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**A computer simulation model for cost-effectiveness analysis
of cardiovascular disease prevention**

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SUMMARY

In this paper a computer simulation model for cost-effectiveness analysis of cardiovascular disease prevention is presented. The computer simulation model was written in Turbo-Pascal to be used on an IBM-PC compatible. The model was based on the 8-year logistic multivariate risk equations for coronary heart disease (CHD) and stroke from the Framingham heart study, but the regression coefficients can easily be changed if local data exists. The main advantages of the model are that it is easy to use, transparent, and flexible. The model was mainly developed for scientific purposes, but should be useful also for educational purposes and clinical decision analysis. The modelling approach should also be useful in many other medical areas.

1 INTRODUCTION

Cardiovascular disease is the most common cause of death in a large number of Western countries (Statistics Sweden, 1989; OECD, 1987). This group of diseases also account for about 15% of total health care expenditures (OECD, 1987). In addition cardiovascular diseases account for a large percentage of non-fatal morbidity involving considerable loss of production due to sickness and disability.

A number of epidemiological studies have shown that the risk of cardiovascular disease depends on factors such as diastolic blood-pressure, serum cholesterol level and smoking (Keys, 1980; Kannel et al [eds], 1986). This has focused interest on various measures - first and foremost pharmaceutical treatment - for intervening against these risk factors in the case of persons at increased risk.

From a social viewpoint it is important to assess both the costs and effects of different interventions to prevent cardiovascular diseases in order to be able to use resources in an efficient manner. Due to the time aspect and the rapid development of medical technology and treatment practices it is unfortunately difficult and costly to empirically study the costs and effects of different interventions in experiments. An alternative approach is to gather data from different sources, e.g. epidemiological studies and clinical trials, to simulate the cost-effectiveness of different preventive activities. As a first step towards such an analysis we have constructed a computer simulation model for cardiovascular disease prevention. The aim of this report is to present and describe the computer simulation model. The model has been written in Turbo-Pascal to be used on a personal computer of IBM-PC type. The report starts with a presentation of the cost-effectiveness formula and then the structure of the model is described. Finally we round off with a discussion.

2 FORMULA FOR CALCULATION OF COST-EFFECTIVENESS

In order to calculate the cost-effectiveness of an intervention it has to be decided what costs and effects to include in the calculation. There is for instance no consensus about what costs to include in cost-effectiveness analysis. We therefore choose to base the simulation model on a specific cost-effectiveness formula, but it is possible for the user to use other formulas. The formula was based on the Weinstein & Stason (1976) formula for the cost-effectiveness of hypertension treatment. However, it differs from the Weinstein & Stason formula in two different respects. Weinstein & Stason included health care costs due to increased life-expectancy and these costs are not included in our formula. There is no difference between these medical costs and other consumption because of longer life (Weinstein, 1990); it seems therefore a little arbitrary which costs are included and which are not. We also included indirect costs because of the intervention and indirect costs of morbidity in our formula.¹ These costs should be included if a societal perspective is taken for cost-effectiveness analysis (Johannesson and Jönsson, 1990). This leads to the following formula for the calculation of cost-effectiveness:²

$$C/E = (DIRIC + INDIRIC - DIRM COST - INDIRM COST) / (LE + LEM - LESE)$$

$$C/E = \text{Cost per quality-adjusted life-year gained.}$$

$$DIRIC = \text{Direct intervention costs.}^3$$

$$INDIRC = \text{Indirect intervention costs.}$$

$$DIRMCOST = \text{Direct costs saved because of reduced morbidity from cardiovascular diseases because of the intervention.}$$

¹ It has also been suggested by some authors that indirect costs (production losses) due to mortality should be included in a cost-effectiveness analysis (Lindgren and Persson, 1989). Including production losses because of mortality should, however, be avoided. This loss of production is used in the human-capital method as an estimate of the value of life, but there is no theoretical basis for doing so (Berger et al, 1987). If the loss of production due to mortality is included anyway as a measure of the value of increased length of life, this involves double counting, because the effects in the form of life-years gained are already included in the cost-effectiveness analysis (Russel, 1986).

² It should be noted that the cost concept in the cost-effectiveness formula is dependent on what is included in the quality adjustment (Johannesson and Jönsson, 1990). If the quality adjustment takes into account all effects that the intervention has on the individual then only those costs not paid by the individual should be included in the costs.

³ The distinction made between direct and indirect costs is that direct costs are health care costs whereas indirect costs are non-health care costs such as loss of production and loss of leisure time.

INDIRMCOST = Indirect costs saved because of reduced morbidity from cardiovascular diseases because of the intervention.

LE = Increased life-expectancy because of the intervention.

LEM = Increased quality of life, valued in terms of number of years, on account of reduced morbidity from cardiovascular diseases because of the intervention.

LESE = Decreased quality of life, valued in terms of number of years, on account of side-effects of the intervention.

3 DESCRIPTION OF THE SIMULATION MODEL

In this section the structure of the simulation model is described and it is shown how an intervention is modelled and the results are presented. A detailed description of the functions of the model is given in appendix 1, which can be seen as a minor users' manual for the model. The present base case assumptions in the model (the default values) are presented in appendix 2.

3.1 Structure of the simulation model

The model was based on the 8-year logistic risk equations for coronary heart disease (CHD) and stroke from the Framingham heart study (Kannel et al 1987b). The logistic risk functions predict the 8-year risk of CHD and stroke for men and women in the age range 35-74. The functions therefore predict the risk until 82 years of age (age 74 years and 8 years onwards).⁴ Four sets of coefficients are used in the model: CHD and stroke for men and for women. The coefficients can easily be changed in the model. To be able to use other time horizons than 8 years the 8-year risks according to the Framingham equations were converted to 1-year risks.⁵ The risk factors included in the model apart from age and sex are diastolic blood pressure, serum cholesterol, smoking, glucose intolerance and left ventricular hypertrophy. For diastolic blood pressure and serum cholesterol it is possible to enter any perceivable value. The three remaining risk factors, smoking, glucose intolerance and left ventricular hypertrophy, are seen as discrete variables (0/1) in the logistic risk equations. 1 is entered if the risk factor is present, 0 otherwise. In our model it is,

⁴ For the ages 82 years and onwards it is possible to choose between two options in the model. In the first option the yearly risks of CHD and stroke are the same as the 81-years risk. In the second option the yearly risks are held constant at the risks of an 81-year-old man/woman with a diastolic blood-pressure of 90 mm Hg and a serum cholesterol level of 230 mg/dl irrespective of the values of the risk factors. Thus with the second option the intervention will not affect the risk of CHD and stroke at the ages 82 years and onwards.

⁵ First the 8-year risk was converted to 1-year risks through the formula: $1\text{-year risk} = -0.125 * \ln(1-(8\text{-year risk}))$. This yearly risk was used for year 5 of the 8 years (to take into account the increase in risk with age). To get the yearly risk for the ages 35, 36, 37 and 38 the risk equations were extrapolated to the ages 31, 32, 33 and 34. To get the yearly risk for ages 79, 80 and 81 the 8-year risk for age 74 was used. The yearly risks obtained in this way were then further adjusted to take into account the mortality risk from causes other than CHD and stroke. This was done since the calculation of the 1-year risk with the method shown above is based on the assumption that the calculated risk is the only risk the individual is exposed to. The 1-year risk is therefore an underestimate of the real risk and the divergence becomes greater the higher the mortality risk from non CHD causes in the CHD case and the higher the mortality risk from non stroke causes in the stroke case. Adjustment of the 1-year risk was done with a weighting system according to the mortality risk from other causes with the aim of getting a close correspondence between the 8-year risk according to the equation for stroke and CHD and the risk in the model of developing stroke or CHD in 8 years.

however, for experimental purposes possible to enter other values than 0 or 1 also for these risk factors. The age range 35-110 is covered by the model.

The disease model is built around the tree structure shown in figure 1. The starting point of the tree is a cohort of "healthy" individuals, which in this case means that they are free from cardiovascular disease, with certain values of the risk factors in the model.⁶ These individuals are each year exposed to three different risks: the risk of CHD, the risk of stroke and the risk of death from other causes than cardiovascular disease. The risk of CHD and stroke depends on the levels of the risk factors through the logistic risk functions. The risk of death from other causes is calculated as the average death risk each year for men and women with the risk of death from cardiovascular disease subtracted from the average risk (Statistics Sweden, 1988, 1989). The CHD state is divided into 5 different disease states: sudden death (defined as death within one hour from the onset of disease), recognized myocardial infarction, unrecognized myocardial infarction, angina pectoris (uncomplicated) and coronary insufficiency, while the stroke state is only one disease state. The structure of the disease model therefore closely follows the structure of the Framingham study to conform with the logistic risk equations.

⁶ The cohort of individuals consists of identical individuals (i.e. individuals with the same values of the risk factors). This means that a cohort is used only to illustrate more easily how the model works. The number of individuals in the cohort can be specified from 1 to 100,000 in the model.

Figure 1. The structure of the model

In all disease states the individuals are exposed to a certain mortality risk each year. Persons that reach a disease state in the model stay in that state for life. In order to calculate disease costs the model keeps track of the number of years after the initial disease event for each individual. Individuals are assigned disease costs each year after the initial event. It is possible to specify the cost the first year after the event and the cost the second and following years after the event. The costs are divided into direct and indirect disease costs and into three age groups for men and women. It is possible to see the expected total disease cost of CHD and stroke in the model for the cohort of individuals.

The model also incorporates quality of life. A value between 0 and 1 can be entered for each disease state to reflect quality of life. The interpretation of the quality of life weights is

that if the quality of life is 0.7 the individual would be prepared to give up 0.3 years of life-expectancy to be free of cardiovascular disease (healthy) for every year in the disease state.

3.2 Modelling of an intervention

The aim of the model is to analyse different interventions. How this is done can easily be seen by considering the structure of the model. For specified levels of the risk factors the cohort will have a certain life expectancy and certain expected disease costs for CHD and stroke. When the risk factors are changed in the model, life expectancy and expected disease costs will change.

It is possible to intervene against all risk factors in the model. How an intervention is specified is illustrated by an example in figure 2, where an intervention against diastolic blood pressure is assumed. The diastolic blood pressure both with and without the intervention is shown in figure 2. Furthermore the risk equivalent blood pressure is shown, which denotes the untreated blood pressure that leads to the same risk as the blood pressure with intervention.

Figure 2, The modelling of an intervention

A number of variables are used to specify the intervention that is illustrated by figure 2. First the change in the risk factor is specified: in this example it is assumed that diastolic blood pressure is lowered from 110 mm Hg to 90 mm Hg. The next variable is duration,

that specifies the number of years of the intervention: in this example the intervention is assumed to last for 10 years. The effectiveness of the intervention is then dependent on a number of parameters that are specified for stroke and CHD separately. To simplify the example it is assumed that all of the parameters are the same for both CHD and stroke. Start delay is the number of years before the intervention affects the disease risk: in the example start delay is set at 2 years. Rise time is the number of years it takes from the end of the start delay until the maximum risk reduction is achieved from the intervention: we have chosen rise time to be a linear function between the end of start delay and the time of the maximum risk reduction. In the example rise time is assumed to be 2 years.

Fraction of reduction decides the maximum risk reduction from the intervention and is a percentage between 0 and 100%.⁷ If fraction of reduction is 100% a reduction of blood pressure from 110 to 90 leads to the same risk as in the case of an individual that has a blood pressure of 90 without intervention. In the example fraction of reduction is set at 50% so the intervention leads to the same risk as an untreated blood pressure of 100 (the risk equivalent blood pressure is 100 mm Hg and the risk equivalent change is 10 mm Hg). Stop delay and set time are defined in an analogous manner to start delay and rise time. In the example both stop delay and set time are set at 2 years. Remaining is the remaining effect of the intervention that is assumed to persist for the rest of the life-time. As with fraction of reduction it is stated as a percentage between 0 and 100% and the interpretation is analogous. In the example remaining is set at 0%. This intervention menu leads to maximal flexibility in the modelling of the effects from an intervention. This is of the utmost importance due to the uncertainty prevailing about the effects on the risk of CHD and stroke from risk factor interventions (MacMahon et al, 1990; Collins et al, 1990; Brett, 1989; Leaf, 1989).⁸

Quality of life during the years of the intervention is specified on a scale between 0 and 1 to allow for the incorporation of side-effects in the analysis. Discounting is also incorporated in the model to take into account the timing of costs and effects. For effects there are two different methods to choose between that give fundamentally different results (Johannesson, 1991). The first method (method 1), that was used by e.g. Weinstein and Stason (1976), discounts life-years per se through discounting cumulative survival probabilities, whereas

⁷ Fraction of reduction was used in the model instead of the more commonly used fraction of benefit (Weinstein and Stason, 1976) since fraction of benefit cannot be defined if the intervention affects more than one risk factor and fraction of benefit varies between the risk factors.

⁸ It is also possible to directly enter the maximal percentage risk reduction for CHD and stroke instead of fraction of reduction and change in the intervention menu. This makes it possible to directly enter the results of clinical trials in the model, that are often presented as percentage risk reduction (Collins et al, 1990; Brett, 1989).

the second method (method 2), that was used by e.g. Jönsson et al (Jönsson et al, 1991), only discounts for the timing of the risk reduction. Finally the intervention cost is entered in the model. The intervention cost is divided into direct and indirect costs and an initial cost (for instance costs of screening) can be specified as well as an annual cost.⁹

3.3 Results of an intervention

The cost-effectiveness is calculated as the change in life expectancy and costs after the intervention. All results are presented per individual. First the gain in life expectancy is shown calculated as the difference in life expectancy before and after the intervention. Then the change in quality of life due to morbidity and side-effects valued in life-years equivalents is shown. Decreased morbidity from the intervention leads to a gain in quality of life and side-effects of the intervention lead to losses in quality of life. This gives the gain in quality-adjusted life-years. After this the intervention costs are shown divided between direct and indirect. Thereafter the change in disease costs is shown also divided between direct and indirect and calculated as the change in expected disease costs after the intervention. This gives the total change in costs. Finally the cost per gained life-year and the cost per quality-adjusted life-year are shown. The division of the cost-effectiveness ratio into these sub-components makes it possible to see how each factor contributes to the cost-effectiveness ratio. It also makes it possible to for instance calculate the cost per gained life-year with only direct costs included.

⁹ The intervention is only assumed to go on for those individuals in the cohort that are still free of cardiovascular disease, and no effects or costs are calculated for the intervention once they enter a disease state. After the individual enters a disease state there is a new decision situation about whether to intervene against risk factors or not that should not affect the decision about interventions for healthy individuals. This new decision situation is not modelled in the current model.

4 DISCUSSION

It is important to keep in mind that this is only a first version of the model. It is our hope that through a thorough evaluation of the model it will be possible to improve many features of it. There are a number of areas where the uncertainty is high.

A tricky empirical question is whether the results of the Framingham study can be extrapolated to other populations as has been done in this study and in many other studies (Weinstein and Stason, 1976; Martens et al, 1989, 1990; Lindgren and Persson, 1989). When the Framingham study has been applied to other populations, it has predicted the absolute risk well in populations with a high incidence of cardiovascular disease, like that of the USA, but overestimated it in populations with a low incidence, like those of Japan, Yugoslavia and Puerto Rico (Keys, 1980; Gordon et al, 1974; Kozarevic et al, 1976; The Pooling Project Research Group, 1978; Gordon and Kannel, 1982; Leaverton et al, 1987). However, according to a recent review of epidemiological studies in this area the extrapolation of logistic risk functions to new populations may not be justified even to predict relative risk levels (Chambless et al, 1990). More research is needed about these issues, including the issue concerning the appropriate functional form to be used for prediction in cost-effectiveness analysis. It can seldom be ruled out that the choice of simulation model, i.e. of the mathematical (functional) form of the correlations, has an effect on the results obtained.

In future work we will establish the validity of the model in Sweden. This can be done through comparing the predicted incidence of different disease events with observational studies. Since the Framingham risk equations may not be representative for Sweden, the model has been designed in such a way as to make it easy to change the regression coefficients. It is thus also possible to carry out sensitivity analysis of the regression coefficients. The Framingham study is, however, the most established epidemiologic investigation in the world and it is therefore a strength to base the model on this study. Relevant comparisons of countries can be made by adjusting the regression coefficients, the survival data and the cost estimates in the model if local data exist.

The model also demands a lot of data about costs and survival after different disease events that are surrounded by uncertainty. Furthermore medical technology and treatment practice are developing rapidly, and what was the cost of, say, treating a patient with myocardial infarction five years ago may bear little resemblance to the cost five years from now.

The main use of this simulation model is obviously in decision analysis comparing the cost-effectiveness of different interventions. But it should also be possible to use the model for

educational purposes in respect of both physicians and patients. It is especially suitable for this task due to its simplicity and transparency.

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APPENDIX 1: FUNCTIONS OF THE SIMULATION MODEL

The user interface of the model is built with pulldown menus. Most of the alternatives have submenus hierarchically arranged below each topic. Selections are made with the arrow keys, the Esc key and the Enter key. Above the main menu there is a short help text to explain the function of the highlighted alternative. The default values of all parameters that can be changed by the user are as far as possible based on available evidence from the literature, but should be interpreted with care due to the great uncertainty in this area. An exception to this is the intervention parameters where no default values have been given. It is left to the user to specify the intervention. The 7 topics in the main menu are: file, focus, conditions, risk, disease, intervention, and calculate. This appendix is divided into 8 sections. The first section deals with the 7 topics in the model and the last section describes the status line showing what assumptions have been made.

1. File

File has 4 alternatives:

Reset: With reset all parameters in the model are set to default values.

Load: Load is used to retrieve parameter values from a file that has been saved earlier. Load is divided into 6 alternatives: risk factors, coefficients, disease, treatment costs, intervention and all. The all alternative retrieves a complete set of parameters, while the former alternatives only retrieve parameters on the specified subject.

Save: Save is used to save parameter values on a file. It is divided in the same way as load.

The Save and Load alternatives are useful when switching between different cost scenarios and different intervention strategies.

Quit: Quit is used to quit the programme.

2. Focus

Focus is used to select the level of the model. With this alternative one can study the different components of the model separately, from the logistic risk function, via the disease tree and cost calculations, to the cost-effectiveness results of the intervention. Some of the levels in the model are included primarily for pedagogical reasons and to increase the transparency of the model. An interested user has hence the possibility of following all the

major calculations in the model.

The first level of the model is risks, where the 8-year risk of stroke and CHD according to the logistic risk functions is shown for the specified levels of the risk factors. The contribution of each risk factor is also shown in a table that illustrates how the risk is calculated from the logistic function. The one-year risk is also shown in this level of the program.

The disease level shows the tree structure of the model. The cohort of healthy individuals with certain specified levels of the risk factors are each year exposed to three different risks: the risk of CHD, the risk of stroke and the risk of death from other causes than CHD and stroke. CHD is divided into sudden death (death within one hour from the onset of disease), recognized myocardial infarction, unrecognized myocardial infarction, angina pectoris (uncomplicated) and coronary insufficiency. Persons that reach a disease state in the model stay in that state for the rest of their life. In the tree structure it is possible to see the risk of CHD or stroke in any specified time period for certain levels of the risk factors.

The third level in the model is called treatment. This level shows how many of the initial cohort of healthy individuals are in a certain disease state and are still alive in the beginning of the year a certain number of years after the initial event. This level is the basis for the treatment cost calculations and is mainly included to increase the transparency of the model.

The next level of the model is treatment costs, that shows the treatment costs of the cohort for CHD and stroke for a specified time horizon. The treatment costs are divided between the different disease states. The costs are furthermore split into three age groups (35-49, 50-64, 65-) and men and women, and are also divided into treatment costs the first year after onset of disease and the second and following years after onset of disease. There are also three different options of treatment costs namely: direct costs, indirect costs and total costs.

Intervention change is the next level in the model. The risk equivalent change of the risk factors is shown for every year within the chosen time horizon. This level is mainly included to show the effect on different risk factors from the specified intervention.

Risk equivalent change is defined as the change in the risk factor that corresponds to the change in risk. Assume for instance that diastolic blood pressure is lowered from 110 mm Hg to 90 mm Hg through antihypertensive therapy and that the risk after the intervention corresponds to a blood pressure of 100 mm Hg. The risk equivalent change in this case is 10 mm Hg and the risk equivalent blood pressure is 100 mm Hg.

The interpretation of risk equivalent change for the discrete variables (smoking, glucose intolerance and left ventricular hypertrophy) is not as straightforward as for the continuous variables. If the risk equivalent change is 0.5 for smoking for a person that quits smoking it means that the coefficient for smoking in the logistic function will be multiplied by 0.5 instead of by 1. This can approximately be interpreted to mean that the gain from quitting smoking is half of the difference in risk between a smoker and a non-smoker. This interpretation is not strictly correct though, since the risk does not increase linearly with increases in the risk factors. The notion of risk equivalent change has been kept for discrete variables as well to allow the fraction of reduction to vary between different risk factors.

The level called intervention cost shows the intervention cost for the cohort every year of the specified time horizon.

The level intervention result is the most fundamental level of the model. This level shows the cost-effectiveness of a specified intervention. All results are presented per individual of the initial cohort. Time-horizon for the intervention result calculations is always life-time (for time-horizon, see conditions below). This ensures that all future effects on costs and life-expectancy of an intervention are calculated.

The final level of the model is setups. Setups consist of a few alternatives where the values of different parameters in the model are shown. They are included to provide an easy way to see the assumptions made. Values of the parameters shown in the setup alternatives can easily be changed by a corresponding entry in the menu.

The different options are:

- Death, other
- Coefficients
- Disease
- Disease costs, direct
- Disease costs, indirect
- Annual costs
- Intervention

In the setup for death, other, the annual risk of death from non CHD and stroke causes is shown for all ages in a table.

In the coefficients' setup the coefficients for the logistic risk functions for stroke and CHD are shown.

In the disease setup the fractions of CHD cases distributed according to respective disease state are shown. These fractions are divided into three age groups: 30-49, 50-64 and 65-.

The mortality risks after each disease state are also shown. They are split up between the first year after the event and the second and following year after the event. The mortality risks after different disease states are given for four ages: 35, 50, 65, and 80 years. The age when the mortality risk is assumed to be 100% is also shown. Finally the quality-of-life values in each disease state are shown.

Different values for men and women can be entered for all parameters. If a cohort of men is chosen for the analysis the parameters for men are used and if a cohort of women is chosen the parameters for women are used.

In the setup menu for direct and indirect disease costs the cost per year of different disease states are shown. There are different costs per year the first year after the disease event and the second and following years for a specified number of years. The costs are divided into three age groups (35-49, 50-64, and 65-) and can be set different for men and women.

In the setup annual costs it is possible to specify an annual cost in four different age groups: 35-49, 50-64, 65-74, 75-. This is to allow the user to for instance calculate the disease costs during gained life-years as in the cost-effectiveness formula used by Weinstein and Stason (1976). It should be stressed that this setup is mainly included for experimental reasons and to increase the flexibility of the model. No base-case values have therefore been entered in the model.

The last setup is intervention, that shows the assumptions made about the intervention.

Below we will return to how the parameters in these setups are specified and changed.

3. Conditions

In this menu conditions for the calculations are determined. It is possible to specify the time horizon for the calculations from 1 to 75 years. An exception is intervention result, where the time horizon always is lifetime.

It is also possible to specify the number of persons in the initial cohort of healthy individuals from 1 to 100,000 persons.

There are three switches in the model. With the first switch it is possible to switch off the intervention for comparisons (this switch does not influence the intervention result calculations). The second switch specifies whether calculations should be carried out with quality adjustment or not and the third switch specifies if the calculations include discounting or not.

These switches can also be changed through a short-cut in the model by pressing the Ctrl key together with I, Q or D. I stands for intervention (in/out), Q for quality adjustment (in/out) and D for discounting (in/out). This can be done at any level in the model.

4. Risk

In this menu values of the risk factors for the cohort are specified. Values of the following risk factors can be specified:

age

sex

diastolic blood pressure in mm Hg

serum cholesterol in mg/dl

smoking (yes/no)

glucose intolerance (yes/no)

left ventricular hypertrophy (yes/no)

For diastolic blood pressure and serum cholesterol it is also possible to specify a yearly increase in the risk factor and when (plane age) the value is assumed to become constant. In this menu the coefficients in the logistic risk functions for CHD and stroke from the Framingham study can be changed. The logistic risk function has the following form:

$$P_{CHD,8-year} = 1/(1+e^{-X})$$

Where:

$$X = a + b_1*age + b_2*age*age + b_3*chol + b_4*chol*age + b_5*dbp + b_6*smoke + b_7*glint + b_8*lvh$$

Where:

Pchd,8-year	is the probability of CHD within 8 years
a	is a constant
b1*age	is the effect of age
b2*age*age	is the effect of age*age
b3*chol	is the effect of cholesterol
b4*chol*age	is the effect of age*cholesterol
b5*dbp	is the effect of diastolic blood pressure
b6*smoke	is the effect of smoking
b7*glint	is the effect of glucose intolerance
b8*lvh	is the effect of left ventricular hypertrophy

The values of the constant a and the coefficients b1-b8 from the Framingham study are used in the analysis (1987b). Four sets of coefficients are used in the model: CHD and stroke for men and for women. The coefficients can easily be changed in the model.

5. Disease

In this menu it is possible to specify what will happen to those individuals that get CHD or stroke.

Under the option CHD type probability the proportion (%) of the total CHD events attributable to the five events are specified (observe that the proportions must add up to 100%): sudden death, myocardial infarction recognized, myocardial infarction unrecognized, angina pectoris and coronary insufficiency. This is done for three age groups (35-49, 50-64 and 65-) and men and women.

The mortality risk for each of the different disease states is specified in CHD death risks and stroke death risks. The death risk is specified for the first year after the event and for the second and following year, this because the excess mortality risk is highest the first year after the event. The death risks are entered for four ages and can be different for men and women. The ages are 35, 50, 65 and 80. The age when the death risk after an event is assumed to be 100% is also entered. To obtain the risks for ages between the specified ages linear interpolation is used. Above the age of 80 linear interpolation of the logarithm of the risk is used.

The model will calculate a mortality risk after the different disease states for every age for the first year after the disease event and the second and following years. This feature makes it possible to specify survival after different events and to easily change the assumptions.

The quality of life for different disease states is specified in the alternatives stroke, quality and CHD, quality. Quality of life is specified between 0 and 1. Quality of life for stroke and CHD can be specified separately for the three age groups (35-49, 50-64 and 65-) and for men and women.

In the disease menu yearly treatment costs of the different disease states are also specified, divided into direct and indirect costs. The costs that are entered should be the differences in costs compared with a stroke- and CHD-free population. The yearly cost the first year after the event is specified and the yearly cost the second and following years is also specified. Then the number of years after the first year after the event that the individual is assumed to have higher costs than individuals free of cardiovascular disease is specified (the number of following years).

Finally an annual cost can be entered in four age groups: 35-49, 50-64, 65-74, 75-. This is to allow the user to for instance calculate the health care costs during gained life-years.

6. Intervention

Under this menu the intervention characteristics are specified. It is possible to intervene against diastolic blood pressure, serum cholesterol, smoking, glucose intolerance and left ventricular hypertrophy. It is possible to model interventions that affect one, two, three or four of the risk factors, or affect all risk factors. It should be stressed that we have included glucose intolerance in the intervention menu for experimental reasons.

A number of variables are used to specify the intervention that was illustrated by figure 4. The change in the risk factor(s) and the duration of the intervention are specified. The effectiveness of the intervention is then dependent on a number of parameters that are specified for both stroke and CHD. Start delay is the number of years before the intervention affects the disease risk and rise time is the number of years from the end of the start delay until the maximum risk reduction is achieved from the intervention. Rise time is a linear function between the end of start delay and the time of the maximum risk reduction. Fraction of reduction, entered as a percentage between 0 and 100%, decides the maximum risk reduction from the intervention. Stop delay is the number of years after the intervention has ended that maximum risk reduction is assumed to persist. Set time is the number of years from the end of stop delay to the time when the remaining effect is reached. Stop delay and set time are accordingly defined in an analogous manner to start delay and rise time. Remaining is the remaining effect of the intervention that is assumed to

persist for the rest of the life-time and is stated as a percentage between 0 and 100%, and the interpretation is analogous to fraction of reduction. It should be mentioned that it is also possible to design interventions that raises some risk factor and the interpretation of the above variables is then analogous.

Quality of life during the years of the intervention is also specified on a scale between 0 and 1 to allow for the incorporation of side-effects in the analysis. The interpretation of this adjustment is analogous to the morbidity case reviewed earlier. Quality of life is divided into three age groups: 35-49, 50-64 and 65-, to allow for changing quality of life over the life cycle.

The rate of discounting of the intervention is also specified in this menu, both for costs and effects. Two different methods are available for the discounting of gained life-years (Johannesson, 1990). The first method (method 1) discounts life-years per se by discounting cumulative survival probabilities. The change in life-years due to the intervention is calculated as the change in the sum of discounted cumulative survival probabilities. This method is included since it is the most commonly used method in this area. The second method (method 2) does not discount life-years per se and is therefore neutral with respect to priorities between age and sex groups. The method only discounts for the timing of the risk reduction. The second method is included to allow the user the use of a method that does not discount life-expectancy per se. It should be noted that the computations take considerably longer with the second method.

Finally the intervention cost is entered in the model. The intervention cost is divided into direct and indirect costs. An initial cost (for instance costs of screening) can be specified for each of them as well as a yearly cost. The intervention cost is divided into three age groups: 35-49, 50-64 and 65-, to allow for changing intervention costs over the life cycle.

It is also possible to specify a decision lag in the intervention menu, which means a specified number of years before the intervention starts. This is included to make it possible to calculate the cost-effectiveness of an intervention that is started e.g. at the age of 50 for a cohort of 35-year-olds.

An alternative intervention menu is also included in the model in which percentage risk reduction for CHD and stroke is included instead of change and fraction of reduction. This makes it possible to directly enter a specified risk reduction based on the results of clinical trials, often expressed in percentage risk reduction, in the model.

The intervention is only assumed to go on for those individuals in the cohort that are still free of cardiovascular disease. No effects or costs are calculated for the intervention once they enter a disease state. After the individual enters a disease state there is a new decision situation about whether to intervene against risk factors or not which is not modelled in the current model.

7. Calculate

With the command auto calculate automatic calculation can be on or off. If auto calculate is on the model will automatically do a new calculation if a parameter is changed. In the level intervention result auto calculate is always off and the model has to be ordered to do the calculation, this is because this is the most time-consuming calculation in the model.

If auto calculate is off the model can be ordered to do the calculation with the calculate option. There is also a shortcut command for this option, Ctrl key pressed together with a C makes the model do the calculation.

Life-expectancy can be calculated with the option life- expectancy in the disease level of the model. Life-expectancy can be calculated for the cohort of healthy individuals and for the individuals with stroke, myocardial infarction recognized, myocardial infarction unrecognized, angina pectoris and coronary insufficiency.

There are five alternatives under the option command:

The first function under option is called high age risk and under this menu different assumptions can be made with respect to the risk of stroke and CHD at high ages. The used logistic risk functions predict the 8-year risk for people between 35 and 74 years, which means that the risk functions predict the risk until the individuals reach 82 years of age (74+8 years). From 82 years of age and upwards it is possible to choose between two different assumptions in the model. The first assumption is called 81-years risk which means that the yearly risk from year 82 and upwards is assumed to be the same as the risk for an 81-year-old with the specified levels of the risk factors. This means that it is possible to model an intervention also after 81 years of age. The alternative is called average risks and means that the risk of stroke and CHD is held constant at age 82 and upwards for all individuals irrespective of the levels of their risk factors. For men the 1 year risk is held constant at the risk of an 81-year-old with a diastolic blood pressure of 90 mm Hg, serum cholesterol of 230 mg/dl, non-smoker and without diabetes. For women the risk is held constant at the corresponding values of the risk factors for an 81-year-old woman. This

means that an intervention will not affect the risk of CHD or stroke beyond the age of 81 years if this alternative is chosen.

The second option is called Cholesterol-Stroke risk and has the alternatives normal and independence. If it is normal it means that the values specified for cholesterol will decide the risk of stroke. This means that the risk of stroke will change if the serum cholesterol level changes. If independence is chosen then the coefficients for cholesterol and cholesterol*age in the risk function for stroke will be set at a value of 220 for cholesterol no matter what value is specified for cholesterol. This means that the risk of stroke will not change when the cholesterol value is changed. The option is included due to the uncertainties prevailing about whether the risk of stroke depends on the serum cholesterol level or not. The coefficients in the stroke equations for cholesterol and cholesterol*age are not significant (Kannel et al, 1987b).

The third option is called intervention target and has the options risk factor reduction and risk reduction. If risk factor reduction is chosen the usual intervention menu is used. If risk reduction is chosen the intervention menu is changed and the intervention is instead specified as a maximal percentage risk reduction. Maximal percentage risk reduction is used instead of fraction of reduction and the variables duration, start delay, rise time, stop delay, set time and remaining are used in a manner analogous to that which is used in the usual intervention menu with the change that they are now used to specify the risk reduction at each point in time. Separate values are entered for stroke and CHD but not for different risk factors, since the values entered are for the total effect of the intervention. The option is included to allow the user to incorporate results of clinical trials in an easy way. Results of clinical trials are usually expressed in percentage risk reduction (Collins et al, 1990; Brett, 1989).

The fourth option is called calculation: disease costs, and has the options dynamic and static. If dynamic is chosen the costs of stroke and CHD during gained life-years will be included in the costs of the intervention and if static is chosen the costs of CHD and stroke during gained life-years will not be included.

The fifth option is called costs during gained life-years and has the alternatives in and out. If out is chosen the results of the intervention will be calculated in the usual way. If in is chosen the costs during gained life-years are calculated and this cost is added to the results of the intervention. Thus this cost is then added to the cost-effectiveness formula in the intervention result.

8. Status line

At the bottom of the screen there is a status line showing what assumptions have been made. The following information is provided on the status line:

Time hzn (1-65): Shows time horizon for the calculations.

Blpr chol (Cnst, Rise): Shows if any risk factor increases with age (rise) or if all values are constant (cnst).

High age (81 yr, Avrge): Shows assumption made with respect to the risks of CHD and stroke at high ages.

Intrv (In, Out): Shows if the intervention is in or out.

Qual (In, Out): Shows if the quality adjustment is in or out.

Discnt (In, Out): Shows if the discounting is in or out.

Calc (On, Off): Shows if the auto calculation is on or off.

APPENDIX 2: THE BASE-CASE ASSUMPTIONS IN THE SIMULATION MODEL

In this appendix the base-case assumptions (the default values) that have been made in the model are shown, together with the sources of the data. All these assumptions can easily be changed in the model by the user. The appendix is divided into 4 sections; coefficients in the logistic risk functions, disease costs, death risks and CHD type probabilities, and quality of life.

1. Coefficients in the logistic risk functions

The coefficients in the logistic risk functions are taken from the Framingham heart study and are shown in table 1.

Table 1, Coefficients in the logistic risk functions

Variable	Men		Women	
	CHD	Stroke	CHD	Stroke
Constant	-17.0053796	-18.3127136	-15.2804537	-18.5522471
age	0.2911648	0.2822610	0.2440214	0.2087615
age*age	-0.0015373	-0.0012949	-0.0012694	0.0000909
chol	0.0216913	0.0064448	0.0110831	0.0275182
chol*age	-0.0002733	-0.0001367	-0.0001115	-0.0005552
dbp	0.0216347	0.0332130	0.0180007	0.0393605
smok	0.4360139	0.5169539	0.0701393	0.1708022
glint	0.2845079	0.5822104	0.8444092	0.1234301
lvh	0.6161197	0.8293135	0.6745513	0.6570233

Source: Kannel et al, 1987b.

2. Disease costs

All disease costs are at 1988 prices. All costs have been assumed to be the same for both men and women due to insufficient data on the variation of cost with sex and age. For the same reason direct costs per year have been assumed to be the same in all age groups. Indirect costs per year have been assumed to vary with age due to differences in labour force participation at different ages. The cost per year for the second and following years has been assumed to prevail for the rest of the lifetime after the different disease events. Indirect costs for individuals in the age group 65- are assumed to be 0 due to retirement at 65 years of age. The direct costs per year are shown in table 2. The direct costs of stroke were taken from a study by Terént (1983), who followed for three years 281 patients in the municipality of Söderhamn (Sweden) who had their first stroke, and calculated direct costs for this time period. The cost of the first year is used as the cost the first year after stroke,

and the cost the third year is used as the yearly cost for the second and following years. For myocardial infarction recognized the cost of care for the first episode of care from a study by Jönsson et al (1988) was used and then the yearly cost was taken from a study by Olsson et al (1987), who calculated the direct costs for three years after the first episode of care. This yearly cost was approximately SEK 5000 and the cost the first year was then calculated as this yearly cost plus the cost of the first episode of care of approximately SEK 20000. For the second and following years the yearly cost of SEK 5000 was used. For myocardial infarction unrecognized half the yearly cost of SEK 5000 was used for the second and following years. It was thus assumed that the CHD of 50% of the individuals with myocardial infarction unrecognized would be discovered after the first year after the event. For coronary insufficiency the same cost as for myocardial infarction for both the first and the second and following years was assumed. For angina pectoris patients we assumed half the cost of the first episode of care for myocardial infarction and then the same yearly cost as for myocardial infarction. For sudden death a symbolic cost of SEK 1000 was assumed for ambulance services.

Table 2, Direct disease costs per year, SEK, 1988 prices.

Disease event	1st year	2nd and following years
Mi rec	25000	5000
Mi unrec	0	2500
Cor insuff	25000	5000
Angina	15000	5000
Sudden death	1000	-
Stroke	130000	40000

Sources: Jönsson et al, 1988; Olsson et al, 1987; Terént, 1983.

The yearly indirect costs are shown in table 3.

Table 3, Indirect disease costs per year, SEK, 1988 prices.

Disease event	Age groups			
	35-49 1st year	2- years	50-64 1st year	2- years
Mi rec	50000	30000	40000	25000
Mi unrec	0	15000	0	12500
Cor insuff	50000	30000	40000	25000
Angina	30000	30000	25000	25000
Sudden death	-	-	-	-
Stroke	100000	70000	80000	60000

Sources: Mills & Thompson (1978); Kannel et al (1979).

To calculate indirect costs we first calculated the yearly labour cost for persons at work

(Statistics Sweden, 1987). This was assumed to equal the value of production. Then we calculated the average value of production in the two age-groups 35-49 and 50-64 by multiplying the yearly labour cost of persons at work by the percentage of persons at work in the different age groups (Statistics Sweden, 1987). The average value of production then became SEK 160000 in the age group 35-49 and SEK 130000 in the age group 50-64. Mills and Thompson (1978) estimated the earning capacity after stroke to be 49% of the average earning capacity in the population. Based on this estimate we assumed the loss of production to be 60% of the average earning capacity the first year after stroke and 45% the second and following years. Kannel et al (1979) concluded return to work to be between 70 and 90% after myocardial infarction. Based on this estimate we assumed the loss of production to be 30% of the average earning capacity the first year after myocardial infarction recognized and 20% the second and following years. The same indirect costs were assumed for coronary insufficiency. For myocardial infarction unrecognized the yearly indirect costs were assumed to be half of those for the second and following years for recognized myocardial infarction. This estimate was used for both the first and the second and following years after myocardial infarction unrecognized. For angina pectoris the loss of production was assumed to be 10% of the average earning capacity for both the first and the second and following years.

3. Death risks and CHD type probabilities

To calculate the death risk from non CHD and stroke causes the proportion of non CHD and stroke deaths at different ages in the Swedish cause of death statistics (Statistics Sweden, 1988) was multiplied by the average mortality risk at different ages according to Swedish statistics (Statistics Sweden, 1989). The distribution of CHD cases among different disease events was based on the Framingham study (1987a). The proportion of the different CHD events was calculated from events counting in section 34 of the Framingham study (1987a). Since the number of events in the age group 35-49 was very small the proportion of events was calculated for the age groups 35-49 and 50-64 together. The distribution of the CHD disease events is shown in table 4.

Table 4, CHD type probabilities (%).

CHD type	35-49		Age groups 50-64		65-	
	Men	Women	Men	Women	Men	Women
Mi rec	35	15	35	15	35	25
Mi unrec	10	10	10	10	25	15
Cor insuff	10	10	10	10	5	10
Angina	35	60	35	60	20	40
Sudden death	10	5	10	5	15	10

Source: Kannel et al, 1987a.

The yearly death risks after different disease events were also based on the Framingham study (Kannel et al, 1988a). In section 35 the survival following initial cardiovascular events was presented. Since these results were presented for two broad age groups 35-64 and 65-94 while we need estimates for exact ages (35, 50, 65 and 80), there is no exact correspondence between the Framingham results and the data we need. We therefore used the Framingham study to approximate the risk at these specific ages. We focused both on the hazard ratio in the Framingham study that shows the mortality risk in proportion to the sex and age matched general Framingham population and the absolute risks. Since the disease risk for men and women for stroke and myocardial infarction during the first year after the event (if age is taken into account) was of the same magnitude the risk was assumed to be the same the first year after these events. For the second and following years after these events the hazard ratio was assumed to be approximately the same for men and women since this was approximately the case in the Framingham study. For angina this pattern was assumed for both the first and the second and following years. It was assumed that the yearly risk of myocardial infarction unrecognized and coronary insufficiency was the same as the yearly risk for the second and following years after myocardial infarction recognized. In the Framingham study the survival after the first year was approximately the same for myocardial infarction recognized and unrecognized (Kannel et al, 1979). It was also assumed that the relative risk increase after the disease events was higher the lower the age while the absolute risk increase was assumed to be higher the higher the age. The assumptions about mortality risks after the different disease events are shown in tables 5 and 6. For angina, coronary insufficiency, and myocardial infarction for both the first and the second and following years the mortality risk was assumed to be 100% at age 110 (approximately the same as for the general population). This was also the case for the risk the second and following years after stroke and myocardial infarction recognized. For the first year after stroke and myocardial infarction recognized the risk was assumed to become 100% at age 95 for stroke and 90 for myocardial infarction recognized. These assumptions were based on decreasing relative risk increase with age.

Table 5, Yearly death risk after different disease events (%), 1st year after disease event.

Age	Disease event									
	Mi rec		Mi unrec		Cor insuff		Angina		Stroke	
	Men	Wom	Men	Wom	Men	Wom	Men	Wom	Men	Wom
35	5	5	1.5	0.75	1.5	0.75	1.0	0.50	5	5
50	10	10	2.0	1.50	2.0	1.50	1.5	0.75	10	10
65	25	25	4.0	2.00	4.0	2.00	3.0	1.50	22	22
80	50	50	15.0	10.00	15.0	10.00	12.0	8.00	45	45
Age when 100% risk	90	90	110	110	110	110	110	110	95	95

Source: Kannel et al, 1988a.

Table 6, Yearly death risk after different disease events (%), 2 and following years after disease event.

Age	Disease event									
	Mi rec		Mi unrec		Cor insuff		Angina		Stroke	
	Men	Wom	Men	Wom	Men	Wom	Men	Wom	Men	Wom
35	1.5	0.75	1.5	0.75	1.5	0.75	1.0	0.50	1.5	0.75
50	2.0	1.50	2.0	1.50	2.0	1.50	1.5	0.75	2.0	1.50
65	4.0	2.00	4.0	2.00	4.0	2.00	3.0	1.50	4.0	2.00
80	15.0	10.00	15.0	10.00	15.0	10.00	12.0	8.00	15.0	10.00
Age when 100% risk	110	110	110	110	110	110	110	110	110	110

4. Quality of life

The quality of life after different disease events has been assumed to be the same in all age groups and for men and women. The quality of life assumptions are shown in table 7. Kawachi & Malcolm (1989) assumed the quality of life to be 0.8 after stroke. Ahlström et al (1984) assessed the quality of life after stroke for a two-year-period using a visual analog scale of 100 mm and found that the quality of life decreased by approximately 20 mm. Wade & Hower (1987) assessed the functional independence after stroke on a scale between 0-20 and the score was 16.9 6 months after the event, e.g. approximately 85% of the full score. Based on these studies we assumed the quality of life for stroke to be 0.8. Vermeer et al (1988) assessed the quality of life the first year after myocardial infarction and found it to be approximately 0.91 on average. They used a weighting system for different degrees of severity to assess quality of life. This conforms with a study by Levin (1990) that measured the quality of life the first year after myocardial infarction using the same methodology as Vermeer et al. The average quality of life was 0.89 during the first year and the quality of life was 0.92 at the end of the first year in the study by Levin. Based on these estimates we

assumed the quality of life after myocardial infarction recognized to be 0.9. For angina and coronary insufficiency the same quality of life as for myocardial infarction recognized was assumed. For myocardial infarction unrecognized the quality of life was assumed to be 0.95 based on the assumption that the CHD of 50% of these individuals would be discovered. It is important to stress that the quality of life weights are extremely uncertain and should be viewed as illustrative only.

Table 7, Quality of life after different disease events.

Disease event	Quality of life
Mi rec	0.9
Mi unrec	0.95
Cor insuff	0.9
Angina	0.9
Stroke	0.8

Sources: Levin, 1990; Kawachi & Malcolm, 1989; Vermeer et al, 1988; Wade & Hower, 1987; Ahlström et al, 1984.

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