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Using risk models to inform health care priority setting: the case of cardiovascular disease progression

Boby Mihaylova, Andy Briggs, Alastair Gray

Health Economics Research Centre, University of Oxford

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Abstract

The development and use of risk models in medicine is receiving growing attention. By far the most commonly used models are derived from the Framingham cohort study of cardiovascular disease. For example, the popular New Zealand risk tables are based on the Framingham study and, by providing a graphical guide to the risk of CVD by age, sex, blood pressure, lipid levels, existence of diabetes and smoking status, are used to inform treatment choices. This paper considers the use of such risk models from the perspective of economic evaluation. First, we review the way such models have previously been used in predicting the health outcome effects and cost-effectiveness of cholesterol lowering therapy. This review allows us to identify a set of recurring issues that analysts confront when adapting such risk models to provide the information necessary for health economic evaluation. Second, we describe the construction of a cost-effectiveness model using the most recent Framingham risk equations and use this process to explore and discuss these issues in more detail. Finally, we consider whether risk tables can be presented in a way that is more in line with the precepts of cost-effectiveness, and put forward some modified tables.

Background

This paper has been developed out of our participation in a workshop on risk scoring for cardiovascular disease, organised by Imperial College and held in November 2002. The topic we addressed was the use of risk scoring as a rationale for setting medical priori ties and expenditure. This manuscript represents our first draft of a paper that may be published in a special issue of *Heart* devoted to that workshop. We therefore welcome comments from our HESG colleagues for this work in progress paper – in particular, we are interested in your thoughts on the alternative graphical presentations we are suggesting. Please do not circulate this paper

beyond those attending the HESG winter meeting. If you wish to reference this work or are otherwise interested, please let us know and we will be happy to send you a final draft when it is prepared. We look forward to your comments.

Introduction

Coronary heart disease (CHD) is a major cause of morbidity and mortality. There is now a large amount of good quality epidemiological evidence concerning the relationship between risk factors (for example, age, sex, cholesterol levels, blood pressure etc.) and CHD morbidity and mortality. A number of CHD and stroke risk models that estimate the probability of experiencing a coronary and/or vascular event as a function of major risk factors have already been published ((1))(2-12)). A number of alternative aids have been developed to facilitate the use of the original risk equations in a clinical decision setting: CHD risk charts (e.g. Wilson and colleagues (13)), various calculators (e.g. Dundee coronary risk disk (10)) and computer programs (e.g. Cardiac Risk Assessor program (14)). While these aids simply quantify the risk of coronary events over a specified time period based on the subject's characteristics, they have increasingly been used as devices to focus onto specific patient groups behavioural and therapeutic interventions that can reduce cardiac risk by changing modifiable risk factors. Indeed, guidelines for prioritising treatment based on predicted risk of coronary events have been published by national professional or healthcare management organizations (14-18) to facilitate patients risk management and provide best prevention of CHD.

Economic analyses provide important additional evidence to support this kind of decision-making in an environment with constrained resources. By considering the incremental cost necessary to achieve incremental benefit, these analyses enable the comparison of interventions in terms of their cost-effectiveness. Within the risk table framework, the cost-effectiveness approach could assist in two ways: first, for individual patients with given levels of modifiable risk factors such as smoking, blood pressure and blood cholesterol, the relative costs and benefits of alternative options for modifying these risk factors could be calculated; second, at the population level, it would be possible to define those patients who could be treated at a cost-effectiveness level within the social willingness to pay for health gain, rather than to define treatment groups (as at present) in terms of fairly arbitrary initial risk levels.

The scope of application of economic analysis mainly depends on the measure of health outcomes employed. The fundamental concern with mortality and morbidity has lead to life-years and/or quality-adjusted life-years being the most commonly employed outcomes in so-called cost-effectiveness analyses. In particular, the use of a broader outcome measure (i.e. quality adjusted life years) makes possible comparisons of different types of health care interventions in terms of their incremental cost for a unit of that incremental outcome. There are two main features of preventive CHD interventions that need to be taken into account when performing an economic analysis: the interventions are usually long-term as are the corresponding benefits and costs. Thus, ideally good quality evidence on both the lifetime costs and lifetime effects of interventions is needed.

The 'gold standard' evidence for effectiveness analyses in medicine, are randomised controlled trials (RCTs), as they provide unbiased evidence for the impact of intervention on patients' outcomes (as defined through the trial main endpoints). RCTs could also be designed to generate evidence sufficient to perform economic analysis. The major drawbacks of RCTs, as related to the economic analysis, are that they are usually run for a limited period of time, under relatively strictly defined protocol of care, frequently not focusing on economically important endpoints and their external validity is unclear. In addition, although they are the best design for the generation of reliable evidence, they are expensive and time consuming. Risk models, however, are already developed and are freely available. They could, in principle, facilitate quicker and relatively inexpensive development of cost-effectiveness evidence.

The objective of this paper is to investigate the usefulness of the risk models, as they are currently developed, for the purpose of economic analysis and to explore what additional information is necessary if these models are to inform decisions based not only the effectiveness of interventions, but also their cost-effectiveness. A further aim is to work towards the development of a risk model that can be used to estimate the outcomes appropriate to economic analysis, while remaining mindful of the need for a model suitable for individual clinical decision-making.

As background to the overall problem we present the results of two reviews. The first summarises the major CHD risk models that have been developed and some of the

limitations of the models for economic analysis. The second review examines economic evaluation studies that have made use of published risk models in order to estimate the cost-effectiveness of cholesterol lowering therapy with a statin, in order to explore exactly how analysts have used the risk models. The second part of the paper then lays out a Markov model constructed using the most recent Framingham risk equations (which include an equation for secondary events). This model is then used to illustrate some of the issues and assumptions necessary in adapting the risk equations to predict economic outcomes. Finally, we present our first attempt at generating a more economic orientated set of CHD tables.

Reviewing the risk models and CEA based on these models

Major CHD risk models and economic studies that have used these risk models to explore the cost-effectiveness of statins were reviewed to identify the main issues pertinent to the use of risk models in economic evaluation studies. The structure of the risk models, the population to which they refer, the risk factors necessary for their use, the outcome they provide and the time-span of their use were reviewed. The additional data, assumptions and modelling used to apply the risk models for the purpose of economic analysis were also explored. The review of cost effectiveness analyses identified thirty-seven published economic evaluations of cholesterol lowering with statins that have reported the use of CHD risk models in some way (19-45). The main issues relevant to economic evaluation based on CHD risk models identified from the two reviews are summarized in Table 1 and are discussed in detail below.

Study population

Risk models have predominantly been developed from observational data relating specific risk factors to coronary heart/vascular disease events over time. The Framingham Heart Study, the Lipid Research Clinic Follow-up Cohorts (LRCP) (46) and the Prospective Cardiovascular Munster study (PROCAM) (4;5) are some of the main examples. The only exception (9) used data from eight RCTs but combined the treatment and control groups so the data resembles cohort data with potentially specifically modified risk factors. The models themselves are statistical models, geared to explain the incidence of events based on the available risk data, and thus they estimate the statistical association and not causal relationships between risks and events. The fact that the source data is based on a cohort of patients from a specific population and a specific time period means that the risk models, if properly

developed, by definition perform best for this population. However, their external validity when applied to different populations and time period therefore needs to be demonstrated rather than assumed. A review of fifteen risk models based on logistic regression models (47) concludes that 'because of great variation in definition of event, duration of follow-up, population characteristics, definition of risk variables, and selection of other variables in the logistic functions, direct use of such established functions would generally not have validity for the prediction of absolute risk levels'.

Economic analyses are a good example of direct use of models developed based on a specific study sample, applied to an entirely different population. In addition, economic analyses, based on risk models, usually do not include individual level data on risk factors and rely heavily on population estimates. This application of risk models to risk factor data that are averaged across population sub-groups such as by age or gender could be problematic. Dobson (48), for example, showed that this approach would systematically underestimate the group hazard when a Cox proportional hazards model was applied, and that similar problems would arise if logistic regression or parametric survival models were employed. She also showed that the level of underestimation would increase with increasing within-group heterogeneity of hazard. A related issue is that if the uncertainty concerning the distribution of risk factors/profiles is not incorporated into the modelling process, the variance associated with the subsequent estimates of cost-effectiveness will be seriously underestimated.

Propagation of impact through risk factors

The observed levels of risk factors in a cohort type population study are typically subject either to natural variation and/or to the impact of a wide range of therapeutic interventions that may have been provided for the population in the specific data collection time period. However, it is unclear whether an observed statistical association between individuals at different levels of risk and their subsequent risk of a particular event such as cardiovascular disease can be equated directly with the effect on subsequent risk of changing the levels of risk factors for a group of individuals by means of, for example, a drug intervention. This issue has led some analysts to introduce various usually conservative assumptions such as that the benefit of a change in risk factor levels achieved by an intervention is 90% of the "naturally occurring" benefit shown be epidemiological association (e.g. Hay *et al*

(31), Glick *et al* (22) and Drummond *et al* (21)), but the evidence underpinning the magnitude and direction of such adjustments is unclear. It has sometimes been possible to compare the predicted effect based on changes in levels of risk factors and epidemiological association with its actual effect of an intervention as measured in a randomised controlled trial: in the UK Prospective Diabetes Study, for example, both improved blood glucose control and improved blood pressure control had a slightly increased effect on the risk of diabetes-related endpoints than the epidemiological association predicted (49;50). Similar issues arise with the assumed effect of initiation (i.e. immediate or delayed impact) and termination of the intervention (i.e. continuous effects or immediate return to the initial risk profile). Morris (40)has compared results achieved when economic analysis was performed based on a RCT compared with results achieved by employing a risk model. Although he reported a general underestimation of non-fatal MIs when a risk model was used, the overall cost-effectiveness results were comparable.

An associated issue is that if the impact of an intervention is estimated based on a risk model, then the implicit assumption is that all the associated changes in health are entirely propagated through changes in risk factors incorporated in the model and captured in the model's specified non-fatal and fatal endpoints. For example if an economic evaluation uses a CHD risk model such as Framingham (1;2;6;13), the potential benefits of cholesterol lowering will be measured entirely in terms of their impact on the risk of CHD events, and the impact of cholesterol lowering on the risk of cerebrovascular events such as stroke – shown by trials such as the Heart Protection Study to be substantial – will be missed. Similarly, if epidemiological evidence indicates an association between a particular risk factor such as HDL cholesterol and CHD, but the model being used does not incorporate that risk factor (i.e. Abbott and McGee (1)), then any benefits that might arise if the intervention increases HDL cholesterol would be at least partially missed. In comparison, a RCT designed to investigate the impact of statin on mortality will provide the overall impact on mortality achieved through known and unknown factors.

Outcomes

The outcomes of risk models are often combinations of fatal and non-fatal events (for example, non-fatal myocardial infarction (MI) and CHD death), an approach which is adopted in order to get better estimation (due to the use of all relevant events) and unbiased inference. However, combining outcomes in this way does not provide the

information that is essential for economic analysis, namely a separate prediction of types of major events (i.e. non-fatal MI and CHD death separately) for the purposes of outcome and cost valuation. Consequently, when an economic model has been based on a risk model estimating the combined probability of overall CHD, it is necessary to introduce additional assumptions such as the proportional division of events into fatal and non-fatal, or by major type.

Very few risk models directly estimate different types of events of interest. Abbott 1987 (1) estimated non-fatal MI and CHD death incidence separately as well as in combination. In addition to these outcomes, Anderson *et al* (3) and Grover *et al* (46) estimated the risks of non-fatal stroke and death from CVD. Morris (40) compared the number of events predicted by Framingham risk equations (1) with those actually experienced in WOSCOPS and found evidence for significant underestimation of non-fatal myocardial infarction rate when a risk model was employed. This may be because of difference in underlying epidemiology or the use of population averages to adjust the model (we return to this issue below). The review of economic studies showed that it is these models that provide direct estimates of separate events that are predominantly employed in economic analyses (i.e. (20-22;28-30;35-39)).

It should also be noted that risk models do not provide all the information necessary to predict lifetime health outcomes. The death rate from causes other than CHD, for example, is indispensable if we are interested in years of life gained from interventions. Economic analyses thus need to incorporate this information from other sources and usually these sources are population data on overall and CHD mortality (22;29;33;35).

Risk models are also generally applicable for a limited period of time (five to ten years). Economic studies, however, are interested in studying the outcomes and costs for the whole relevant period for the impact of the intervention to be exhausted. If analysis is restricted to a certain time point, potentially relevant future outcomes and costs would be missed. This problem is of course relevant not only to risk models but even more so to RCTs. However, in using risk models to extrapolate beyond the follow-up point of an RCT, the fact that the risk model is itself based on censored data and may only be applicable for a limited period of time is often ignored or circumvented by the introduction of additional assumptions.

Risk models are also almost invariably published without sufficient accompanying data (in particular the covariance matrix) to enable the estimation of the standard error of the mean estimate of the predicted probabilities of events. This severely restricts the ability of economists to provide an estimate of the uncertainty surrounding their estimates.

We have tried to outline the main additional types of information and assumptions that frequently need to be added to risk models in order to enable their use in economic analysis. However, it is noteworthy that in our review of studies examining the cost-effectiveness of statin therapy it was rare to find any specific or detailed description of the modelling process. Instead, most analysts made more general statements such as 'the CHD event rates were estimated from the Framingham equations'. This makes it difficult to observe the many assumptions required, and almost impossible to replicate the specific approach used. Consequently, in the next section we set out in more detail the steps involved in constructing a coronary heart disease model suitable for economic evaluation.

Developing a model of coronary heart disease

Most of the model-based analyses reviewed in the previous section were designed for the evaluation of a specific intervention - statin treatment. Our interest was to develop a more general model from the Framingham equations that could serve to facilitate and tailor treatment choices for individual subjects. More general disease models have been employed before. Perhaps the best-known example is the Coronary Heart Disease Policy model, constructed by Weinstein and colleagues in the 1980's (51). However, this model is now quite old (based on risk equations from 1973 (52)), and is calibrated to the US population. In this section, we describe the construction of our model with a focus on the assumptions that are necessary to estimate the economic outcomes of interest.

Model structure and risk factors for CHD

The structure of the model that we have adopted is closely related to the information available from the Framingham study. We chose to use the most recently published Framingham Risk equations (D'Agostino *et al* (6)), since these include secondary event equations, which therefore allow modelling of subsequent CHD events for

subjects experiencing a nonfatal CHD event. These risk equations are reproduced in Table 2 for men and women separately.

We chose to use a simple Markov model as the basis for our CHD model following a similar structure to other authors (Glick *et al* (22), Asraf *et al* (19), Caro *et al* (53), Huse *et al* (33) and this is presented as a state transition diagram in Figure 1. Notice that the risk equations from Table 2 predict a composite CHD event rather than separate CHD events, hence the use of a single 'CHD history' state for the Markov model. The distinction between fatal and the different types of non-fatal coronary events is made by apportioning the results using the rates from Framingham data by age and sex (33).

Estimation of model transition probabilities

The risk equations were estimated from the Framingham study using a parametric Weibull survival distribution (note that the coefficients in Table 2 are from the accelerated time form where negative coefficients indicate shorter times to event and therefore higher risk). Since the original analysis was only on four years worth of data, we employed annual transition probabilities within four years with the transition probabilities estimated from the Weibull hazard functions evaluated at years one to four. After each four years we updated the age and recalculated transition probabilities for the next four years. This assumes that as patients age over time they assume the risk profile of the older patients in the Framingham cohort. Other cause mortality in the model was estimated from standard all-cause mortality life-tables by age and sex after first adjusting for CHD mortality (54).

Population versus individual averaged models

Of course, the Framingham study provides risk models based on the inhabitants of a small town in the US. Of interest therefore, is how well these risk equations can predict CHD events in other populations. The West of Scotland Coronary Prevention Study (WOSCOPS) (55) was a large placebo-controlled trial of primary prevention with statin treatment undertaken in the one of the UK countries. The trial followed 6595 patients for an average of 4.9 years and therefore offers the opportunity to test the predictions from our Framingham based model against a published data set – having used the equations to adjust the predictions for any differences in the risk factors in the WOSCOPS population. Indeed, this is exactly what Morris (40) has done with a similarly constructed model – concluding that a model based on the

Framingham risk equations underpredicts CHD events compared to those observed in WOSCOPS.

However, it is important to recognize the important influence of heterogeneity in the Markov model when seeking to both adjust and predict events in a different population. For example, it is not appropriate to simply use the population averages from WOSCOPS in the Framingham risk equations and to expect the Markov model to predict the numbers of events. This is because there is a non-linear relationship between the risk factors and the events. In order to accurately predict the event rates it is necessary to simulate the individual characteristics of subjects in the target population, to evaluate the model separately for individuals with given characteristics and then to average over the outcome of interest to give the average for the population.

If we had access to the original WOSCOPS data, we could simply take the observed characteristics for each patient and simulate the expectation of the outcome of interest and average across these to get the population average. However, with only access to the summary data of the subject characteristics in WOSCOPS we had to adopt an alternative approach. Based on the means and standard deviations of age, systolic blood pressure, and total and HDL cholesterol reported for WOSCOPS we draw samples from a multivariate normal distribution. As correlations between characteristics were unavailable from the published reports, we used correlations between the same variables from an alternative dataset where we had access to patient level data (56). An indicator of smoking status and sex was sampled independently.

Results from running the model for the WOSCOPS placebo group data are reported in Table 3, showing the combined CHD event rate from WOSCOPS in the first column, followed by non-fatal MI rate and CHD death rate in the second and third columns. The results reported from Morris are reported for reference. The results from evaluating the model at the population averages for WOSCOPS and the results of the simulation of individual characteristics from the WOSCOPS population are reported in the last two rows. As expected the means from the individual simulations are above the means from the population analysis. It is also clear that the model is

significantly underestimating the non-fatal CHD event rates observed in the WOSCOPS placebo group.

Although the model is still being tested there are a number of additional considerations that could have had an impact on the performance:

- We have transformed the average values and standard deviations for SBP, total cholesterol and HDL cholesterol into means and standard deviations for Ln(SBP) and Ln(Total-cholesterol/HDL-cholesterol) based on the assumptions of lognormal distributions of SBP and Total/HDL-cholesterol and employing Delta method for the standard deviation of Total/HDL-cholesterol ratio.
- In all our analysis we do not update Ln(SBP) and Ln(Total-cholesterol/HDL-cholesterol) with age when passing from one 4-year cycle to another. In effect, these variables are constant within the model.
- We have used the CHD events structure witnessed in Framingham data to split the CHD death and non-fatal MI from the combined CHD event, predicted from the risk equations (incl. CHD death, non-fatal MI, Angina and Coronary Insufficiency).
- Our estimates of first MI or CHD death does not include some of non MI first CHD events (i.e. angina or coronary insufficiency) that have resulted in a MI or CHD death. A more complicated Markov model is needed for this purpose and the conditional transition probabilities, necessary to populate it, are unlikely to be similar for different health states.
- We have applied directly the risk equations from D'Agostino et al. A possible need of calibration of risk equations when applied to different populations was recently expressed(57). Considering our general underestimation of both CHD death and MI it is possible that the risk equations needed to be calibrated when applied to WOSCOPS population.

It may of course be the case that there are substantial epidemiological differences between the Framingham and West of Scotland populations, making extrapolation of a risk model estimated in one population to them other unreliable. However, it is also clear that there are many steps required in using such a risk model in an economic evaluation, each of which may have a significant impact on the results. It is unlikely that analysts will always choose identical methods of implementing such models, and this emphasises that the current state of play, with little standardization or consensus

on methods and low standards of documentation, is unsatisfactory and may well be influencing reported cost-effectiveness ratios.

Presenting the results for individual decision-making

In the introduction above, we highlighted the use of decision aides for clinicians based on CHD/CVD risk models, and emphasized that these aides are already being used to prioritise treatments. For example, the British Cardiac Society, the British Hyperlipidaemia Association, the British Hypertension Society and the British Diabetic Association have developed joint recommendations for the treatment of patients at high risk of CHD. Included in these recommendations is a set of Coronary risk prediction charts that illustrates CHD risk over the next 10 years by age, sex, lipid level, SBP, smoking states and whether the subject has diabetes or not ((14;58)). These coronary risk prediction charts are now reproduced in the back of every BNF, giving every general practitioner a readily available decision aid when making treatment decisions for individual patients. Colour coding is introduced to differentiate patients whose CHD risk over 10 years is <15%, 15% to 30% or over 30%. The intended interpretation is clearly that these represent low, medium and high-risk subjects and that treatment should be directed toward higher risk groups.

Two things are apparent. Firstly, the visual nature of this type of chart is extremely appealing, and this has undoubtedly aided their widespread dissemination. Yet, perversely, by focusing on risk, which is very strongly age related, the charts divert attention from the real concern of many practicing clinicians – the desire to prevent premature death. Of course, a measure of premature death is embodied in the notion of life years gained, which forms a fundamental part of economic evaluation. Therefore, we have attempted to adapt the presentation of the model reported in the section above to present the information in the same form as the coronary risk tables, but with a focus on life expectancy and potential years of life gained, rather than on risk per se. We have also attempted to separate modifiable risk factors (blood pressure, blood cholesterol, smoking status) from non-modifiable risk factors such as age, sex and diabetes. To do this we generated, for age, sex cholesterol ratio, SBP and smoking status combinations corresponding to those in the Joint British Guidelines, the predicted life expectancies from the Markov model. These are presented in Figure 2 and show that life expectancy does indeed vary across the risk factors modeled as expected. However, it is also clear that life expectancies

increase with age due to the conditional nature of starting a model with subjects at increasingly higher age (i.e. since by definition assigning a starting age of 70 to a subject in the model is conditional to them having survived to age 70). Therefore, to look at potential gains from successfully altering modifiable risk factors we calculated the reductions in life expectancy relative to the lowest risk group of patient within each age-sex-diabetes status group (i.e. relative to the non smoking group with SBP of 120 and Total/HDL ratio of 4). This focuses attention on the risk factors that are modifiable within a group characterized by non-modifiable risk factors. The results of this are presented in Figure 3(a), together with a colour coding to show the highest potential life-years gained.

What is interesting about Figure 3(a) is its direct comparison with the risk charts: there is still a clear benefit to reducing modifiable risk factors, but the patterns across age now clearly show an advantage for younger rather than older patients. Of course, what is presented in Figure 3(a) is the straightforward life-expectancy gains – in Figure 3(b) the results are presented employing a discount rate of 1.5% per annum. Discounting clearly reduces the potential life-year gains, but it also has the effect of shifting the balance away from the younger age groups for whom benefits are less immediate. The focus on life expectancy ignores morbidity concerns – these can be included by adding quality of life weights to the Markov model. Figure 4 presents quality adjusted life years gained with and without discounting for comparison with Figure 3 assuming that a history of myocardial infarction, angina pectoris or coronary insufficiency reduce quality of life by 0.055 quality-adjusted life-years (QALYs) (as shown by Clarke (59)) annually from the time of event. The potential to gain QALYs is lower than life years due to the fact that absence of CHD history is assigned an age-sex adjusted value of quality of life less than one taken from the Health Survey for England 1996. It is clear that the inclusion of quality of life adjustments further changes the distribution of potential benefits of reducing modifiable risk factors, with subjects aged around 50 years seeming to have the most potential benefit.

Summary

In this paper, we have attempted to explore how risk models, in particular the Framingham risk equations, have been used to prioritise health care in the prevention of CHD. It is quite clear that aids to the implementation of the risk models, in

particular colour coded risk charts, have become a popular way in which to disseminate and implement the results from the risk equations. These aides have much to commend them – they can make complicated equations quite accessible and much easier to understand and we suspect that the popularity of their use partly stems from the fact that they can be used directly with patients to help them understand their own risks and to encourage them to undertake behavioural changes in their lifestyle, such as dietary changes and stopping smoking. Nevertheless, these tables also have their limitations – in particular, the focus on risk over time means that the fundamental consequences on health, i.e., morbidity and mortality are less clear. Indeed, there are concerns that individuals may not always understand risk statement fully.

This paper reports our first attempts to improve on these charts by focusing on life expectancy gains and quality adjusted life expectancies in order to centre the debate on the prevention of morbidity and mortality. It should of course be acknowledged that life expectancy may also be frequently misunderstood. Detsky and Redelmeier (60) note that although people expect to add the average life expectancy gains to their present life expectancy, most gains in life expectancy imply actually immediate rather than a distant benefit. Nevertheless (quality-adjusted) life-expectancy charts are useful additional evidence for the relative benefits from interventions. Further research is now required on a) the modelling processes underlying these risk tables; b) the relative performance of life expectancy charts in comparison with risk tables in persuading patients to modify their risk factors as clinicians to make efficient treatment choices, and c) ways in which cost and cost-effectiveness information can be directly incorporated in a simple and informative way in such decision aids.

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Table 1
Identified Issues relevant to economic evaluations based on risk models

From the review of risk models	From the review of economic evaluations
Study sample • All models but one were based on population cohort data; • Risk profiles for participating individual in time;	Study population • Average data for risk factors by age and gender patient groups • The uncertainty related to distribution of risk factors/profiles not studied
Impact propagation • Through close to natural variation of risk factors or combined treatment and control groups;	Impact propagation • Impact of interventions entirely propagated through the impact on the relevant risk factors. • Artificial modification of risk factors is assumed to achieve benefits relevant for naturally varying risk factors was made.
Outcome • The outcomes of the risk models are usually combined CHD or CVD events (i.e. fatal CHD and specified non-fatal CHD events); • The estimates are limited to a relatively short time period (up to 5 or 10 years); • The risk models usually do not provide enough data to enable estimation of the uncertainty of the estimated outcomes;	Outcome • Life table data or other cohort data used to provide information on non-CHD related mortality. • Risk models that estimate separately fatal and non-fatal events are predominantly used. • In the case of an estimate of probability of combined CHD (i.e. coronary death and MI) additional assumptions used to split events on fatal and nonfatal • Extrapolation beyond the original time span of evidence

Table 2

Framingham risk equations for initial and subsequent CHD events[a]

Adapted from Tables III and IV of D'Agostino et al 2000

	Initial CHD events		Subsequent CHD events	
Variable	**Men**	**Women**	**Men**	**Women**
Intercept	12.7868	20.4049	4.995	13.537
Age	-0.0405	-0.0622	-0.0145	-0.0225
Menopause		-3.8236		
Age x menopause		0.0717		
ln(total/HDL cholesterol)	-0.9494	-0.8902	-0.6738	-0.834
ln(SBP[b])	-1.0163	-2.3607		-1.3713
Antihypertensive therapy*	-0.0161	-0.0097		
Diabetes	-0.4412	-0.5734	-0.3042	-0.7829
Smoker	-0.6042	-0.4041		-0.3669
Alcohol		0.0461		
Extreme value scale parameter	0.7764	0.7333	0.9994	1.0313

[a] Coefficients refer to Weibull model estimated as accelerated failure time

[b] SBP – Systolic blood pressure

[c] Interaction with SBP>110mm/hg

Table 3

5-year probabilities of CHD end points based on Framingham risk models

WOSCOPS placebo arm data	P (non-fatal MI or death from CHD) (1)	P (non-fatal MI) (2)	P (death from CHD) (3)
Woscops (55)	0.075	0.062	0.016
Abbot&McGee(40)	0.116	0.028	0.019
Anderson et al (40)	0.065		
D'Agostino (population)	0.055	0.039	0.016
D'Agostino (simulation of individual risk profiles)	0.061	0.044	0.017

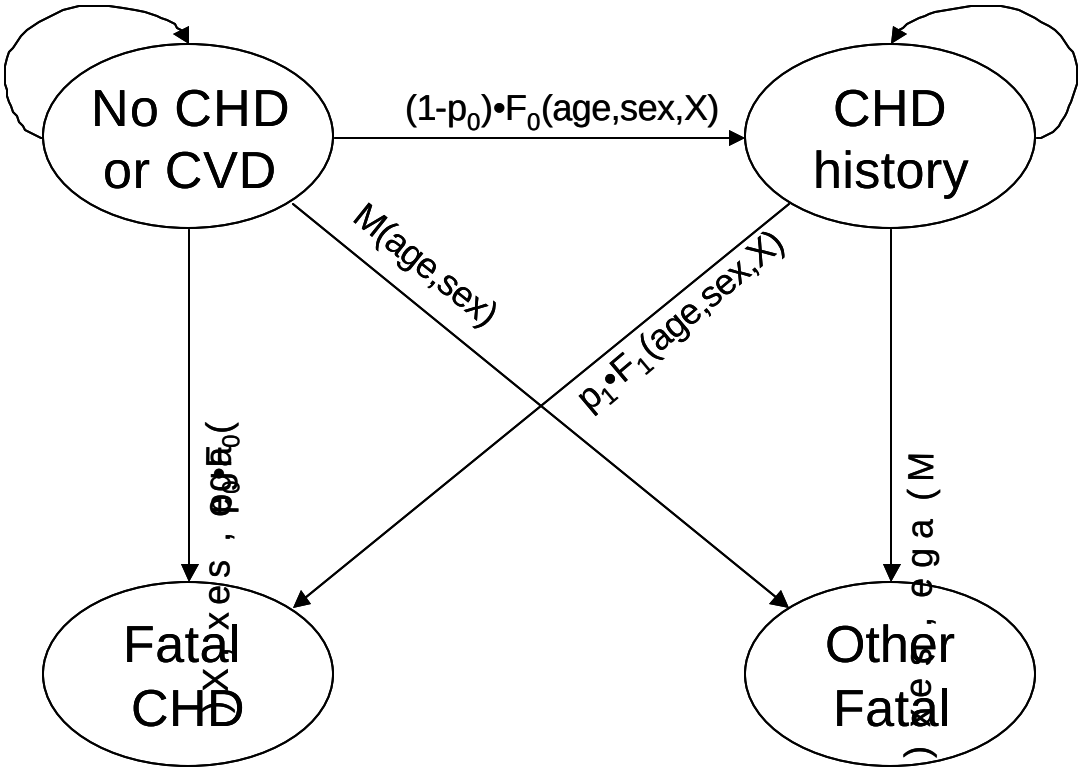


Figure 1
Structure of the Markov model including transition equations
F_0(age, sex,X) indicates a transition probability estimated from the Framingham equation for initial events as a function of age, sex and other risk factors, X (see Table 2 for details). Likewise for F_1(age, sex, X) but estimated from the Framingham equation for subsequent events (also Table 2). M(age, sex) indicates other cause mortality by age and sex (estimated from all cause life tables adjusted for CHD death). Note that p_0 and p_1 represent the proportion of fatal CHD events fr om the total for first and subsequent events respectively.

No Diabetes

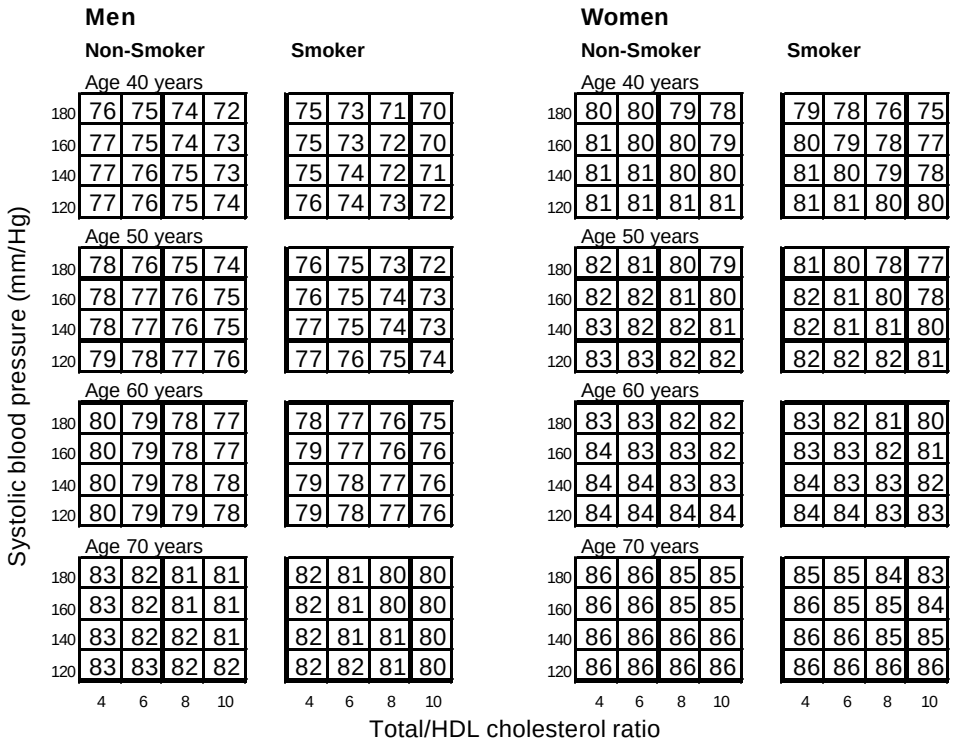
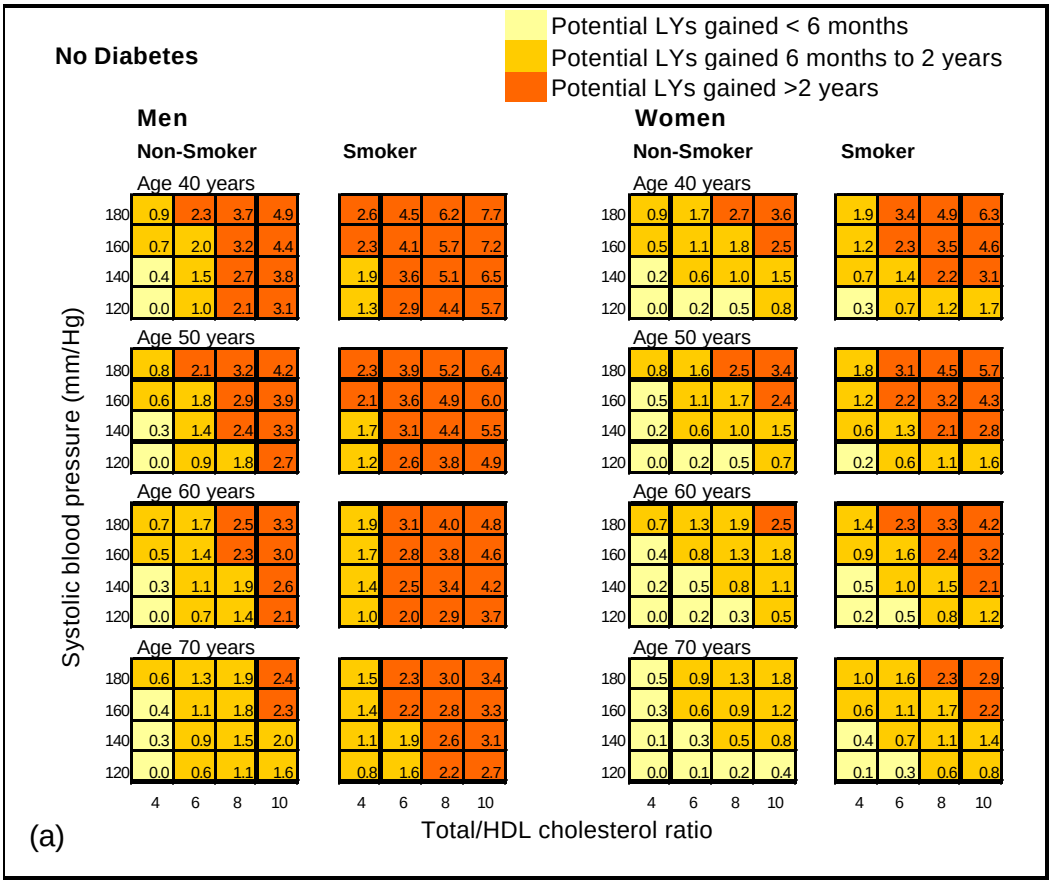


Figure 2
Life expectancy for patients initially free of CHD/CVD and without diabetes predicted from the Markov model



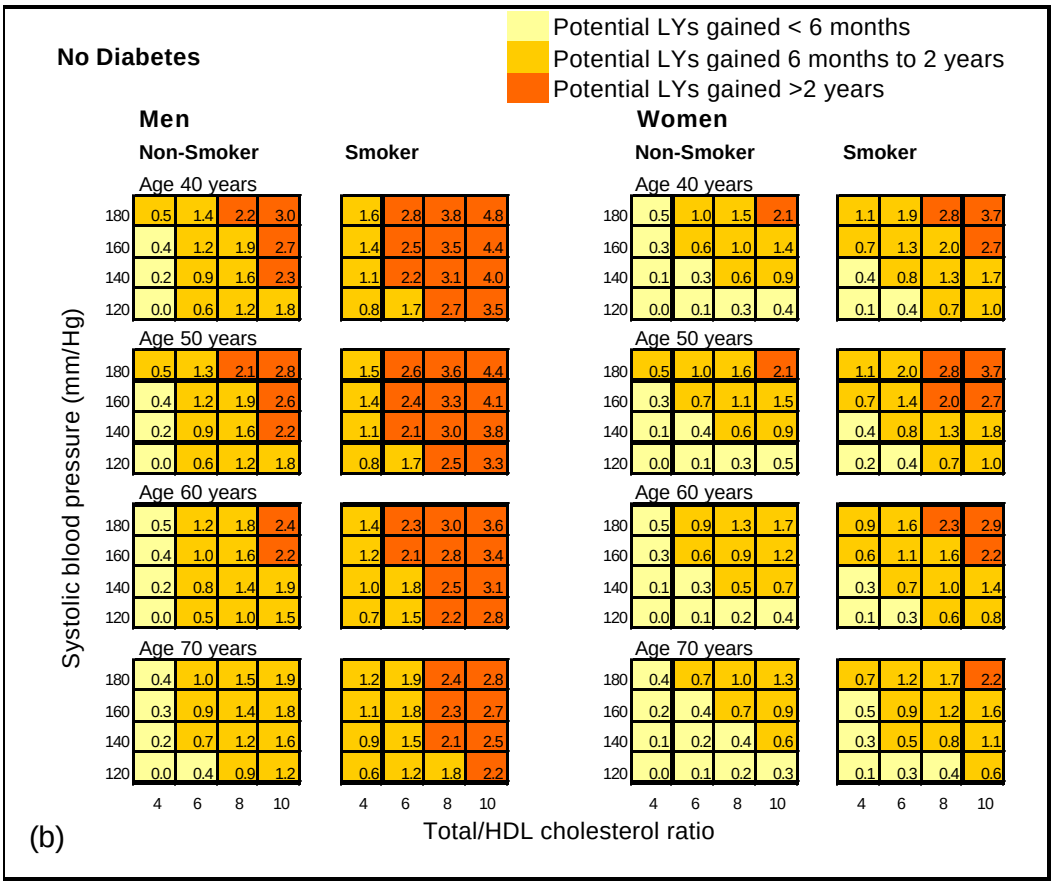
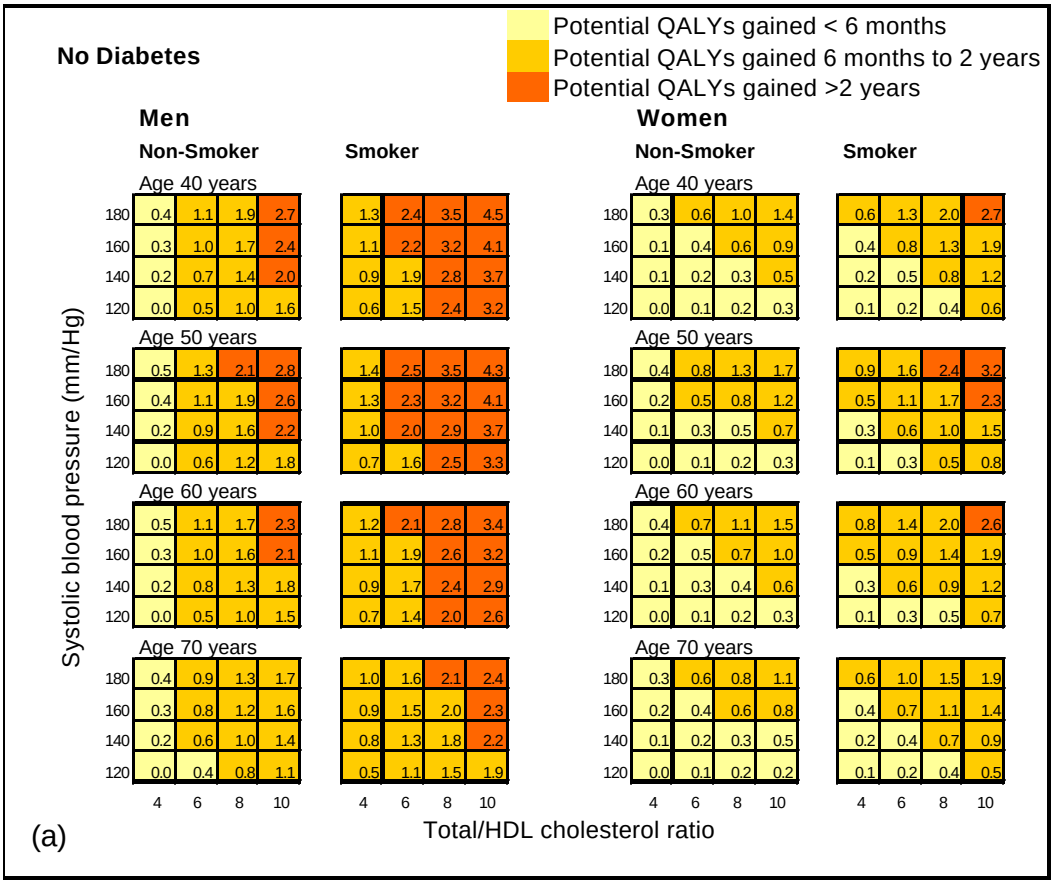


Figure 3
Potential years of life gained by reducing modifiable risk factors to lowest of age/sex group
(a) without discounting, and (b) discounting at rate of 1.5% per annum



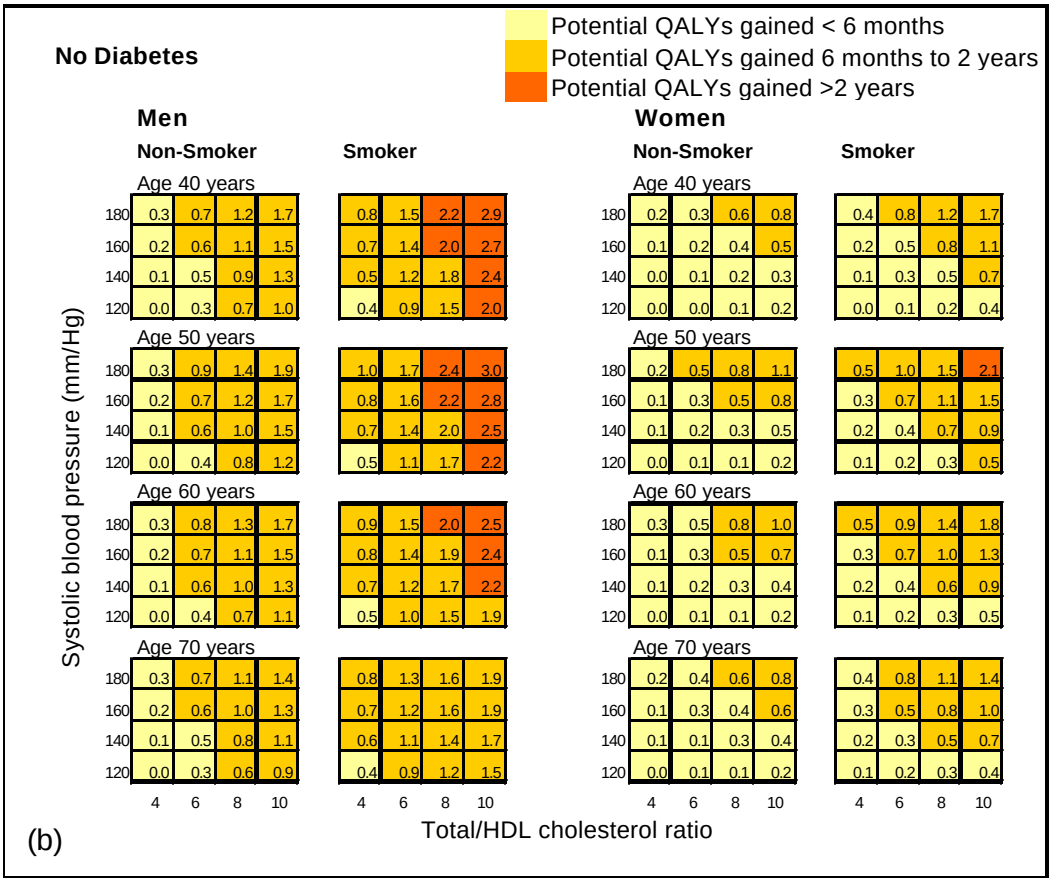


Figure 4
Potential years of life gained by reducing modifiable risk factors to lowest of age/sex group
(a) without discounting, and (b) discounting at rate of 1.5% per annum