is lower and where they remain until death.

iv) Inclusion of secondary events in the TASMIN-SR model

TASMIN-SR did not consider recurrence of cardiovascular events due to the unavailability of suitable epidemiological data to reflect the transition of elderly and high risk patients after a primary cardiovascular event. After carefully reviewing sources of data and literature, including relevant NICE guidelines, no additional suitable data were identified. Therefore in this study assumptions based on expert clinical advice were adopted. In Model 4, individuals that survive a primary acute event can either move into a chronic post event phase (asymptomatic) or may experience a recurrent cardiovascular event one year after the first event. In Model 4 we assume that patients will experience only one cardiovascular event per year and following a primary event, patients may experience a second event one year after the first event with the same probability as for the first event. Transitions from a more severe health state (e.g. stroke) to a less severe state (e.g. unstable angina) are omitted from the model because such transitions would imply lower costs and improvements in quality of life that may not reflect clinical reality (Figure 1 and Table 1) (43).

v) Identification of alternative model input parameters and analysis

Information from the literature was sought to populate all input parameters for models 1 to 4 (Table 1) for a UK setting. When information on transition probabilities or age-related relative risks was not readily available, figures were estimated using a weighted average based on the distribution of patients to primary CVD events (48). Costs were derived from a combination of standard unit costs (49, 50) and previously published literature and models (48, 50), and were adjusted using the Hospital and Community Health Service index to the price year of 2014/15 (49). The acute and chronic cost of CVD were estimated using a weighted average based on the distribution of patients to primary CVD events (48). The probabilities of death due to CV events within a year of the event are reported in Table 1 and were applied to the first year after an event (first two cycles in the model). Life tables were used to determine the overall mortality for each model dependent on age and gender (51). Risks of death following a second event and utility values following a second event used in Model 4 were taken from the literature (Table 1).

A cost-utility analysis was undertaken for all models to calculate the cost per quality-adjusted life year (QALY) gained. Results from each alternative model specification are presented as scenario analyses. Probabilistic

sensitivity analysis (PSA) was conducted to assess parameter uncertainty. The PSA was run with 10,000 Monte Carlo simulations allowing cost-effectiveness planes (CEP) and cost-effectiveness acceptability curves to be constructed to estimate the probability of self-management being cost effective at different willingness-to-pay thresholds.

Additional sensitivity analyses (SA) were conducted to assess uncertainty in the results of each model (TASMIN-SR and Model 1-4). Deterministic sensitivity analysis was undertaken around key parameters and assumptions. All cost variables were increased or decreased simultaneously by 200% and 50% respectively. The time horizon for each model was varied from 30 years (lifetime) to 10, 5, 3, 2 and 1 year. In addition, the impact of doubling or halving the probabilities of having a second cardiovascular event was tested in Model 4.

We present the impact of structural uncertainty in terms of the impact on the cost-effectiveness results of a model and the expected value of perfect information (EVPI). Including different parameters in the model can be expected to alter the extent of uncertainty captured in the EVPI calculation. Because the models have different parameter sets, comparisons of expected value of partial perfect information would not be helpful.

Results

The main cost-effectiveness results obtained in the TASMIN-SR study were found to be robust to changes in model structure (Table 2) and to the inclusion of secondary events. Self-management of BP remained dominant (more effective and cheaper than usual care) for all models.

The highest QALY outcomes for both interventions were found by implementing Model 2 (restricted version). Higher incremental QALYs were found for Models 3 and 4 between self-management and usual care. Differences found between incremental QALYs for TASMIN-SR and Models 2 and 3 were marginal (0.0001 and 0.0002 respectively) (Table 2).

The CEP (Figure 2) shows the results from the Monte Carlo simulation for 10,000 replications. All the results were in the north-east and south-east quadrants indicating that self-management was always more effective but may be more or less costly. The cost-effectiveness acceptability curves (CEAC) shown in Figure 3 were derived from the joint density of incremental costs and incremental QALYs for the self-management of BP. Each CEAC presents the probability that the self-management intervention is cost-effective for the different model structures. For a willingness to pay of £20,000 per QALY, the proportion of model replications that were cost-

effective was higher than 99% for all model structures (Figure 3). For Models 3 and 4, the proportion of model replications that were cost-effective was 100%.

All sensitivity analyses undertaken appear to indicate that individual results for the various models remained aligned after increasing or decreasing total costs (Appendix 1 Table 4 and 5), varying the length of time horizons (Appendix 1 Table 6), and varying transition probabilities to secondary events (Appendix 1 Table 7). Self-management in Models 1-4 was found to be dominant if the time horizon was two years or more (Appendix 1 Table 6). Lifetime EVPI for alternative model structures compared to TASMIN-SR was reduced substantially for Model 1 at all willingness to pay thresholds. For all other model structures, there was a smaller decrease, again observed at all thresholds (Figure 4).

Discussion

DAM represents an organised way to synthesise evidence currently available on the outcomes and costs of alternative health care interventions (52, 53). The results derived from a DAM will depend on how the model structure has been defined and the data used to populate the model. The analysis of uncertainty in DAM has mainly focused on parameter uncertainty, taking account of any uncertainties in the data inputs (8, 10, 13, 16, 30). Such analyses are usually based on the premise that the model has been correctly specified. However, an inappropriate model structure can potentially invalidate estimates of cost-effectiveness and therefore, is also of little value to a decision maker (8, 13, 16). Although limitations in model structure are usually acknowledged, there is a lack of clarity about methods to evaluate structural uncertainty (8, 13, 16).

This study identified competing and credible model structures in the assessment of the cost-effectiveness of primary care interventions for the management of hypertension in patients at risk of or with established CVD. The results of each alternative model specification, including EVPI were presented and compared.

The main cost-effectiveness results obtained in the TASMIN-SR study did not change when alternative model structures (Model 1 to 3) were implemented or after adjusting TASMIN-SR model for the effect of secondary events (Model 4), suggesting that structural uncertainty was not important in this model. This case study showed similar results for EVPI across the range of model structures, except for Model 1, where the restricted parameter set meant that a large part of the decision uncertainty was not apparent in the model.

Our findings in terms of highest QALY outcomes found by implementing Model 2 may be explained by the fact that when compared with TASMIN-SR, the population entering Model 2 was exposed to an overall reduced risk of CVD due to the exclusion of the angina state, thus leading to increased QALYs. The lowest QALY gained for both interventions and higher self-management costs from Model 3 (expanded model) can be explained by the additional burden of mortality for patients presenting HF and TIA. Model 1 (single CVD state) produced lower QALYs compared to TASMIN-SR and this can be explained by the increased overall risk of CVD due to the added individual risks of stroke, MI and UA used to estimate the risk of CVD. The results of Model 4 show self-management to be even more cost-effective than usual care when compared with results from the case study and alternative Models 1-3. This can be explained by the increased overall risk of CVD due to the occurrence of additional events, and therefore more scope for preventing these events.

The main conclusions drawn from the cost-effectiveness analyses were not altered when alternative model structures were implemented or in the presence of secondary events. This result may lead to the conclusion that a simple model will suffice when examining the potential impact of anti-hypertensive strategies on the primary care prevention of CVD.

This study may well be a reflection of the average level of complexities faced by current practice when undertaking an assessment of structural uncertainty. Currently, guidance regarding the assessment of structural uncertainty in DAM by bodies such as ISPOR or NICE in the UK go as far as recommending to parameterize uncertainties (19) and if this is not possible then the use of sensitivity analysis (19, 54).

The wide variation in the model structures that were identified by our review supports the need for improved guidance to handle the implications of potential sources of structural uncertainty and, most importantly, the need for a disease-specific or generic model to examine the CEA of self-management of hypertension in patients with established CVD. Challenges across different disease areas are so varied that it may well be the case that only studies such as this can shed any light on the importance of model uncertainty in different settings.

The illustration of various scenarios representing structural uncertainty offers the decision maker the opportunity to decide on which model structure or assumption(s) he/she believes and make policy decisions on that basis. However, it does not provide any explicit framework for quantifying the uncertainty or offer any guidance to decision makers that have no clear preferences over alternative model assumptions.

The assessment of structural uncertainty shown in published studies in the area of primary prevention of CVD has mainly focused on assessing parameter uncertainty and there have been relatively few studies that have

attempted to examine structural uncertainty in the extend that this study has done. Studies that considered the assessment of structural uncertainty varied in scope (5, 37-39), however, none attempted to show the effect of different model structures on the cost-effectiveness of anti-hypertension treatments.

Current practice seems bound by data availability whilst methods proposed to assess structural uncertainty have been borrowed from other disciplines oblivious to the needs in a health care setting where patient level data is most of the time not readily available.

Strengths and limitations

A weakness of our approach to assess structural uncertainty is that there are no established methods to formally assess the plausibility of alternative models and it is not clear which type of, or how many scenarios should be considered.

Our choice of model type was limited to a cohort Markov model. Some may argue that a microsimulation or Discrete Event Simulation (DES) may offer some advantages such as flexibility in incorporating individual heterogeneity and tracking individual event history. However, our review indicated that all economic evaluations in this disease area had utilized Markov models, presumably based on the trade-off between model flexibility and analytical input (35). Furthermore, chronic and recurring diseases are often reflected by using Markov models in which individuals move between clinical states of interest in discrete time periods, and each state is associated with a cost and utility (32). Due to a lack of epidemiological data, Models 1 to 3 did not capture structural uncertainty arising from the exclusion of secondary events of CVD for high risk patients. However, using assumptions based on expert opinion, we assessed the risk of secondary events in Model 4. The exclusion of secondary events in Models 1 to 3 was a conservative assumption, as a reduction in BP was expected to reduce the risk of these events in addition to the primary events already considered, making self-management even more cost-effective as demonstrated in Model 4.

In this study we could not implement more sophisticated methods, for example, model selection, model averaging, or discrepancy approach to select the best model on the basis of how well the model's output match observed data (commonly judged by the likelihood-based information criteria). This was because we only had single point estimates for key parameters (transition probabilities) taken from the literature which do not allow the estimation of the maximum likelihood of parameters for which, actual patient level data is required. Furthermore, results of previous research seem to indicate that standard likelihood-based approaches to choose

between may be unsuitable when underlying datasets are different (26). Renal failure and peripheral artery disease were not considered in this study as additional health states as they are part of the broader set of diseases that indirectly may lead to CVD and data to populate input parameters for these sates was not available. Finally, the results of cost-effectiveness for self-management of blood pressure in the case study, TASMIN-SR model, were of dominance. It may be that if the results were near the £20,000 threshold, changes in model structure could have led different results of cost-effectiveness and possible EVPI.

The assessment of structural uncertainty shown in published studies in the area of primary prevention of CVD has mainly focused on assessing parameter uncertainty and there have been relatively few studies that have attempted to examine structural uncertainty in the extent that this study has done, showing the effect of different model structures on the cost-effectiveness of anti-hypertension treatments and implementing extensive sensitivity analyses and EVPI.

Conclusions

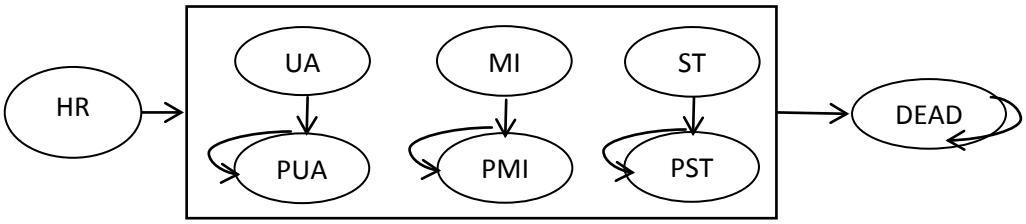
The results of this study indicate that the main conclusions from the TASMIN-SR model of cost-effectiveness are robust to changes in model structure. The cost-effectiveness results and the EVPI were not sensitive to model structure specification.

Even though the results from Model 1 were not similar to those of TASMIN-SR, the fact that the main conclusions are the same raises the question whether, in this particular case study, a more parsimonious model would have sufficed. Currently there are no available guidelines indicating how structural uncertainty arising from the structure of a model, should be identified, assessed, and reported. Therefore, further research should focus on the development of general agreed guidelines on how to address issues pertaining to structural uncertainty and, more specifically, how to deal with challenges across different disease areas, perhaps incentivising the development of more studies such as the present study, focusing on disease specific areas.

Based on the findings of this study, the following recommendations are put forward:

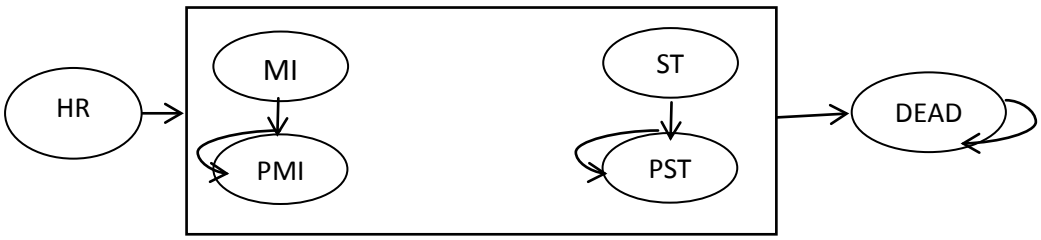
1. The assessment of structural uncertainty should not be ignored as it is an integral part of good practice DAM
2. The reasons why an assessment of structural uncertainty is not possible or not needed should be always stated in the limitations section
3. Data limitations to undertake an assessment of structural uncertainty should be clearly stated and discussed
4. If there is a reason to believe that structural uncertainty is an issue that may have affected the results of CE, then an assessment of structural uncertainty should be included
5. Ideally, sound statistical methods should be used in the assessment of structural uncertainty (discrepancy approach, model averaging, parameterization, model selection, scenario analysis) but if none of the above is possible due to data limitations, then at least appropriate sensitivity analysis should be routinely conducted, as per current ISPOR-SMDM guidelines

TASMIN-SR model

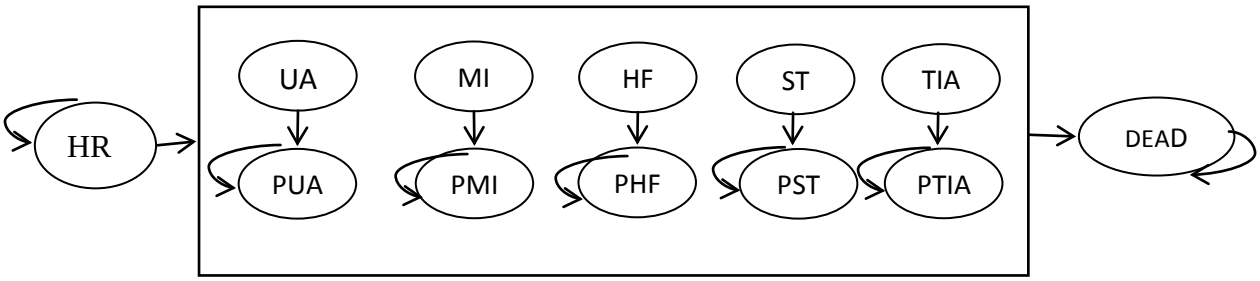


Model 1 Single state structure

Model 2 Two health state structure



Model 3 Expanded structure



Model 4 TASMIN-SR and the inclusion of secondary events

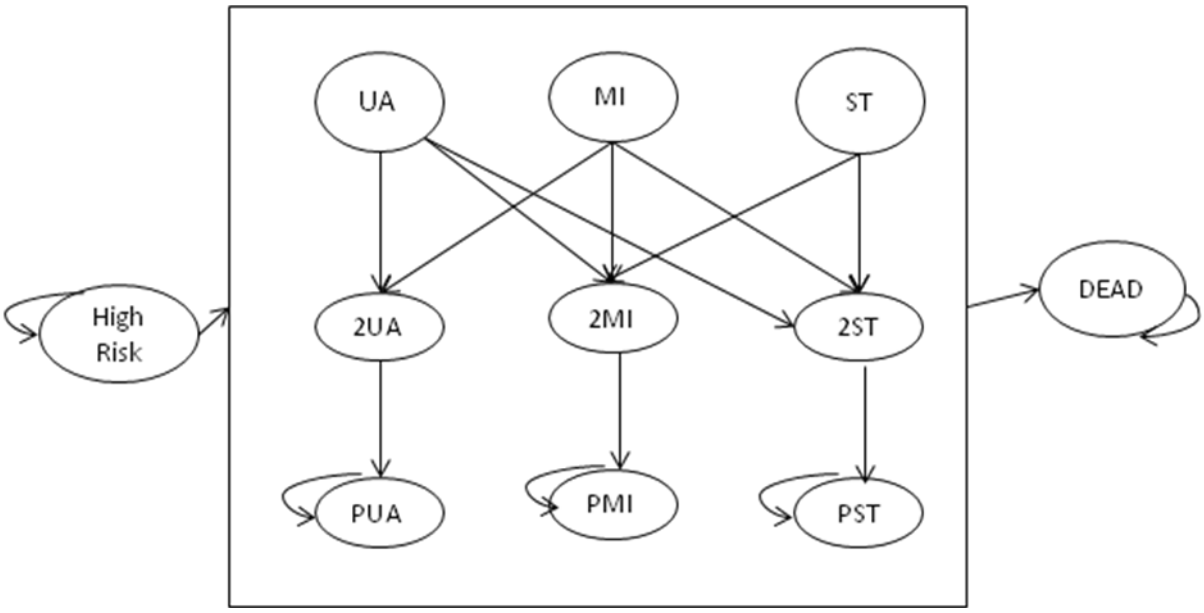


Figure 1: The model structures for the case study and models 1-4

HR = High Risk, UA= Unstable Angina; MI= Myocardial Infarction; HF = Heart Failure; ST = Stroke; TIA = Transient Ischemic Attack; CVD = Cardiovascular Disease.

All names preceded by a 'P', for example, PMI refers to a post event (chronic) health state for a patient surviving an event (MI)

All names preceded by '2', for example, 2UA refers to the occurrence of a second event consisting of a UA

Patients can move to the 'Dead' state from any of the health states in the models

Table 1 Parameters used in the assessment of structural uncertainty for the case study and alternative model structures

Parameter	TASMIN-SR	Model 1	Model 2	Model 3	Model 4	Sources
Annual CVD events for patients with DM						
Stroke						
60-69 years old	0.0196		0.0196	0.0196	0.0196	NICE, Diabetes guidelines(55)
70-79 years old	0.0262		0.0262	0.0262	0.0262	
80-89 years old	0.0298		0.0298	0.0298	0.0298	
MI						
60-69 years old	0.0089		0.0089	0.0089	0.0089	NICE, Diabetes guidelines(55)
70-79 years old	0.0100		0.0100	0.0100	0.0100	
80-89 years old	0.0111		0.0111	0.0111	0.0111	
UA						
60-69 years old	0.0041			0.0041	0.0041	NICE, Diabetes guidelines(55)
70-79 years old	0.0047			0.0047	0.0047	
80-89 years old	0.0052			0.0052	0.0052	
TIA						
60-69 years old				0.0053		NICE, Diabetes guidelines(55)
70-79 years old				0.0059		
80-89 years old				0.0066		
HF						
60-69 years old				0.0197		NICE, Hypertension Guidelines(3)
70-79 years old				0.0236		
80-89 years old				0.0264		
CVD						
60-69 years old		0.0323				Added risks*

Parameter	TASMIN-SR	Model 1	Model 2	Model 3	Model 4	Sources
70-79 years old		0.0405				
80-89 years old		0.0456				
Annual CVD events for patients with CKD						
Stroke						
60-69 years old	0.0072		0.0072	0.0072	0.0072	
70-79 years old	0.0147		0.0147	0.0147	0.0147	Kerr et al (2012)(56)
80-89 years old	0.0189		0.0189	0.0189	0.0189	
MI						
60-69 years old	0.0051		0.0051	0.0051	0.0051	
70-79 years old	0.0113		0.0113	0.0113	0.0113	Kerr et al (2012)(56)
80-89 years old	0.0171		0.0171	0.0171	0.0171	
UA						
60-69 years old	0.0024			0.0024	0.0024	
70-79 years old	0.0054			0.0054	0.0054	Kerr et al (2012)(56)
80-89 years old	0.0081			0.0081	0.0081	
TIA						
60-69 years old				0.0600		
70-79 years old				0.1303		Koren-Morag et al (2006)(57)
80-89 years old				0.1867		
HF						
60-69 years old				0.0269		
70-79 years old				0.0585		Shiba et al (2011)(58)
80-89 years old				0.0838		
CVD						
60-69 years old		0.0146				Added risks*

Parameter	TASMIN-SR	Model 1	Model 2	Model 3	Model 4	Sources
70-79 years old		0.0311				
80-89 years old		0.0435				
Annual CVD events for patients with a previous stroke						
Stroke						
60-69 years old	0.0348		0.0348	0.0348	0.0348	PROGRESS (1999) & NICE, Lipid modification guidelines(59, 60)
70-79 years old	0.0590		0.0590	0.0590	0.0590	
80-89 years old	0.0715		0.0715	0.0715	0.0715	
MI						
60-69 years old	0.0139		0.0139	0.0139	0.0139	PROGRESS (1999) & NICE, Lipid modification guidelines(59, 60)
70-79 years old	0.0232		0.0232	0.0232	0.0232	
80-89 years old	0.0232		0.0232	0.0232	0.0232	
UA						
60-69 years old	0.0139			0.0139	0.0139	PROGRESS (1999) & NICE, Lipid modification guidelines(59, 60)
70-79 years old	0.0232			0.0232	0.0232	
80-89 years old	0.0232			0.0232	0.0232	
TIA						
60-69 years old				0.5000		Hankey GL (2003)(61)
70-79 years old				0.0848		
80-89 years old				0.1027		
HF						
60-69 years old				0.0115		NICE, Hypertension guidelines(3)
70-79 years old				0.0193		
80-89 years old				0.0207		
CVD						
60-69 years old		0.0615				Added risks*

Parameter	TASMIN-SR	Model 1	Model 2	Model 3	Model 4	Sources
70-79 years old		0.1022				
80-89 years old		0.1141				
Annual CVD events for patients with CHD						
Stroke						
60-69 years old	0.0348		0.0348	0.0348	0.0348	NICE, Lipid modification and Hypertension guidelines(3, 59)
70-79 years old	0.0590		0.0590	0.0590	0.0590	
80-89 years old	0.0715		0.0715	0.0715	0.0715	
MI						
60-69 years old	0.0666		0.0666	0.0666	0.0666	NICE, Lipid modification and Hypertension guidelines(3, 59)
70-79 years old	0.1112		0.1112	0.1112	0.1112	
80-89 years old	0.1112		0.1112	0.1112	0.1112	
UA						
60-69 years old	0.0528			0.0528	0.0528	NICE, Lipid modification and Hypertension guidelines(3, 59)
70-79 years old	0.0882			0.0882	0.0882	
80-89 years old	0.0882			0.0882	0.0882	
TIA						
60-69 years old				0.0499		NICE, Lipid modification guidelines(59)
70-79 years old				0.0820		
80-89 years old				0.1046		
HF						
60-69 years old				0.0304		NICE, Lipid modification guidelines(59)
70-79 years old				0.0512		
80-89 years old				0.0653		
CVD						
60-69 years old		0.1467				Added risks*

Parameter	TASMIN-SR	Model 1	Model 2	Model 3	Model 4	Sources
70-79 years old		0.2373				
80-89 years old		0.2475				
Probability of death for those who have suffered an event						
Fatal Stroke	0.23		0.23	0.23	0.23	Bamford et al (1990)(62)
Fatal MI						
65-74 years old	0.23		0.23	0.23	0.23	ONS, Deaths registry (2011) & Kerr et al (2012)(51, 56)
75-84 years old	0.39		0.39	0.39	0.39	
85 and over	0.52		0.52	0.52	0.52	
Fatal TIA				0.11		Mant et al (2008) & Gattellary et al (2012)(63, 64)
Fatal HF						
Male				0.17		NorCAD model (2008)(65)
Female				0.16		
Fatal CVD						
65-74 years old		0.20				Weighted average†
75-84 years old		0.25				
85 and over		0.29				
Probability of death from a second cardiovascular event, one year after the first event						
Stroke after a first stroke					0.34	NICE, Statins guidelines(48)
UA after first UA					0.02	
MI after first MI					Same as first year event	
Age-related relative risks at 12 months						
MI, UA and HF – self-management						

Parameter	TASMIN-SR	Model 1	Model 2	Model 3	Model 4	Sources
60-69 years old	0.63		0.63	0.63	0.63	TASMIN-SR trial & Law et al (2009)(6, 66)
70-79 years old	0.69		0.69	0.69	0.69	
80-89 years old	0.75		0.75	0.75	0.75	
Stroke and TIA – self-management						
60-69 years old	0.54		0.54	0.54	0.54	TASMIN-SR trial & Law et al (2009)(6, 66)
70-79 years old	0.59		0.59	0.59	0.59	
80-89 years old	0.75		0.75	0.75	0.75	
CVD – self-management						
60-69 years old		0.60				Weighted average†
70-79 years old		0.65				
80-89 years old		0.75				
MI, UA and HF - usual care						
60-69 years old	0.82		0.82	0.82	0.82	TASMIN-SR trial & Law et al (2009)(6, 66)
70-79 years old	0.85		0.85	0.85	0.85	
80-89 years old	0.88		0.88	0.88	0.88	
Stroke and TIA - usual care						
60-69 years old	0.76		0.76	0.76	0.76	TASMIN-SR trial & Law et al (2009)(6, 66)
70-79 years old	0.81		0.81	0.81	0.81	
80-89 years old	0.88		0.88	0.88	0.88	
CVD - usual care						
60-69 years old		0.80				Weighted average†
70-79 years old		0.83				
80-89 years old		0.88				
Age-related relative risks at 6 months						
MI, UA and HF – self-management						

Parameter	TASMIN-SR	Model 1	Model 2	Model 3	Model 4	Sources
60-69 years old	0.71		0.71	0.71	0.71	TASMIN-SR trial & Law et al (2009)(6, 66)
70-79 years old	0.75		0.75	0.75	0.75	
80-89 years old	0.80		0.80	0.80	0.80	
Stroke and TIA – self-management						
60-69 years old	0.62		0.62	0.62	0.62	TASMIN-SR trial & Law et al (2009)(6, 66)
70-79 years old	0.68		0.68	0.68	0.68	
80-89 years old	0.80		0.80	0.80	0.80	
CVD – self-management						
60-69 years old		0.68				Weighted average†
70-79 years old		0.72				
80-89 years old		0.80				
MI, UA and HF - usual care						
60-69 years old	0.83		0.83	0.83	0.83	TASMIN-SR trial & Law et al (2009)(6, 66)
70-79 years old	0.85		0.85	0.85	0.85	
80-89 years old	0.89		0.89	0.89	0.89	
Stroke and TIA - usual care						
60-69 years old	0.77		0.77	0.77	0.77	TASMIN-SR trial & Law et al (2009)(6, 66)
70-79 years old	0.81		0.81	0.81	0.81	
80-89 years old	0.89		0.89	0.89	0.89	
CVD - usual care						
60-69 years old		0.80				Weighted average†
70-79 years old		0.84				
80-89 years old		0.89				
Costs (UK 2014/15 £)						
Costs of acute disease one-off cost						

Parameter	TASMIN-SR	Model 1	Model 2	Model 3	Model 4	Sources
Stroke	11,433		11,433	11,433	11,433	Youman et al (2003)(67)
MI	5,693		5,693	5,693	5,693	Palmer et al (2004)(68)
UA	3,416			3,416	3,416	Assumed 60% of MI
TIA				1,715		NHS Reference costs 2013-14(50)
HF				2,797		NHS Reference costs 2013-14(50)
CVD		7,235				Weighted average‡
Costs for long-term (chronic) disease per year						
Stroke	2,823		2,823	2,823	2,823	Youman et al (2003)(67)
MI	593		593	593	593	Cooper et al (2008)(69)
UA	593			593	593	Cooper et al (2008)(69)
TIA				333		NICE, Statins guidelines(48)
HF				1,274		Stewart et al (2002)(70)
CVD		1,432				Weighted average†
Utilities						
Utilities for acute events						
UA	0.77			0.77	0.77	NICE, Lipid modification, Hypertension and Statins guidelines; TASMIN-SR trial(3, 6, 48, 59)
MI	0.76		0.76	0.76	0.76	
Stroke	0.63		0.63	0.63	0.63	
TIA				0.90		
HF				0.68		
CVD		0.76				
Stroke after stroke					0.479	Ara, et al (2011)(71)
UA after UA					0.615	

Parameter	TASMIN-SR	Model 1	Model 2	Model 3	Model 4	Sources
MI after MI					0.700	
MI and Stroke					0.479	
Angina and Stroke					0.596	
Angina and MI					0.541	
Utilities for long term (chronic) disease						
UA	0.88			0.88	0.88	NICE, Lipid modification and Statins guidelines, TASMIN-SR trial(6, 48, 59)
MI	0.88		0.88	0.88	0.88	
Stroke	0.63		0.63	0.63	0.63	
TIA				0.90		
HF				0.68		
CVD		0.78				NICE, hypertension guidelines(3)
Dead	0	0	0	0	0	By definition
Annual discount rate for costs and utility	0.035	0.035	0.035	0.035	0.035	Gray et al (2011)(72)

*The probability of CVD was estimated as the added risks of the individual risk probabilities for stroke, MI and UA
†Weighted averages were estimated based on the distribution of patients to primary event health states in the ScHARR economic model
‡Weighted average using TASMIN-SR trial data

Table 2 Cost-Effectiveness results for the case study and each one of the alternative model structures

	Costs	QALYs	Incremental cost	Incremental QALYs	ICER
TASMIN-SR model					
Usual care	9,860	7.0946			
Self-management	8,997	7.4390	-864	0.3444	Dominant
Model 1					
Usual care	9,452	6.9102			
Self-management	8,813	7.2311	-639	0.3210	Dominant
Model 2					
Usual care	9,854	7.1612			
Self-management	8,858	7.5057	-996	0.3445	Dominant
Model 3					
Usual care	9,696	5.9274			
Self-management	9,156	6.2721	-539	0.3446	Dominant
Model 4					
Usual care	11,651	7.0704			
Self-management	10,378	7.4207	-1,273	0.3503	Dominant

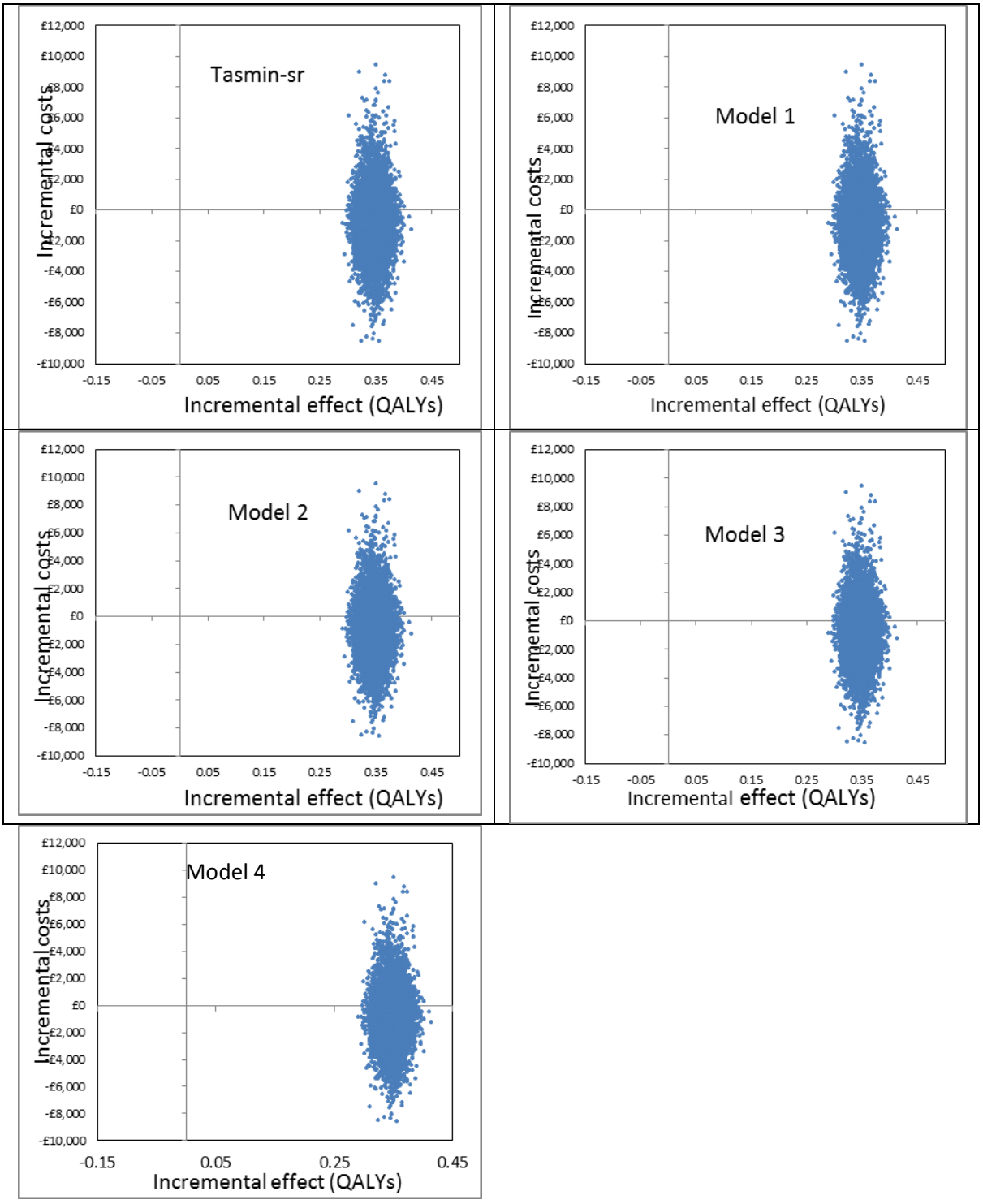


Figure 2 Cost-effectiveness plane for the case study and models 1 to 4

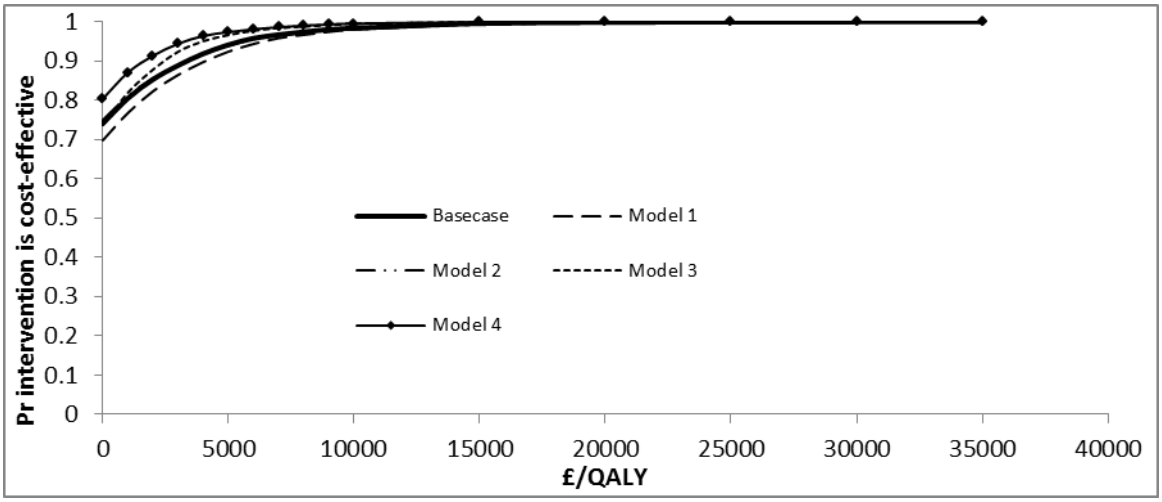


Figure 3 The cost-effectiveness acceptability curves (CEAC) for the probability that self-management is cost-effective for different model structures

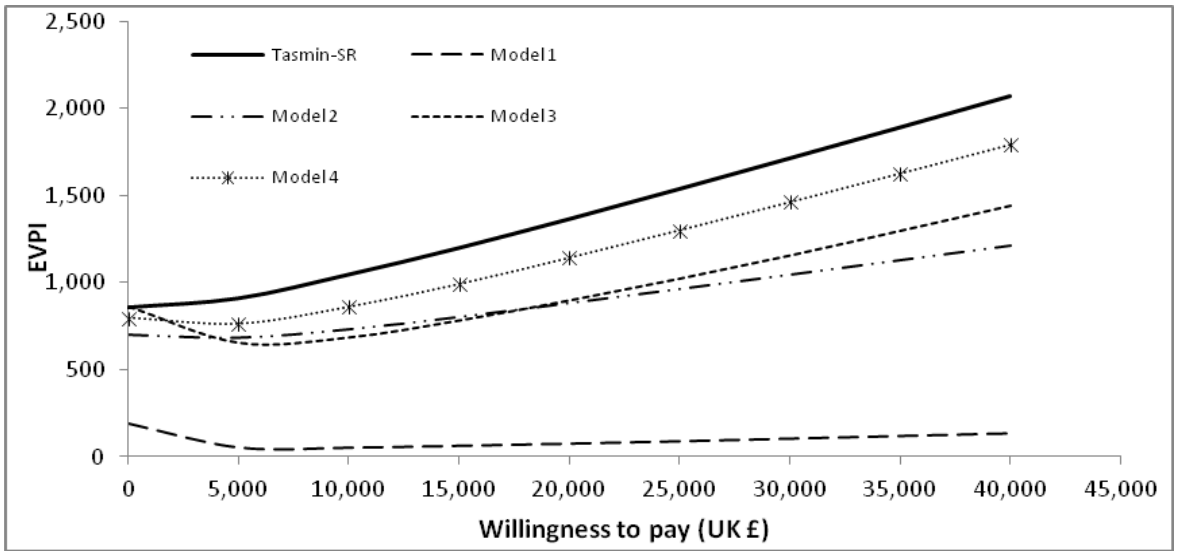


Figure 4 Per-Patient Expected Value of Perfect Information (EVPI) across varying Willingness to Pay Values for the TASMIN-SR and Models 1 to 4

Reference List

1. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002;360(9349):1903-13.
2. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. The Lancet. 2010;380(9859):2095-128.
3. NICE. Hypertension: clinical management of primary hypertension in adults. NICE clinical guideline 127. London: National Institute for Health and Clinical Excellence; 2011.
4. NHS England. Factsheet: Improved detection and management of hypertension 2014 [Available from: https://www.england.nhs.uk/ourwork/futurenhs/deliver-forward-view/sop/red-prem-mort/php/.
5. Kaambwa B, Bryan S, Jowett S, Mant J, Bray EP, Hobbs FDR, et al. Telemonitoring and self-management in the control of hypertension (TASMINH2): A cost-effectiveness analysis. European Journal of Preventive Cardiology. 2014;21(12):1517-30.
6. McManus RJ, Mant J, Haque MS, Bray EP, Bryan S, Greenfield SM, et al. Effect of self-monitoring and medication self-titration on systolic blood pressure in hypertensive patients at high risk of cardiovascular disease: the TASMIN-SR randomized clinical trial. Jama. 2014;312(8):799-808.
7. Penaloza-Ramos MC, Jowett S, Mant J, Schwartz C, Bray EP, Sayeed Haque M, et al. Cost-effectiveness of self-management of blood pressure in hypertensive patients over 70 years with suboptimal control and established cardiovascular disease or additional cardiovascular risk diseases (TASMIN-SR). Eur J Prev Cardiol. 2015.
8. Afzali HH, Karnon J. Exploring structural uncertainty in model-based economic evaluations. Pharmacoeconomics. 2015;33(5):435-43.
9. Stevenson M, Tappenden P, Squires H. Methods for handling uncertainty within pharmaceutical funding decisions. International Journal of Systems Science. 2014;45(1):60-8.
10. Strong M, Pilgrim H, Oakley J, Chilcott J. Structural uncertainty in health economic decision models. ScHARR Occasional Paper2009.
11. Manning WG, Fryback DG, Weinstein MC. Reflecting uncertainty in cost-effectiveness analysis. In: Gold MR SJ, Russell LB, et al, editor. Cost-effectiveness in health and medicine. New York (NY): Oxford University Press; 1996. p. 247-75.
12. Mentz RJ, Bakris GL, Waeber B, McMurray JJV, Gheorghiade M, Ruilope LM, et al. The past, present and future of renin-angiotensin aldosterone system inhibition. International Journal of Cardiology. 2013;167(5):1677-87.
13. Jackson CH, Bojke L, Thompson SG, Claxton K, Sharples LD. A framework for addressing structural uncertainty in decision models. Medical Decision Making. 2011;31(4):662-74.
14. Bilcke J, Beutels P, Brisson M, Jit M. Accounting for methodological, structural, and parameter uncertainty in decision-analytic models: a practical guide. Medical Decision Making. 2011;31(4):675-92.
15. Bilcke J, Chapman R, Atchison C, Cromer D, Johnson H, Willem L, et al. Quantifying Parameter and Structural Uncertainty of Dynamic Disease Transmission Models Using MCMC: An Application to Rotavirus Vaccination in England and Wales. Medical Decision Making.35(5):633-47.
16. Bojke L, Claxton K, Sculpher M, Palmer S. Characterizing structural uncertainty in decision analytic models: A review and application of methods. Value in Health. 2009;12(5):July/August.
17. Briggs AH. Handling uncertainty in cost-effectiveness models. Pharmacoeconomics. 2000;17(5):479-500.

18. Briggs AH, Gray AM. Handling uncertainty when performing economic evaluation of healthcare interventions. Health Technology Assessment. 1999;3(2):1999.
19. Briggs AH, Weinstein MC, Fenwick EAL, Karnon J, Sculpher MJ, Paltiel AD. Model Parameter Estimation and Uncertainty: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force-6. Value in Health. 2012;15(6):835-42.
20. Jackson CH, Sharples LD, Thompson SG. Structural and parameter uncertainty in Bayesian cost-effectiveness models. Journal of the Royal Statistical Society: Series C (Applied Statistics). 2010;59(2):233-53.
21. Jackson CH, Thompson SG, Sharples LD. Accounting for uncertainty in health economic decision models by using model averaging. Journal of the Royal Statistical Society Series A, (Statistics in Society). 2009;172(2):383-404.
22. Price MJ, Welton NJ, Briggs AH, Ades AE. Model averaging in the presence of structural uncertainty about treatment effects: influence on treatment decision and expected value of information. Value Health. 2011;14(2):205-18.
23. Strong M, Oakley JE, Chilcott J. Managing structural uncertainty in health economic decision models: a discrepancy approach. Journal of the Royal Statistical Society: Series C (Applied Statistics). 2012;61(1):25-45.
24. Brisson M, Edmunds WJ. Impact of model, methodological, and parameter uncertainty in the economic analysis of vaccination programs. Medical decision making : an international journal of the Society for Medical Decision Making. 2006;26(5):434-46.
25. Frederix GW, van Hasselt JG, Schellens JH, Hovels AM, Raaijmakers JA, Huitema AD, et al. The impact of structural uncertainty on cost-effectiveness models for adjuvant endocrine breast cancer treatments: the need for disease-specific model standardization and improved guidance. Pharmacoeconomics. 2014;32(1):47-61.
26. Thom HH, Jackson CH, Commenges D, Sharples LD. State selection in Markov models for panel data with application to psoriatic arthritis. Stat Med. 2015;34(16):2456-75.
27. Caro JJ, Moller J. Decision-analytic models: current methodological challenges. Pharmacoeconomics. 2014;32(10):943-50.
28. Afzali HH, Karnon J, Merlin T. Improving the accuracy and comparability of model-based economic evaluations of health technologies for reimbursement decisions: a methodological framework for the development of reference models. Medical decision making : an international journal of the Society for Medical Decision Making. 2013;33(3):325-32.
29. Peñaloza Ramos MC, Barton P, Jowett S, Sutton AJ. A Systematic Review of Research Guidelines in Decision-Analytic Modeling. Value in Health. 2015;18(4):512-29.
30. Peñaloza-Ramos MC, Barton P, Jowett S, Sutton AJ. Do economic evaluations in primary prevention of cardiovascular disease conform to good practice guidelines? A systematic review. (In Press) MDM Policy & Practice. 2016.
31. Kourlaba G, Fragoulakis V, Theodoratou D, Maniadakis N. Economic evaluation of telmisartan, valsartan and losartan in combination with hydrochlorothiazide for treatment of mild-to-moderate hypertension in Greece: A cost-utility analysis. Journal of Pharmaceutical Health Services Research. 2013;4(2):81-8.
32. Briggs AH, Claxton K, Sculpher MJ. Decision Modelling for Health Economic Evaluation: Oxford, University Press; 2006.
33. Jowett S. Using Decision Analytical Modelling Techniques in Health Economics: An Application to Screening for and Treatment of Atrial Fibrillation. PhD Thesis: University of Birmingham; 2007.
34. Barton P, Bryan S, Robinson S. Modelling in the economic evaluation of health care: Selecting the appropriate approach. Journal of Health Services Research and Policy. 2004;9(2):April.

35. Karnon J. Alternative decision modelling techniques for the evaluation of health care technologies: Markov processes versus discrete event simulation. Health Economics. 2003;12(10):01.
36. Montgomery AA, Fahey T, Ben-Shlomo Y, Harding J. The influence of absolute cardiovascular risk, patient utilities, and costs on the decision to treat hypertension: A Markov decision analysis. Journal of Hypertension. 2003;21(9):1753-9.
37. Perman G, Rossi E, Waisman GD, Aguero C, Gonzalez CD, Pallordet CL, et al. Cost-effectiveness of a hypertension management programme in an elderly population: A Markov model. Cost Effectiveness and Resource Allocation. 2011;9(4).
38. Stevanovic J, O'Prinsen AC, Verheggen BG, Schuiling-Veninga N, Postma MJ, Pechlivanoglou P. Economic evaluation of primary prevention of cardiovascular diseases in mild hypertension: A scenario analysis for the Netherlands. Clinical Therapeutics. 2014;36(3):368-84.e5.
39. Ekman M, Bienfait-Beuzon C, Jackson J. Cost-effectiveness of irbesartan/hydrochlorothiazide in patients with hypertension: An economic evaluation for Sweden. Journal of Human Hypertension. 2008;22(12):845-55.
40. Nordmann AJ, Krahn M, Logan AG, Naglie G, Detsky AS. The cost effectiveness of ACE inhibitors as first-line antihypertensive therapy. PharmacoEconomics. 2003;21(8):573-85.
41. Gandjour A, Stock S. A national hypertension treatment program in Germany and its estimated impact on costs, life expectancy, and cost-effectiveness. Health Policy. 2007;83(2-3):257-67.
42. Granstrom O, Levin L, Henriksson M. Cost-effectiveness of candesartan versus losartan in the primary preventive treatment of hypertension. ClinicoEconomics and Outcomes Research. 2012;4(1):313-22.
43. Wisloff T, Selmer RM, Halvorsen S, Fretheim A, Norheim OF, Kristiansen IS. Choice of generic antihypertensive drugs for the primary prevention of cardiovascular disease - A cost-effectiveness analysis. BMC Cardiovascular Disorders. 2012;12(26).
44. Baker TM, Goh J, Johnston A, Falvey H, Brede Y, Brown RE. Cost-effectiveness analysis of valsartan versus losartan and the effect of switching. Journal of medical economics. 2012;15(2):253-60.
45. Ward S, Jones ML, Pandor A, Holmes M, Ara R, Ryan A, et al. A systematic review and economic evaluation of statins for the prevention of coronary events. Health Technology Assessment. 2007;11(14):iii-160.
46. Wu Y, Zhou Q, Xuan J, Li M, Zelt S, Huang Y, et al. A cost-effectiveness analysis between amlodipine and angiotensin ii receptor blockers in stroke and myocardial infarction prevention among hypertension patients in China. Value in Health Regional Issues. 2013;2(1):75-80.
47. Ekwunife OI, Okafor CE, Ezenduka CC, Udeogaranya PO. Cost-utility analysis of antihypertensive medications in Nigeria: A decision analysis. Cost Effectiveness and Resource Allocation. 2013;11(1).
48. NICE. Statins for the prevention of cardiovascular events. NICE guideline TA94. London: National Institute for Health and Clinical Excellence; 2006 2006.
49. Curtis L, Burns A. Unit Costs of Health & Social Care. Kent: Personal Social Services Research Unit; 2015.
50. Department of Health. NHS Reference Costs Schedule 2013-14. London; 2013 2013.
51. Office for National Statistics. Interim Life Tables for England [Available from: http://www.ons.gov.uk/ons/rel/lifetables/interim-life-tables/2012-2014/indexhtml.2014.
52. Brennan A, Chick SE, Davies R. A taxonomy of model structures for economic evaluation of health technologies. Health Economics. 2006;15(12):December.
53. Raiffa H. Decision analysis: introductory lectures on choices under uncertainty. 1968. MD computing : computers in medical practice. 1993;10(5):312-28.

54. NICE. Guide to the methods of technology appraisal 2013. Process and methods guides. London: National Institue for Health and Care Excellence; 2013.
55. NICE. National guidelines for the management of blood glucose levels in people with type 2 diabetes. NICE guidelines CG87. London: National Institue for Health and Clinical Excellence; 2002 9/17/2002.
56. Kerr M, Bray B, Medcalf J, O'Donoghue DJ, Matthews B. Estimating the financial cost of chronic kidney disease to the NHS in England. Nephrology Dialysis Transplantation. 2012;27(Supplement 3).
57. Koren-Morag N, Goldbourt U, Tanne D. Renal dysfunction and risk of ischemic stroke or TIA in patients with cardiovascular disease. Neurology. 2006;67(2):224-8.
58. Shiba N, Shimokawa H. Chronic kidney disease and heart failure—Bidirectional close link and common therapeutic goal. Journal of Cardiology. 2011;57(1):8-17.
59. NICE. Lipid modification: Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. NICE guidelines CG67. London: National Institute for Health anc Clinical Excellence; 2008.
60. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. The Lancet. 2001;358:1033-41.
61. Hankey GJ. Long-term outcome after ischaemic stroke/transient ischaemic attack. Cerebrovascular diseases (Basel, Switzerland). 2003;16 Suppl 1:14-9.
62. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. A prospective study of acute cerebrovascular disease in the community: the Oxfordshire Community Stroke Project--1981-86. 2. Incidence, case fatality rates and overall outcome at one year of cerebral infarction, primary intracerebral and subarachnoid haemorrhage. Journal of neurology, neurosurgery, and psychiatry. 1990;53(1):16-22.
63. Gattellari M, Goumas C, Garden F, Worthington JM. Relative survival after transient ischaemic attack: results from the Program of Research Informing Stroke Management (PRISM) study. Stroke. 2012;43(1):79-85.
64. Mant J, Barton P, Stevens A, Ford G, Rothwell PM. What is the optimum model of service delivery for Transient Ischaemic Attack? Report for the National co-ordinating Centre for NHS Service Delivery and Organisation R&D (NCCSDO). 2008.
65. Wisløff T. Norwegian Cardiovascular Disease Model (NorCaD): a simulation model for estimating health benefits and cost consequences of cardiovascular interventions. Oslo: Norwegian Knowledge Centre for the Health Services; 2008. 69 s. digital, PDF-fil p.
66. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemilogical studies. BMJ. 2009;338:b1665.
67. Youman P, Wilson K, Harraf F, Kalra L. The economic burden of stroke in the United Kingdom. Pharmacoeconomics. 2003;21:43-50.
68. Palmer AJ, Annemans L, Roze S, Lamotte M, Lapuerta P, Chen R, et al. Cost-effectiveness of early irbesartan treatment versus control (standard antihypertensive medications excluding ACE inhibitors, other angiotensin-2 receptor antagonists, and dihydropyridine calcium channel blockers) or late irbesartan treatment in patients with type 2 diabetes, hypertension, and renal disease. Diabetes Care. 2004;27(8):1897-903.
69. Cooper A, O'Flynn N. Risk assessment and lipid modification for primary and secondary prevention of cardiovascular disease: summary of NICE guidance. BMJ. 2008;336(7655):1246-8.
70. Stewart S, Jenkins A, Buchan S, McGuire A, Capewell S, McMurray JJ. The current cost of heart failure to the National Health Service in the UK. European journal of heart failure. 2002;4(3):361-71.

71. Ara R, Brazier JE. Using health state utility values from the general population to approximate baselines in decision analytic models when condition specific data are not available. 2011.
72. Gray AM, Clarke PM, Wolstenholme JL, Wordsworth S. Applied Methods of Cost-Effectiveness Analysis in Health Care. Oxford: Oxford University Press; 2011 2011.