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## Pharmacoeconomics of cardiovascular disease prevention

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## Chapter 2

### **A systematic review on the application of cardiovascular risk prediction models in pharmacoeconomics, with a focus on primary prevention**

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## ABSTRACT

**Background:** Long-term trials on the effectiveness of pharmacological treatment for primary cardiovascular disease prevention are scant. Risk prediction models are used as a tool to project changes in cardiovascular disease incidence due to changes on risk factor levels observed in short-term randomised clinical trials. In this article, we summarize the literature on the application of these risk models in pharmacoeconomic studies for primary cardiovascular disease prevention interventions in high income countries.

**Methods and results:** We systematically reviewed the available literature on the application of cardiovascular disease risk models in pharmacoeconomic studies and assessed the quality of incorporation of risk models in these studies. Quality assessment indicated the distance between the characteristics of populations of the risk model and the studies reviewed, the frequent disagreement between risk model- and study- time horizons and the lack of proper consideration of the uncertainty surrounding risk predictions.

**Conclusion:** Given that utilizing a risk model to project the effect of a pharmacological intervention to cardiovascular events provides an estimate of the intervention's clinical and economical impact, consideration should be paid to the agreement between the study and risk model populations as well as the level of uncertainty that these predictions add to the outcome of a decision-analytic model. In the absence of hard endpoint trials, the value of risk models to model pharmacological efficacy in primary cardiovascular disease prevention remains high, although their limitation should be acknowledged.

## **INTRODUCTION**

Cardiovascular disease (CVD) accounts for a major share of overall morbidity and mortality in the Western world (1,2). Furthermore, due to the high inpatient costs of most common CVDs, it is the most significant contributor of health care expenditures, e.g. treatment costs of CVD in European Union comprise 12% of all health care costs (€105 billion)(3). Given the health and economic burden of CVD, its primary prevention is of high importance to society.

The onset of CVD has been associated with a number of, often correlated, risk factors. Elevated blood pressure (BP), cholesterol or glucose levels, smoking and age have been identified as the most important of them, whose conjoint influence can lead to CVD. Based on these observations, during the last 25 years, different multivariable risk prediction models have been developed, to assist identification of patients at risk of CVD in clinical practice (4-23). These models have been generally based on large cohorts that are being followed for a sufficient length of time and for which both risk factors and outcomes are known over time. The models often differ in the risk factors they comprise and the underlying study populations, as well as the definition of the CVD risk studied. Furthermore, they make predictions for different time horizons and for different clinical CVD-specific endpoints.

The utilization of CVD risk prediction models in the economic evaluation of pharmacological primary prevention has already been established in various studies (24,25). Their value stems from the fact that there is limited evidence on the long-term benefits of the drugs used in CVD prevention. Therefore, these models provide a linkage between the treatment effectiveness on intermediate endpoints, observed in short-term randomised-clinical trials (RCTs) (e.g. change in cholesterol, BP), and the long-term benefits of treatment (e.g. reduced number of CVD events). Furthermore, prediction of the number of CVD events avoided due to treatment also offers a way to estimate the future financial savings on these events.

In this article, we systematically summarize the available literature on the application of CVD risk prediction models in pharmacoeconomic studies that explore interventions for primary CVD prevention in high income countries.

## **METHODS**

Pharmacoeconomic studies of different primary CVD prevention strategies were systematically reviewed using the PubMed database and NHS Economic Evaluation Database. We used the following keywords: "risk assessment" or "risk prediction model" or "risk model" or "risk function" or "risk equation" or "risk factor" or "risk score" and "cardiovascular diseases" or "cardiovascular" or "coronary heart disease" and "cost-benefit" or "costs and cost analysis" or "health care costs" or "cost-benefit" or "cost-

effectiveness" or "cost-utility" or "economic evaluation" or "decision model". The search was limited to studies published until December 2011.

Studies were included in the reviewing process if they:

- 1) were strictly classifiable in one of the pharmacoeconomic categories of cost-effectiveness analysis (CEA), cost-utility analysis (CUA) or cost-benefit analysis (CBA);
- 2) were written in English and published in peer-reviewed journals;
- 3) presented a decision-analytic model that has utilized a risk prediction model; and
- 4) explored pharmacological, primary prevention of overall CVD, or some of its constituents, in populations with no prior CVD events or diabetes.

Hence, we excluded studies exploring either secondary, or primary combined with secondary CVD prevention, or studies where CVD was considered as comorbidity to an underlying disease (e.g. HIV/AIDS or diabetes).

Editorials, letters, clinical conference abstracts and reviews were excluded. Finally, we focused only on pharmacoeconomic studies in high income countries (defined according to their gross national income per capita (26)). All abstracts retrieved from the electronic databases were independently screened and reviewed by two team members (JS and PP). Disagreements were resolved through discussions.

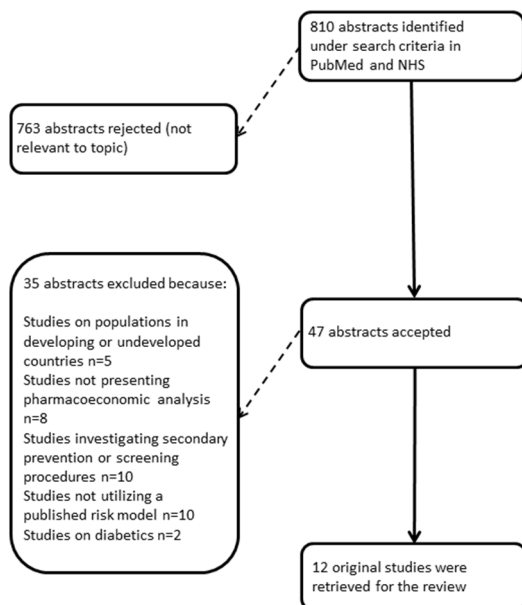
The appropriateness of the application of the CVD risk models in the pharmacoeconomic analyses was evaluated using a set of the criteria similar to that proposed by Grieve et al.(24). These criteria relate to:

- 1) the agreement between the time horizons of the risk model and the decision-analytic model;
- 2) the comparability between the study population and the risk model population;
- 3) whether the risk model comprises the key risk variable influenced through pharmacological intervention;
- 4) the availability of evidence on prediction accuracy in the study population; and
- 5) the approach followed in incorporating the uncertainty related to CVD risk projection into the overall decision-analytic model uncertainty(25,27).

## RESULTS

Through our search strategy, we retrieved 810 studies. The flow chart of the literature search is presented in Figure 1. After implementing all the inclusion criteria, our search highlighted 12 relevant studies. Of the 12 studies included, four referred to the United States (US)(28-31), two to the United Kingdom (UK)(32,33), two to Sweden (34,35), and

one to each of Germany (36), Greece (37), Canada (38), and Japan (39). The main characteristics of the pharmacoeconomic studies are summarized in Table 1, while information regarding the utilization of CVD risk models and their incorporation in the decision-analytic models is summarized in Table 2. A more detailed description of the reviewed studies can be found in the appendix.



**Figure 1** Search results and culling process of retrieving pharmacoeconomic studies of pharmacological interventions for primary CVD prevention in high income countries that utilized published CVD risk prediction models.  
CVD, cardiovascular diseases

### Summarizing the CVD risk models

The majority of the studies reviewed have utilized CVD risk prediction models based on a Framingham population. We encountered five Framingham risk prediction models projecting different endpoints for various time horizons (4,5,10,16,22). Such widespread application of the Framingham risk models is not surprising. These risk models are widely used in clinical guidelines (40,41) and are validated in not only Caucasian- and African-American but also in some European and Asian populations, to accurately predict CVD risk in asymptomatic patients (42). They comprise a variety of easily obtained and clinically relevant risk factors (43). Furthermore, their advantage, which facilitates their applicability, is that they are developed on a general population.

The risk prediction models developed by Anderson et al.(4) were used in five studies (28,29,32-34) and their adjusted form in one (39), while another Framingham model predicting coronary heart disease (CHD) risk(5) was used in one study (36). Johannesson

(34) utilized a different risk model (16) that was also developed on data from the Framingham population. Pignone et al. (28) used two Framingham based risk models for stroke (10,22) next to the one from Anderson et al. (4). The CHD Policy Model (44) was also designed using Framingham data (45).

Out of 12 studies, three utilized CVD risk models that were not developed on a Framingham population. Specifically, Maniadakis et al. (37) utilized a risk model by Glynn et al.(11), which was developed on two RCTs populations (46,47). These RCTs investigated the effects of aspirin and beta-carotene in male, and the effects of aspirin and vitamin E in female health professionals, on prevention of CVD and cancer. The Cardiovascular Disease Life Expectancy (CVDLE) Model (48) used by Grover et al.(38) was based on a logistic regression function developed on the Lipid Research Clinic (LRC) cohort (49,50). This cohort consisted of patients older than 30 years, from 10 clinics in North America that were followed for more than 12 years. Lofroth et al.(35) developed separate risk equations for myocardial infarction (MI) and stroke that utilized data from two Swedish hospital registers and from the Swedish Nora study (35,51).

### **Critical assessment of the risk models**

#### ***Time horizon***

Five of the reviewed studies (28,29,33,34,39) utilized the CVD risk prediction functions of Anderson et al.(4) to estimate annual transition probabilities for Markov models with lifetime horizons. However, these risk models are designed to predict a cumulative CVD risk in a 4-12 years time horizon. This discrepancy evokes two concerns. The first relates to the method the authors used to transform the cumulative risk to annual probabilities and the second considers the extrapolation of these probabilities to periods beyond the risk model's time horizon. Pignone et al. (28) and Ernshaw et al.(29) assumed an underlying exponential distribution to obtain annual CVD probabilities for estimating the Markov models. Saito et al.(39) neither reported their method of obtaining annual CHD probabilities nor their assumptions related to extrapolating them to a lifetime horizon.

The risk models by Anderson et al.(5) also provide cumulative CHD risk predictions for 4-12 years. Brennan et al. applied this risk model annually and for a time horizon of 5 years.(36) This application is also of concern given that this risk model in quite short horizons cannot specify the exact time of onset of the events.(5)

The CHD Policy Model (44) used by Lazar et al.(31) and Pletcher et al.(30) is a Markov model with a 30-year time horizon, where the age- and gender- specific CHD risk is based on logistic regression models that are estimated using longitudinal Framingham data(45). This approach, although reducing the problems related to the translation or the extrapolation of the risk, suffers from the need of long follow-up periods and a large cohort size.

Johannesson (34) applied a previously published Markov model based on a risk model by Kannel et al.(16) This risk model predicts the 8-year CHD and stroke risk. However, his decision-analytic model is run for a lifetime horizon. The 8-year cumulative risks are transformed into annual probabilities but no exact information is given on how this transformation takes place.

A risk model developed by Glynn et al.(11) that predicts a 5-year CVD risk, was used in the model of Maniadakis et al. (37) assuming a lifetime horizon. Maniadakis et al. (37) noted that they transformed 5-year probabilities into annual ones, but without reporting the method for that or for extrapolating them through lifetime.

Finally, the CVDLE Model (46) was utilized in a study by Grover et al.(38,48) Even though this model is run through a lifetime, it utilizes logistic regression functions developed on the LRC cohort (47,51), which gives 10-year predictions. In the article where the original model was published (48), the authors assumed equal annual risks. To obtain these annual risks they have falsely divided the 10-year risk by 10. This generally results in an underestimation of the annual risk (52).

### **Population characteristics**

Predictions of CVD risk in decision-analytic modelling can be biased due to differences between the risk model and the study populations. Such differences appear more frequently when the risk model is estimated using a RCT population. These risk models usually overestimate the CVD risk and therefore application of them in a general population is not recommended, at least not without proper validation (24). Furthermore, significant differences in the socio-economic and educational status between populations could lead to considerable prediction discrepancies (43).

In order to compare these populations in the reviewed studies we evaluated the differences in the risk factor levels between the study and the risk model populations. In the CUA by Pignone et al. (28), the study population had lower levels of risk factors compared with the Framingham one. Therefore, applying the risk model by Anderson et al. in this study population might lead to a risk overestimation (4). Risk factors of the study cohort in the analysis by Ernshaw et al. (29) were comparable with the Framingham population, for the corresponding age and gender. In the study of Brennan et al. (36), specific risk factor characteristics of the populations investigated were not provided, which hindered us from making any comparisons. Population characteristics in the study by Caro et al.(32) were comparable with the ones in Framingham. In the studies by Montgomery et al. (33) and Lofroth et al.(35) different strata of risk profiles were assumed; therefore, the appropriateness of the risk models for extreme risk factor strata would be questionable. Saito et al. (39) did not fully report risk factor characteristics (e.g. smoking, left ventricular hypertrophy), thus complicating the comparison. However, the model they used has been adjusted to the studied population. Risk factor levels of the study population in the analysis by Johannesson were not explicitly stated (34).



Maniadakis et al.(37) studied a population with risk factor levels that were slightly elevated compared with those in the risk model study. Another discrepancy was that the risk model used was based on a population of health care professionals from two RCTs, which was not representative of the general population. Grover et al.(38) populated the CVDLE Model (46) with risk factor levels from a Canadian population that was comparable with the risk model's population. With respect to the CHD Policy Model (44), given that it was calibrated to reproduce USA data on the distribution of the risk factors and CHD events, its utilization in the studies by Lazar et al.(31) and Pletcher et al.(30) concerning USA population older than 35 years, seems appropriate.

### ***Key risk variable***

The assessment of the long-term effectiveness of a change in a risk factor level can be most clearly observed through a risk model that comprises the risk variable of concern (24). The majority of the studies reviewed, investigated either the influence of antihypertensives on systolic BP (SBP) and/or diastolic BP (DBP) levels (37,39) or the influence of statins on cholesterol levels (30,31,38). In cases where there was no risk factor that could be modifiable through a certain treatment, such as for aspirin, a relative risk reduction of that treatment, observed through RCTs was modelled to lead to a risk reduction (28,29). The same method was also implemented in studies investigating treatments for obesity that in general lead to a change in body mass index (32,36). Finally, in three studies, although the risk model used could accommodate the effect of statin or antihypertensive treatment through cholesterol or BP reductions, the authors incorporated it as a multiplicative effect on the CVD risk, drawn from published RCTs (33-35). The drawback of such method is the potential bias of the risk prediction due to differences between the RCT population and the population studied.

### ***Validation of the risk prediction model***

When making the decision to apply a risk model to a certain population, one should first consider the existing evidence of its performance in this population. A necessity for using the externally validated risk model is even more pronounced in the case of geographically or racially diverse populations (53). Additionally, the time when validation took place is of significant importance, given the recent decline in CVD mortality in the western world.(54) The Framingham based risk models (4) were found to generally overestimate the CVD risk in a variety of European populations (55-57). Given this evidence, the use of Framingham in a German setting, as used in the study by Brennan et al.(36), seems questionable. A similar overestimation of CHD risk based on the Framingham study (5) was observed for British men (55), which questions its utilization in the studies by Montgomery et al.(33) and Caro et al. (32). On the contrary, even though Framingham based risk models were not validated for a Japanese setting, utilization after adjustment for the Japanese population, as done by Saito et al.(39), seems appropriate (4).

Maniadakis et al.(37) used a risk model by Glynn et al.(11) that has not been validated for a Greek setting. The risk model utilized by Grover et al.(38) has been recently shown to accurately predict the 10-year CVD risk for a Canadian setting (58). Finally, the risk models developed by Lofroth et al. were not validated for a Swedish setting, although the model assumes the age- and sex- specific incidence of MI and stroke in Sweden (35).

### **Sensitivity analysis**

Nowadays, it is almost a compulsory requirement from pharmacoeconomic analyses to provide an insight into uncertainties surrounding the model inputs as well as the structure and the assumptions related to the model (25,27). In the reviewed studies, however, the risk prediction uncertainty was rarely incorporated. Specifically, only one study has incorporated the uncertainty of the risk model parameters in the probabilistic sensitivity analysis (PSA). We considered that a major drawback for the studies lacking incorporation of the risk model uncertainty in the PSA, since this uncertainty can be responsible for a large share of the overall model uncertainty.

**Table 1** Basic characteristics of the pharmacoeconomic studies included in the systematic review.

Main author (year), country	Year of values, currency	Study objective	Evaluation type (outcome measure)	Discount rate (costs; health benefits)	Source of efficacy/effectiveness data	Cost components (study perspective)	Source of cost data	Results
Pignone (28)(2007), US	2005, US \$	CUA of primary CVD prevention with aspirin in 65-year-old women	CUA (QALY)	3: 3	Published sources (mostly on men)	Costs of drug, adverse drug events and CVD events (health)	Published literature and national databases	13300 \$/QALY
Ernshaw (29)(2011), US	2009, US \$	CUA of aspirin alone or combined with PPI in men at different risks for CHD and GI bleeding	CUA (QALY)	3: 3	Meta-analysis and RCTs	Costs of drug, CVD events, outpatient physician visit (health care)	Costs retrieved from authors' previous study	Strategy- and age-specific CU outcome
Brennan (36)(2006), Germany	2003, €	CUA of sibutramine combined with non-pharmacological practice (diet and lifestyle advice) versus non-pharmacological practice alone	CUA (QALY)	5: 5	RCTs	Costs of drug, disease-specific costs (health care)	Published literature, surveys and authors opinions	13706 €/QALY
Caro (32)(2007), UK	2005, UK £	CUA of adding rimonabant for 1 year to exercise and diet in obese patients with and without diabetes, compared to exercise and diet alone	CUA (QALY)	3.5: 3.5	RCTs	Costs of drug, adverse drug events, disease-specific costs (health care)	Costs of hospitalizations from in-patient UK records, other costs from NHS guidelines	8574 £/QALY
Pletcher (30)(2009), US	2006, US \$	CUA of adherence to the ATP III guidelines against other risk- and age- based lipid lowering strategies	CUA (QALY)	3: 3	Published studies	Costs of drug, adverse drug events and CHD events (health care)	National specific costs	Strategy-specific CE outcome

Main author (year), country	Year of values, currency	Study objective	Evaluation type (outcome measure)	Discount rate (costs; health benefits)	Source of efficacy/effectiveness data	Cost components (study perspective)	Source of cost data	Results
Lazar (31)(2011), US	2008, US \$	CUA of low-cost generic statins compared to no intervention and examine the circumstances under which their application would be cost-effective	CUA (QALY)	3; 3	Published studies	Costs of drug, adverse drug events and CHD events (health care)	Assumption of drug costs, other costs come from national and Californian data	Strategy-specific CE outcome
Johannesson (34)(2001), Sweden	1999, US \$	To estimate a 5-year coronary risk at which cholesterol lowering with statins is cost-effective	CUA (QALY)	3; 3	Published studies	Costs of drug, disease-specific costs, costs due to productivity loss (societal)	Published studies	Fixed CE outcome
Montgomery (33)(2003), UK	2002, UK £	CUA of BP lowering compared to no intervention	CUA (QALY)	6; 1.5	Published studies	Costs of treatment, costs of cardiovascular	Published studies	Strategy-specific CE outcome
Maniadakis (37)(2011), Greece	2008, €	CUA of hypertension treatment with losartan, valsartan and irbesartan when combined with hydrochlorothiazide	CUA (QALY)	3; 3	RCTs	Costs of drugs, costs of CVD events, costs of maintenance of patients posthospital discharge (health care)	Derived from national databases	ICERs not presented
Grover (38)(2008), Canada	2002, Canadian \$	CEA of antihypertensive and lipid-lowering treatment advocated by Canadian guidelines	CEA (YOLS)	3; 3	RCTs	Costs of drugs, costs of cardiovascular events (health care)	Resource use from national surveys	16700/YOLS for statins 37100/YOLS for antihypertensives
Saito (39)(2005), Japan	2004(2003), Japanese	CEA of different antihypertensive drug	CEA (YOLS)	3; 3	Review and published	Costs of drugs, disease-specific	Published studies	ICER not presented

Main author (year), country	Year of values, currency	Study objective	Evaluation type (outcome measure)	Discount rate (costs; health benefits)	Source of efficacy/effectiveness data	Cost components (study perspective)	Source of cost data	Results
Japan	yen	regimes			studies	costs, outpatient management (health care)		
Lofroth (35)(2006), Sweden	2000, €	CUA of antihypertensive, lipid lowering or smoking cessation interventions with the aim of optimal resource allocation	CUA (QALY)	3; 3	Review and published studies	Costs of drugs, costs of anti-smoking counseling, disease-specific costs, costs due to production loss (societal)	Published sources	Strategy-specific CE outcome

US, United States; CUA, cost-utility analysis; CVD, cardiovascular diseases; QALY, quality-of-life-year; PPI, proton-pump inhibitors; CHD, coronary heart disease; GI, gastro-intestinal; RCT, randomized clinical trials; CU, cost-utility; EUR, euro; UK, United Kingdom; NHS, National Health Service; ATP, adult treatment panel; CE, cost-effectiveness; BP, blood pressure, ICER, incremental cost-effectiveness ratio; CEA, cost-effectiveness analysis; YOLS, years of life saved.

**Table 2** Study design of economic evaluations on cardiovascular diseases (CVD) primary prevention with pharmacological treatment. Studies utilizing risk prediction models.

Study	Modeling (time horizon)	CVD risk model	Risk model time span	Risk model validated / recalibrated	PSA of risk model parameters
Pignone et al.(28)	Markov model (Lifetime)	Framingham based risk (4,10,22)	4-12 years (CHD); 10-years (stroke)	Yes*	No
Ernshaw et al.(29)	Markov model (Lifetime)	Framingham based risk(4)	4-12 years	Yes*	No
Brennan et al.(36)	Decision tree (5-years)	Framingham based risk(5)	4-12 years	No	No
Caro et al.(32)	Markov model (Lifetime)	Framingham based risk(4)	4-12 years	No	No
Pletcher et al.(30)	CHD Policy Model <sup>44</sup> (Lifetime)	Framingham based risk(45)	Not-stated	Yes	Yes
Lazar et al. (31)	CHD Policy Model <sup>44</sup> (Lifetime)	Framingham based risk(45)	Not-stated	Yes	No
Johannesson (34)	Markov model (Lifetime)	Framingham equations(16)	8-years	No	No
Montgomery et al.(33)	Markov model (Lifetime)	Framingham based risk(4)	4-12 years	No	No
Maniadakis et al.(37)	Markov model (Lifetime)	Glynn et al. equation(11)	5-years	No	No
Grover et al.(38)	CVD Life Expectancy Model(46) (Lifetime)	Logistic regression model based on the LRC(47,51)	10-years	Yes	No
Saito et al.(39)	Markov model (Lifetime)	Adjusted Framingham based risk(4)	4-12 years	Yes	No
Lofroth et al.(35)	Markov model (Lifetime)	Functions developed on Swedish registers(48)	10-years	No	No

CVD, cardiovascular diseases; PSA, probabilistic sensitivity analysis; CHD, coronary heart disease; LRC, Lipid Research Clinic follow-up cohort

\*Validated in White and African-American

## DISCUSSION

This systematic review of pharmacoeconomic analyses of primary CVD prevention strategies in high income countries identified 12 studies that have used published CVD risk prediction models. The majority of these prediction models were based on a Framingham population and focused on the CHD and stroke risk. The studies demonstrated the usefulness of projecting intermediate effectiveness endpoints to long term, health and cost related, benefits. However, after assessing the quality of incorporation of these risk models in pharmacoeconomic analyses we identified a distance between the populations of the risk model and the study population, a frequent disagreement between risk model- and study- time horizons and a lack of proper consideration of the uncertainty surrounding the prediction of the risk.

In order for a risk model to be able to predict accurately the CVD events of a study population, there must be a relative agreement between the study and the risk model populations with respect to the main CVD risk factors (24). In the reviewed studies, this criterion was generally met. However, characteristics that have been earlier identified as influential on CVD risk and relate to temporal, regional, demographic and socio-economic characteristics have not been adequately assessed in the reviewed studies. For example, the Framingham population, which was widely used among the reviewed studies, has been earlier found to overestimate CVD risk in the western world, especially in lower socio-economic populations (55,59,60). Similar problems can be encountered when the risk model is based on special populations, such as populations from RCTs. One such example is that of Glynn et al. where the risk model population consisted of health care providers, who cannot be considered as representative of the general population (11).

Pharmacoeconomic analyses generally require the estimation of both costs and effects for a lifetime horizon. In this review, most studies were characterized by a disagreement between the risk model and the decision-analytic model horizons. Specifically, risk models provided a considerably smaller time horizon, forcing the authors to project the estimated risks for time horizons for which the risk models were not validated. However, increasingly more risk predicting models that are developed on cohorts with longer follow up times are becoming available. The risk model by Pencina et al., which is based on the Framingham population and can estimate a 30-year CVD risk, might be a valid tool for a more accurate estimation of lifetime risk, which is necessary for pharmacoeconomic analyses (19). One other such long-term risk model is the QRISK2 model (12), developed using general practitioner collected data from the UK, which can be utilized for the estimation of lifetime CHD and stroke risk in the general population.

The usage of a CVD risk model to project the effect of a pharmacological intervention from risk factors to CVD events provides an estimate of the intervention's clinical and

economical impact. However, this projection introduces an additional uncertainty level associated with the accuracy of the CVD prediction on the specific population. Although pharmacoeconomic evaluations require this uncertainty to be studied together with the overall model uncertainty, this has been rarely observed in our review. The means of incorporation of this uncertainty has been described in detail in the literature and involve the consideration of the level of uncertainty and correlation of the parameters of the risk model (27).

Concluding, we provide some suggestions with respect to the appropriate use of a CVD risk model in pharmacoeconomic analysis. First, incorporating a risk model into a pharmacoeconomic analysis must be done after the compatibility of the risk model and the study populations has been thoroughly investigated. Additionally, the study should report the method used for the translation of cumulative risks to short-term probabilities and should clearly describe the method behind extrapolating this risk to a lifetime horizon. Finally, the uncertainty introduced due to CVD risk prediction should be incorporated in a transparent way in the estimation of the overall uncertainty of the decision-analytic model, as this prediction parameter is one of the main contributors of uncertainty.

## **Appendix**

### ***General description of selected studies***

Pignone et al.(28) performed a cost-utility (CUA) of the use of aspirin for primary prevention compared to no intervention in 65-year-old women in a USA setting. For this purpose, they developed a Markov model that incorporated disease-specific health states and health states related to adverse effects of aspirin. The cardiovascular diseases (CVD) risk prediction models used were based on the Framingham Heart Study (4,10,22). The cost-effectiveness (CE) of aspirin treatment was modelled in a lifetime horizon. The authors concluded that preventive use of aspirin is beneficial in women with a higher risk for ischemic stroke but potentially harmful for women with a relatively low stroke risk.

A CUA was conducted by Ernshaw et al.(29) to compare aspirin alone or in combination with a proton-pump inhibitor (PPI) with no treatment, in primary CVD prevention. The authors used a Markov model similar to the one of Pignone et al. (28) However, their pharmacoeconomic study was focused on a population of 45-year-old men. The CVD risk prediction was based on the Framingham Heart Study. Results were explored in time horizons of 5, 10, 25 years and lifetime. Higher incremental cost-utility ratios were observed for shorter time horizons. The authors concluded that CVD prevention with aspirin alone in 45-year-old men was less costly and more effective than no treatment.

Brennan et al.(36) investigated the cost-utility of sibutramine combined with diet and lifestyle advice in obese patients, in comparison with a non-pharmacological intervention. They constructed a decision tree model where they modelled weight loss after one year of drug treatment and four years of follow up. Two Framingham based risk models (5,61)



were used to translate weight loss into coronary heart disease (CHD) risk reduction. Their conclusion was that, for German, obese patients, sibutramine is more cost-effective against non-pharmacological interventions.

Caro et al.(32) explored the cost-utility of adding rimonabant to exercise and diet, compared to exercise and diet alone, in obese patients with and without diabetes. Since our focus is on primary prevention in non-diabetic populations, we incorporated in our review only the part that applies to non-diabetic patients. The authors designed a one-month cycle Markov model with three CVD-related health states and a lifetime horizon. Framingham risk models (4) were used for calculating the primary CVD risk, as a composite of the risk for CHD and stroke. Given that those models do not incorporate body mass index (BMI) as a risk factor, the authors incorporated in the estimation of the risk of CHD an additional risk for patients with high BMI (62).The authors concluded that adding rimonabant to exercise and diet seems to be cost-effective.

Pletcher et al.(30) explored the cost-utility of statin treatment adherent to the Adult Treatment Panel III (ATP III) guidelines (63) against various other risk- and aged- based statin treatment strategies. For this purpose, they utilized an updated version of the, previously published, CHD Policy Model (44). This is a Markov model based on a USA population older than 35 years of age. Risk functions for incident CHD and non-CHD related death were based on longitudinal data from the Framingham Heart Study (45). The cost-utility estimates were calculated for a 30-year time horizon. The main effect of statin use was the reduction of low-density lipoprotein (LDL), with a subsequent estimated effect on CHD risk reduction. Pletcher et al.(30) concluded that lipid-lowering strategies adherent to the ATP III guidelines are relatively more cost-effective compared to other risk- and age- guided alternatives.

A CUA by Lazar et al.(31) assessed primary prevention with low-cost generic statins compared with no intervention and examined under which circumstances their application is cost-effective. For this purpose, they utilized the CHD Policy Model (44). Lazar et al. (31) incorporated statin-induced diabetes as an additional possible adverse effect to statin treatment, next to myopathy and hepatitis. Statin induced diabetes was directly incorporated in the model, given that it is considered as one of the CHD risk factors. Lazar et al. (31) concluded that statin use in people with even modestly elevated LDL or any CHD risk factor could be considered as a cost-effective option.

Johannesson conducted a study to estimate the 5-year coronary risk level at which statin application is considered to be cost-effective in Sweden (34). He utilized a previously published Markov model for cost-effectiveness analysis (CEA) in cardiovascular prevention (64). In this model, transition probabilities to each of the CHD states were estimated through logistic risk models from a study based on the Framingham population (16). In order to assess the coronary risk level at which statin use was cost-effective, the author

varied the CHD risk level until the cost per QALY reached a certain willingness-to-pay threshold.

Montgomery et al. explored the cost-utility of an antihypertensive intervention compared with no intervention in cohorts of 20 different strata of age, gender and high or low CVD risk (33). They used a Markov model in which CVD-related transition probabilities were estimated through a Framingham Heart study (4). The authors modified the estimated baseline CVD risk depending on the probability of successful systolic blood pressure (SBP) control. According to Montgomery et al. (33), estimates of cost-utility ratios were higher for low-risk women compared with men, while high-risk patients had more favourable cost-utility ratios than low-risk patients.

A CUA of hypertension treatment among combinations of different angiotensin-receptor blockers (ARBs) and hydrochlorothiazide (HCTZ) in a Greek setting was performed by Maniadakis et al. (37). The authors designed a Markov model with eight CVD-specific health states for a lifetime horizon. The risk models developed by Glynn et al., in combination with gender- and disease-specific incidence rates were utilized to model transitions between CVD states (11). The authors concluded that application of irbesartan in combination with HCTZ was the most favourable compared with the other ARBs.

Grover et al. performed a CEA of antihypertensive and lipid-lowering treatment as recommended by the 2003 Canadian Working Group guidelines, in comparison with no treatment (38). They utilized the Cardiovascular Disease Life Expectancy (CVDLE) Model (48). Probabilities of CVD events in this model were based on logistic regression functions developed using data from the Lipid Research Clinic cohort (LRC)(49,50). The authors concluded that lipid-lowering and antihypertensive therapies in accordance with the Canadian guidelines are cost-effective in most of the age-gender groups of patients.

A CEA in a Japanese setting concerning different antihypertensive drug regimes was conducted by Saito et al.(39). The authors utilized a Markov model in which a hypothetical cohort of 55-year old patients with essential hypertension was followed lifelong and incidence of CHD and stroke was monitored (65). Transition probabilities to CHD states were calculated through adjusted Framingham risk models (4). These risk models were adjusted to a Japanese setting under the assumption that the incidence of CHD in Japan is 20% of that in USA. Saito et al. did not observe any relative advantage in terms of costs and expected survival among the applied drug regimes.

Lofroth et al. performed a CUA of primary CVD prevention through a combination of antihypertensive, lipid-lowering or smoking cessation interventions, with the aim of optimal resource allocation within the Swedish health care system (35). The authors designed a Markov model with disease-specific health states reflecting myocardial infarction (MI) and stroke. The model was run through a lifetime horizon. In order to calculate the risk of MI and stroke, the authors developed risk functions that were based on the Swedish Nora study and the Swedish Hospital Patients Discharge Register and

Cause of Death Register (51). The authors based the 1-year risk for MI and stroke on a combination of the annual age- and gender- specific incidence and a number of risk factors (cholesterol, blood pressure, smoking). The study displayed that resources in the studied regions are inefficiently allocated and should be primarily reallocated towards smoking cessation interventions and lipid-lowering therapies.

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