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MODELING THE ECONOMICS OF PREVENTION

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To my family

ABSTRACT

Cardiovascular disease, particularly coronary heart disease and stroke, is the most common cause of death world wide, with a prevalence that is expected to increase. The consequences of the modern lifestyle such as obesity and physical inactivity are also associated with the risk of developing diabetes, another risk factor for the development of cardiovascular disease. Patients who have developed cardiovascular disease are also of high risk of subsequent events. Measures to prevent disease would lead to health gains in the population, but such measures come at a cost. As health care systems have come under increasing economic strain, it is necessary to carefully assess the economic consequences of new interventions to see if they represent money well spent. The purpose of this thesis was to explore the use of different epidemiological materials when conducting economic evaluations. This was done by performing economic evaluations based on four different trials: two in primary prevention and two in secondary prevention.

In primary prevention, a program of diet and/or exercise to prevent cardiovascular disease directed towards 60 year old men and an intensive lifestyle intervention program to prevent the development of type 2 diabetes mellitus in patients with impaired glucose tolerance was evaluated. In secondary prevention, the use of clopidogrel in addition to acetylsalicylic acid was evaluated in patients with acute coronary syndromes and in the subset of patients undergoing percutaneous coronary intervention.

To perform the economic evaluation, computer simulation models were constructed. These models used data from the clinical trials and from different epidemiological data sources to estimate the risk of events in different populations and to extrapolate the effects on mortality caused by the end-points used in the clinical trials. Where surrogate endpoints (such as blood pressure reduction) were used, risk-functions based on epidemiological data were used to translate these results into cardiovascular events. In the primary prevention studies, a large population based cohort was used to get good estimates on the distribution of risk factors.

In all four cases, the interventions were found to be cost-effective and in one case (that of prevention of diabetes) even cost-saving to the health care payer. It was found that epidemiological data can be used in several ways in the economic evaluations, and that the intended use puts different demands on the underlying data.

LIST OF PUBLICATIONS

I. Lindgren P, Fahlstadius P, Hellenius ML, Jönsson B, de Faire U. Cost-effectiveness of primary prevention of coronary heart disease through risk factor intervention in 60-year old men from the county of Stockholm – a stochastic model of exercise and dietary advice. Preventive Medicine, 2003. 36(4): p. 403-9.

II. Lindgren P, Lindström J, Tuomilehto J, Uusitupa M, Peltonen M, Jönsson B, de Faire U, Hellenius ML. Lifestyle intervention to prevent diabetes in men and women with impaired glucose tolerance is cost-effective. Manuscript.

III. Lindgren P, Jönsson B, Yusuf S. Cost-effectiveness of clopidogrel in acute coronary syndromes in Sweden: a long term model based on the CURE trial. Journal of Internal Medicine, 2004. 255(5): p.562-70.

IV. Lindgren P, Stenestrand U, Malmberg K, Jönsson B. The long-term cost-effectiveness of clopidogrel in addition to aspirin in patients undergoing percutaneous coronary intervention in Sweden. Clinical Therapeutics, 2005. 27(1): p. 100-10.

CONTENTS

LIST OF ABBREVIATIONS

ASA	Acetylsalicylic acid
CABG	Coronary Artery Bypass Graft
CHD	Coronary Heart Disease
CURE	Clopidogrel in Unstable angina to prevent Recurrent ischaemic Events
CVD	Cardiovascular Disease
DM2	Diabetes Mellitus type 2
DPS	The Diabetes Prevention Study
GDP	Gross Domestic Product
GP	General Practitioner
ICER	Incremental Cost-Effectiveness Ratio
LYG	Life Years Gained
MI	Myocardial infarction
NSTEMI	Non-ST-segment elevation MI
PCI	Percutaneous Coronary Intervention
QALY	Quality-Adjusted Life Years
RIKS-HIA	Register of Information and Knowledge about Swedish Heart Intensive care Admissions
SEK	Swedish Kronor
USD	US Dollars

1 INTRODUCTION

1.1 CARDIOVASCULAR DISEASE AND ITS PREVENTION

Cardiovascular disease (CVD), particularly coronary heart disease and stroke, is the most common cause of death world wide, with a prevalence that is expected to increase. [1-4] Some 200 risk factors for cardiovascular disease have been identified. These include dyslipidaemia, hypertension, smoking, physical inactivity, diet, heredity and age. [5] Alarmingly, the prevalence of many of these risk factors is increasing as we are moving towards a more sedentary lifestyle. [6] The consequences of the modern lifestyle such as obesity and physical inactivity is also associated with the risk of developing diabetes, another risk factor for the development of cardiovascular disease. [7, 8] 150 million people are estimated to suffer from type 2 diabetes mellitus (DM2) in the world. [9]

Although there is little to be done about the genes we have inherited or the fact that we are getting older, the remaining risk factors can be influenced. The INTERHEART study, a case-control study in 52 countries throughout the world, has showed that nine risk factors are responsible for 90%of the population attributable risk in men and 94 % in women. These factors can all be modified. [10] The chief candidates for intervention have been hypertension and dyslipidaemia. Traditionally, these conditions have been seen as separate diseases treated individually but there is now a shift towards focusing on the patients global risk level instead. [5] An example of this is the lipid-lowering arm of the Anglo Scandinavian Cardiac Outcomes Trial where patients treated for hypertension but who wouldn't normally be on lipid-lowering treatment also were treated with a statin with good results. [11]

Life-style intervention, in its nature multifactorial, is thus a natural way of lowering cardiovascular risk. Since smoking is one of the most influential risk factors, smoking cessation is a high priority. Improved diet and regular exercise (at least 30 minutes 3-5 times weekly) are also part of the European guidelines. [5]

Patients who fail to reach target levels from lifestyle intervention alone are targets for pharmacological intervention. The current European treatment goals recommend a total cholesterol level below 5.0 mmol/l and LDL cholesterol level below 3.0 mmol/l. In high-risk individuals the recommended levels are 4.5 and 2.5 mmol/l for total cholesterol and LDL respectively. The blood pressure should be below 140/85 mm Hg. Lipid lowering is usually achieved using statins. Blood pressure reduction can be achieved using a variety of substances. A recent review by the Swedish board for technology assessment (SBU) concluded that the treatment effect is similar among the commonly used substances. [12]

Patients with manifest cardiovascular disease are known to have higher risk and are thus candidates for (secondary) prevention. The treatment recommendations and goals are the same as in primary prevention, but in addition to these interventions thrombolytic therapy (acetylsalicylic acid) should be administered. In patients with myocardial infarction, beta-blockers should also be administered.

Fewer studies have been performed to study the prevention of diabetes mellitus. However, three randomized controlled studies have reported the benefit of intensive life-style intervention. [13-15] One of these studies also included an arm where patients were treated with metformin, which was also shown to reduce the incidence of DM2.

1.2 ECONOMIC EVALUATION

1.2.1 The rationale for performing economic evaluations

The mixing of economics and health care is an issue that to some people seems controversial, something that is anathema to all that a caring society is meant to stand for. However, regardless of our reluctance to put a price tag on pain and suffering (or even death), society's resources will always be limited with an upper bound on how much of our total resources can be allocated to the health care sector. This is true irrespective of if the decision to allocate resources is made through political decision or through market mechanisms. This implies that we will always have to make choices on whether a given intervention is worth the investment, or if the money is better spent elsewhere in the health care sector or in the society as a whole. The purpose of economic evaluations is to help in these decisions by providing a structured framework to assess both the costs of interventions and the health gains achieved. The principle is simple: Given that a new treatment strategy is better than the existing treatments, we need to assess its costs. If the overall costs (including the costs for the new treatment but also all potential savings due to the better treatment effect) are lower we should of course use it since it frees up resources for use elsewhere. If they are higher, we need to assess if the better treatment effects are worth the higher cost and if so find the necessary funds to use it either by make more resources available or by stop using something that is less cost-effective.

1.2.2 The concept of costs

A cost is defined as the value of a resource in its best alternative use of the resources. This is known as the opportunity cost.

Costs are usually divided into direct costs, indirect costs and costs due to changed survival. Direct costs refer to the costs directly incurred by the disease, such as medical expenses for treatment, but they may also occur outside the health care sector, e.g. due to transport costs for the patient. Sometimes these costs are reported as medical (cost occurring within the health care sector) and non-medical (cost occurring outside the health care sector) respectively.

Indirect costs are costs due to lost production, which could occur because of short term work absence, early retirement or lessened productivity while at work. The most common approach to estimate the indirect cost is through the human-capital approach where the production is valued based on the salary paid. [16] It should be noted that, from a societal perspective, the cost of a person not being in the workforce is not represented by the compensation that is being paid to this individual (such as e.g. sick pension) which merely represents a transfer of money from one part of society to another but of the value of the production not being done because of the disease.

Recently, Meltzer has convincingly argued that to estimate full societal effects of a new intervention, we need also take into consideration that if a treatment prolongs life this will also change costs in the future. These costs amount to the difference in future consumption minus future production. As only little production is performed following retirement, this means that interventions which save lives early will be more beneficial (in the economical sense) than intervention that saves lives in higher age groups. [17, 18]

What costs are included in the analysis is decided by the perspective of the study. The perspective could be that of any payer or group, e.g. the patients (only including costs paid by the patients themselves in the analysis), the county councils (including most medical costs but excluding e.g. the cost of home-help which is paid by the communities), the health-care sector as a whole or all of society (including all costs irrespective of where they occur). If the goal is to try to optimize the total use of resources, the societal perspective is the preferred one. When comparing different studies it is important to keep in mind what costs have been included in the analysis.

1.2.3 Cost-effectiveness

Having estimated the full costs of a new intervention and compared these to the cost of the most relevant comparator, we come to a point where we need to decide whether the intervention should be implemented or not. It is common to discriminate between four types of analyses that can be performed in order to assist this decision (see e.g. Drummond [19] and Johannesson [20]). The difference between the methods lies solely in how we take the health effects of the intervention into account.

The easiest approach is to perform a **cost-minimization analysis**, in which the treatments are assumed to have the same health effects, both positive and negative. In this case, the treatment alternative with the lowest total cost is the preferred option. The assumption that two treatments have identical health effects is a very strong one, which is false in most cases. For this reason, cost-minimization studies are rarely seen in the scientific literature.

When the health effects differ between the comparators (either in terms of outcomes or in terms of side-effects) and the better intervention is more expensive we need to decide if the health gains are large enough to motivate the increased cost. (If the total cost of the better treatment is lower than the comparator, the decision is of course an easy one; this is referred to as a dominant strategy, which is both cheaper and better). In a **cost.-effectiveness analysis** treatment effects could be measured in several different ways, e.g. events (such as myocardial infarctions) avoided or life-years gained (LYG). We estimate the net cost difference between the treatments, and divide this by the net treatment effect to create an incremental cost-effectiveness ratio (ICER). The ICER shows the mean cost of treatment to avoid one event (or to gain one year of life if we are using LYG as our measure of effectiveness). It is then up to the decision maker to judge whether or not this is money well spent.

A difficulty with cost-effectiveness analyses is the comparison between studies, as different outcomes may be used as the measure of effectiveness. LYG is more standardized, but this outcome cannot be used when studying interventions that have no effect on mortality, e.g. treatments against pain. For this reason, **cost-utility analysis** is often the preferred option. Cost-utility analysis is in principle the same as cost-effectiveness analysis but using quality adjusted survival as the measure of effectiveness. Utility is thought of as weight between 1 and 0 where 1 corresponds to perfect health and 0 to a health state equal to death. The quality adjusted survival is estimated based on these weights. Living two years with a utility of 0.5 would be equal to 1 quality adjusted life year (QALY), i.e. being equivalent to living one year with perfect health. By improving the quality of life so that the utility would be 0.75, would lead to 1.5 QALYs during the two years, an improvement of 0.5 QALYs. The same effect could be achieved by prolonging life with one year, thus both improvements in survival and improvements in quality of life can be captured through this measure.

What then is an acceptable cost-effectiveness ratio? There exists no theoretical derivation of this value. Earlier, a value of 50,000 USD per QALY gained was often quoted as a suitable threshold value. This was referred to as the dialysis standard and was assumed to be the cost-effectiveness of dialysis treatment, a costly but effective and widely accepted treatment. There have also been some attempts to perform willingness to pay studies in the general population giving a range of threshold values between 27,000 USD to 645,000 USD per QALY gained. Recently, the World Health Organization (WHO) has recognized that the investment in health should be related to the resources available to the society and thus, based on expected direct and indirect benefits to national economies proposed a threshold value of 3 times the gross domestic product (GDP) per capita per disability adjusted life year gained. This threshold value is now frequently used in the literature as a threshold value per QALY gained as well. [21] In Sweden, this would imply a threshold value of roughly 800 000 SEK.

One way of dealing with the uncertainty around what is considered an acceptable threshold value is to present results in the form of a cost-effectiveness acceptability curve. [22] These curves are constructed from the underlying uncertainty of the data (which can be estimated by bootstrapping or by Monte Carlo-simulation). This is done by estimating how large a fraction of the results would fall below different threshold values and plotting this fraction in a graph. From a Bayesian perspective, the curve can be interpreted as showing the probability that an intervention is cost-effective for different levels of willingness to pay to gain one unit of the measure of effectiveness.

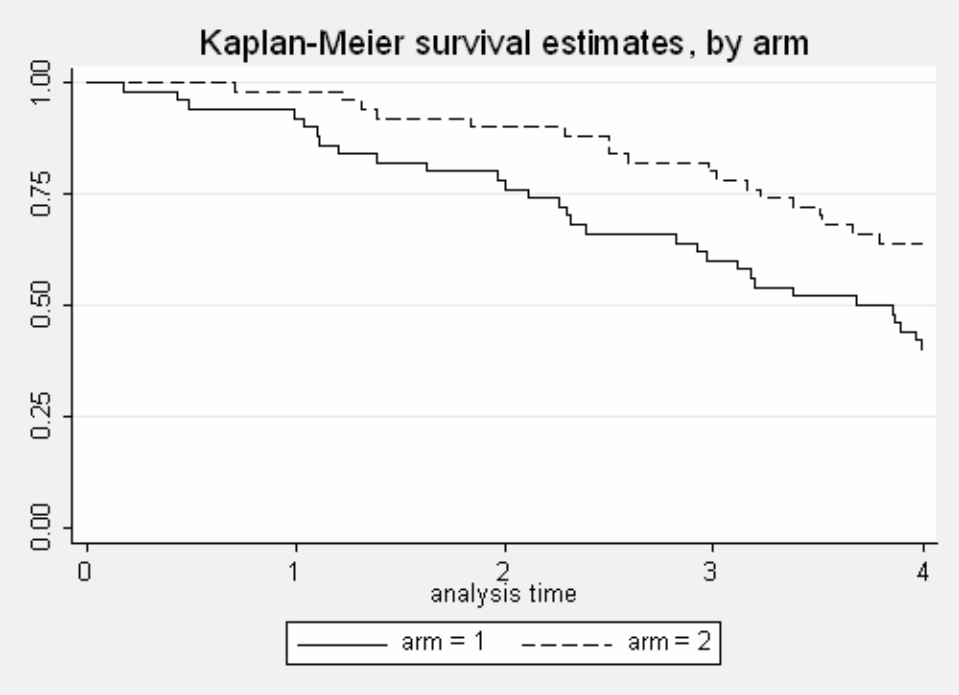
In **cost-benefit analysis** finally, the measure of effectiveness is assigned a monetary value, and if the value of the benefits exceeds the costs the program should be implemented. As can be understood from the discussion around threshold values, giving a specific monetary value to a health state is difficult and this method is therefore rarely used.

1.2.4 Modeling

In order to estimate the full economic impact of an intervention, it is often necessary to use a simulation model to make a forecast. The rationale for this can be easily realized

by studying figure 1 which shows the survival of patients receiving two different treatments during a trial. Treatment 2 is more effective, and patients on this treatment live longer. The mean gain in survival during the trial period is given by the area between the curves. As there are more survivors on treatment At the end of the trial, limiting the analysis to the trial period would therefore underestimate the difference between the arms even if we assume no treatment effect after this. In fact, if we only analyze the trial period, we are implicitly assuming that all the extra survivors on treatment A would die instantaneously at the end of the trial and that there would be no difference between the arms beyond this point.

Figure 1. Survival in a hypothetical trial.



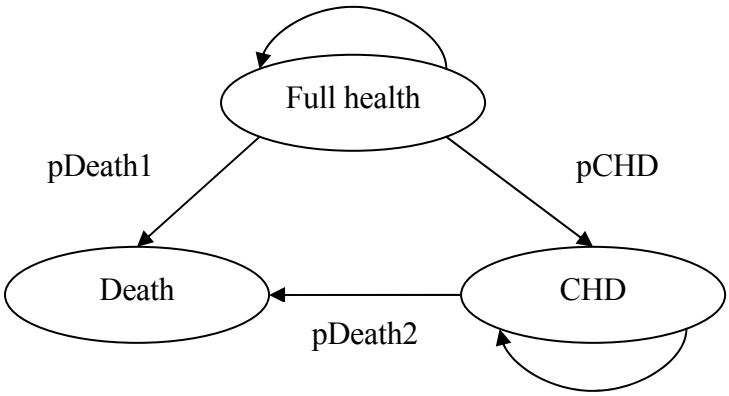
If we consider another example where we assume that the curves in figure 1 show not survival but time to a MI we can identify another rationale for modeling: At the end of the trial we have avoided a number of events, but many events are likely to be postponed rather than avoided completely during the lifespan of the patients. The number of events avoided is thus dependant on how long we follow the patients. The costs and health effects of suffering an MI also span a longer time period than what is captured in the trial, potentially they can last for the remainder of the patient's life.

A third rationale for modeling is that it allows for the inclusion of quality-of-life weighting of the events included in the trial when such data is available. This takes into account that patients who have suffered from e.g. a MI will have a reduced quality of life for some time following the event. Based on the difference in the number of events, the gain in quality adjusted life years can be estimated and used as the outcome measure in the economic evaluation.

There are different ways of constructing a model. Three main frameworks can be identified: Markov models, decision trees and discrete event simulation (DES), but it is easy to find examples of deviations from the main frameworks.

A Markov model divides the modeled disease process into discrete states. [23, 24] Each of these states is associated with costs and health effects (such as quality of life weights). Patients spend a fixed amount of time (referred to as a cycle) in each health state, and then have a probability of moving to different states of the model or remain in the present one. A Markov model can be represented as a state-transition diagram. An example of a very simple Markov model with three possible states (full health, CHD and death) can be found in figure 2. Patients in the "Full health" state have a yearly probability (pCHD) of suffering from CHD and a yearly probability of dying (pDeath1). If neither of this happen, patients remain in the "Full health" state. Once patients have CHD they have a yearly probability of dying (pDeath2), which is higher than the mortality from the "Full health" state. Survivors remain in the CHD state. The transition probabilities may be influenced by various patient characteristics such as age, gender and others, but not by what has happened previously in the model, i.e. the model has no memory. This is known as the Markovian assumption.

Figure 2. State transition diagram of a simple Markov model.



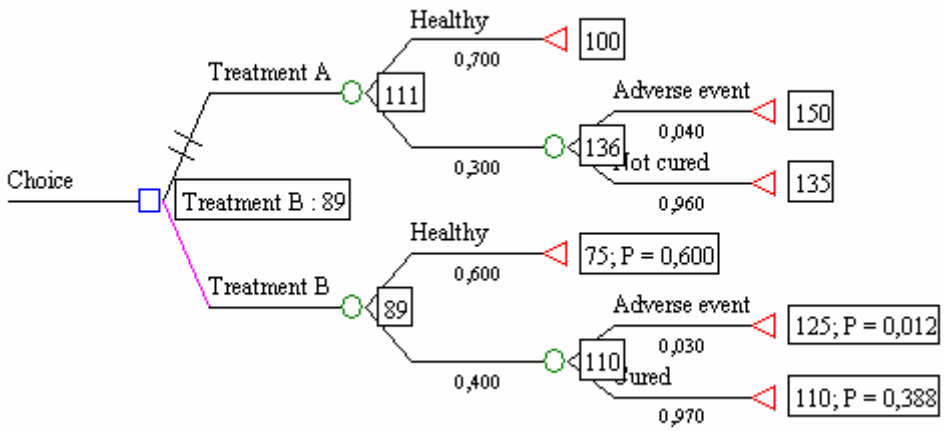
The easiest way of evaluating a Markov model is through deterministic simulation. This is done by moving a hypothetical cohort of patients through the model, where fractions of the cohort moves to different states each cycle based on the transition probabilities in the model. This generates an estimate of e.g. mean cost and mean survival. The same model is then run, incorporating the effects of intervention, e.g. by adjusting the risk of events and adding the cost of treatment during the treatment interval. The results of the intervention and no intervention simulations can then be compared and the net costs and effects calculated. The impact of uncertainty around key parameters in such a model is evaluated through sensitivity analysis, where one or several of the parameters are varied to test the impact on the results.

Should the distribution around parameters be known, it is possible to get an estimate of the spread around the predicted mean values. This is done through stochastic simulation where the model is evaluated with the value of each parameter drawn at random from

the underlying distribution. This is done a large number of times (until stable results are achieved), a process known as Monte Carlo simulation.

A decision tree is basically a sophisticated way to estimate expected probabilities and payoffs. A simple decision tree is shown in figure 3. Different strategies are represented by separate arms emanating from the initial node in the tree (the choice node). Uncertain events such as treatment options or health states are represented by probabilities forming a pathway of potential outcomes. The expected value (costs and health effects) of each arm in the tree is calculated by starting from the end nodes and successively calculating the expected value at each branch, moving towards the choice node, an operation known as rollback. The tree can be evaluated in the same way as a Markov model, i.e. either through deterministic calculation or by stochastic simulation. [25]

Figure 3. A simple decision tree where the rollback is being performed. Treatment B is the least costly option.



Discrete event simulation is commonly used in engineering and operations research, and has recently been proposed for use in health economics. [26] In discrete event simulation focus is on events rather than health states. An event is something that occurs at a given point in time, it could be e.g. a MI or that a patient is discharged from hospital. When an event occurs, the entire system that is being modeled is said to change state. Events occur at discrete points in time (hence the name discrete event simulation), and a list (called the event queue) is maintained to keep track of when events occur. The triggering of an event may lead to that new events will occur later, and they are then placed at the appropriate place in the queue. As an example, a patient may be hospitalized at a certain point in time. When this happens, the time to discharge is calculated, and the event hospital discharge is added to the event queue. The model will then move to the next event in the queue to determine what will happen next. The hospitalization as such is referred to as an activity. The advantage of discrete event simulation is that patients can be involved in several activities at the same time which in a Markov model would require a separate state for each possible combination of

activities. Discrete event models are always evaluated using Monte Carlo simulation, moving a large number of patients through the model and calculating a grand mean based on all the simulations performed. This puts high demands on both the available data to represent the process accurately and on computing power.

It should be recognized that the choice of modeling framework is one of convenience. A discrete event simulation model can be replaced by a Markov model with a sufficient number of states and sufficiently short cycle length. In turn, any Markov model can be represented by a large decision tree. The results from the economic analysis are thus not dependent on what type of model is being used, provided that the model is constructed so that all relevant costs and health effects are captured.

1.2.5 The link between health economics and epidemiology

Having established the need for modeling to estimate the potential effects of novel treatment strategies, the link between health economics and epidemiology becomes apparent. In any disease model we try to estimate the natural progression of a disease incorporating data on development of the disease (the risk of onset, the progression of the disease and so on) as well as the associated mortality. Once a general model of the disease has been developed, the effects of an intervention can be estimated by modifying the relevant parameters in the model. In a preventive model this could mean to modify the risk of developing the disease or suffering a cardiovascular event where as it in a model of progressive disease it could mean slowing the progression to more severe disease states by some factor when a drug is used.

All these steps require that epidemiological data (or results) are incorporated. When studying heart disease, it is necessary to have good estimates on the risk of the occurrence of cardiovascular events, and on covariates affecting the risk of events as well as on the survival following these events. This must be established using methods from epidemiology such as logistic regression or through survival analysis of time to event data. The data can be used in the models either by including the risks directly, or by using risk factors which can be modified by an intervention.

The incorporation of the effects of an intervention also relies heavily on the use of epidemiological studies. In principle, there are two ways that the effects of an intervention can be incorporated into a model: the most straightforward one is to apply a risk reduction known to be associated with the treatment to the baseline risk used in the model. The relative risk used is most commonly gathered from a clinical trial (or from a meta–analysis of several trials) and this is of course a form of applied epidemiology. The second option is to model the effect of an intervention through the reduction in risk factors when a risk function is used.

1.3 ECONOMIC EVALUATION OF PREVENTION

The following sections present the results of previously performed studies in the field of cardiovascular prevention deemed to be of relevance for comparison with the studies included in the thesis. In order to facilitate comparison between studies, results have been converted to SEK using the average conversion rate between the currency used in the study and SEK during the year indicated as the year of costing in the study using

figures from the Riksbank. [27] The results were the inflated too year 2004 value using the consumer price index. [28]

1.3.1 Studies in primary prevention

The economic evaluations of primary preventive measures can be divided into those studying life-style interventions such as dietary advice or exercise, studies of lipid lowering drugs and studies of treatment against hypertension. This overview starts with studies of life-style intervention.

The first study in the field was performed by Hatziandreu et al. [29] They evaluated a hypothetical exercise program consisting of 5 hours of jogging each week. The risk of events and mortality were estimated based on the Framingham study. Costs included both direct and indirect costs as well as the value of the leisure time lost by the participants. It was assumed that the relative risk of events in the non-exercise group was 2. The predicted cost-effectiveness ratio was 176 782 SEK/QALY.

Jones and Eaton studied the effect of walking to prevent coronary heart disease using a simulation model where the relative risk of heart disease and the risk reduction associated with walking was varied. [30] Not surprisingly, they found that great savings could be achieved if the sedentary population could be persuaded to walk regularly. The cost of this was limited to the cost of the leisure time spent in patients disliking exercise.

A hybrid of life-style intervention and pharmaceutical treatment was studied by Johannesson and colleagues who used a Markov model with risk and mortality figures based on the Framingham study to estimate the effect of a risk-factor intervention program with individual and group advice, complemented with drug therapy if patients failed to reach the treatment goals (total cholesterol <6.0 mmol/l, HbA1c<6.0%, and diastolic blood pressure < 90 mmHg) compared to conventional pharmacological treatment. [31] The study contained a detailed cost calculation of costs both inside and outside the health care sector. As the patients in the study were older than 65 years, no indirect costs were included in the base case. The study reported an ICER of between 76 190 SEK/LYG and 200 306 SEK/LYG when modeling the risk reduction directly through the risk function and 4 915 SEK/LYG when using the observed risk reduction in the trial. The authors stress that the latter figure may be an underestimation of the ICER due to an unexpected high reduction in the number of strokes.

Salkeld et al investigated a lifestyle intervention program consisting of either information videos or a combination of video and a self-help booklet. [32] The GPs included in the study underwent training in risk factor assessment and the risk reduction program. The same Markov model as in the studies by Johannesson was used to perform the evaluation. [31, 33] Due to no or low effect on the measured risk factors, the health gain predicted by the model were non-existent in the video only group and extremely small in the video + self help group. The predicted cost-effectiveness ratios were thus very high (in excess of 850 000 SEK/LYG).

Rubió studied the cost-effectiveness of dietary advice to lower cholesterol levels in a Spanish setting. [34] A hypothetical dietary program which was assumed to reduce cholesterol levels by 5% was evaluated in a Markov model with risk of events taken from the Framingham study and mortality figures from Catalonian statistics. Only direct costs are included. The study indicates that cost-effectiveness improves with higher risk (higher cholesterol levels, higher age and male sex).

The cost-effectiveness of exercise has been studied by Lowensteyn and colleagues. [35] They used the Cardiovascular Disease Life Expectancy Model which is based on data from the Lipid Research Clinics Program Prevalence and Follow-up data to model the effects of intervention. The effect of exercise was based on a meta-analysis of published trials. An unsupervised program showed a cost-effectiveness ratio of less than 87 732 SEK/LYG while a more expensive supervised program showed ratios between 87 732 SEK and 314 372 SEK per LYG.

Moving on to economic evaluations of the use of lipid-lowering drugs in primary prevention there are a couple of studies published on this topic. The cost-effectiveness of lipid lowering trial (CELL) used the model developed by Johannesson to estimate the cost-effectiveness of a combination of usual or intensive advice with treatment with pravastatin. [33] The Advice only and intensive advice in combination with pharmacological intervention showed no effect on the measured endpoints and intensive advice alone was eliminated through extended dominance. The cost per LYG of pharmacological treatment compared with no treatment was 449 768 SEK.

The West of Scotland Coronary Prevention Study (WOSCOPS) studied the use of pravastatin in middle aged men with no previous heart disease. An economic evaluation of WOSCOPS was performed by Caro et al who used a model to extrapolate the findings in the trial over a longer time frame. [36] They found that the predicted cost-effectiveness ratio was 232 450 SEK per LYG, including only direct costs. This model has also been adapted to other countries, Sweden among them. In this case the ICER was 67 534 SEK per LYG. [37]

All of these studies have studied interventions and estimated a cost-effectiveness ratio which can then be judged to fall below or above a threshold value that is considered cost-effective. In an interesting study by Johannesson, the question was asked the other way around: If we can agree on a threshold value that is considered cost effective, how high should the absolute risk in patients be for cost-effectiveness ratios to fall below that value. [38] The study used the risk reduction from the WOSCOPS study and risk estimates from Sweden. If society was willing to pay $60,000 to gain a QALY it was cost-effective to initiate treatment if the 5-year-risk of coronary heart disease exceeded 2.4% for 35-year-old men, 4.6% for 50-year-old men, and 10.4% for 70-year-old men. The corresponding risk cut-off values for women were 2.0%, 3.5% and 9.1%.

Nordmann and colleagues used a Markov model to study the use of ACE-inhibitors as first-line antihypertensive treatment compared to beta-blockers and diuretics in Canada and Switzerland. [39] The difference in predicted QALYs between the comparators was very small leading to very high cost-effectiveness ratios for the ACE-inhibitors (in excess of 6 000 000 SEK per QALY gained).

The HOT-study investigated the effect of lowering the diastolic blood pressure to different threshold levels (<= 90 mmHg, <= 85 mmHg and <=80 mmHg) and the economic consequences of the three strategies in Sweden has been assessed by Jönsson et al.[40] The cost-effectiveness of avoiding a cardiovascular event varied between 41 600 and 477 400 SEK, and it was concluded that for diabetics patients, intensive blood pressure lowering would be worthwhile.

Table 1. Economic evaluations in primary prevention.

Study	Intervention	Comparator	Country	Direct costs	Indirect costs	Outcome	ICER[1] (2004 SEK)
Life-style intervention							
Hatziandreu et al	Jogging 5 hrs/week	No exercise	USA	Yes	Yes	QALY	176 782
Johannesson et al	Advice, drugs if necessary	Conven-tional	Sweden	Yes	No[2]	LYG	76 190
Salkeld et al	Video and self-help booklet	No inter-vention	Australia	Yes	Yes	LYG	>850 000
Rubió	Diet	No inter-vention	Spain	Yes	No	LYG	Varies with risk
Lowensteyn et al	Unsuper-vised exercise	No inter-vention	Canada	Yes	No	LYG	<87 732
	Supervised exercise	No inter-vention	Canada	Yes	No	LYG	<314 372
Cholesterol lowering							
Johannesson et al	Pravastatin	No intervention	Sweden	Yes	Yes	LYG	449 768
Caro et al	Pravastatin	No intervention	UK	Yes	No	LYG	232 450
Caro et al	Pravastatin	No intervention	Sweden	Yes	No	LYG	67 534
Blood-pressure lowering							
Jonsson et al	Felodipin	Different targets	Sweden	Yes	No	Event avoided	Varying
Nordmann et al	ACE-inhibitors	Beta-blockers or diretucs	Canada and Switzer-land	Yes	No	QALY	6 000 000

[1]Incremental Cost Effectiveness Ratio
[2]Age in the studied group was above 65 years.

The Swedish board for technology assessment (SBU) has performed two reviews on the treatment of essential hypertension including the economic evidence. [12, 41] The reports concluded that it is cost-saving to treat patients with hypertension in patients above 65 years of age if the cheaper substances are used and that treatment of hypertension is cost-effective in younger patients. It was also noted that it would be

more cost-effective to lower the blood pressure more in currently treated patients with elevated blood pressure than to treat additional patients with lower levels.

1.3.2 Studies in secondary prevention

Secondary prevention has received considerably more attention than primary prevention in the economic literature. The reason for this is that the high absolute risk of new events makes patients with previous cardiovascular disease natural candidates for risk reduction. The type of intervention that has been most widely studied is cholesterol lowering with various statins. A summary of these studies can be found in table 2.

The landmark study in the field was the Scandinavian Simvastatin Survival Study (4S) investigating the effects of treatment with 20-40 mg simvastatin compared to placebo in patients with angina pectoris or MI.[42] An economic evaluation of this study was performed by Jönsson and colleagues estimating the net cost of treatment and hospitalizations during the trial and extrapolating the observed survival benefit to the lifetime perspective, resulting in an ICER of 61 801 SEK per LYG. [43] The data from 4S was also used by Johannesson et al to construct a Markov model to evaluate the cost-effectiveness in different subgroups defined by age and cholesterol levels. [44] The results varied between cost-savings and 103 972 SEK/LYG. The authors in both these studies conclude that this treatment strategy is cost-effective. As the price of simvastatin has decreased drastically following the expiration of the patent, the cost-effectiveness of this strategy would be even lower today.

Four studies have investigated the cost-effectiveness of pravastatin in secondary prevention. Ashraf et al performed a modeling study based on the Pravastatin Limitation of Atherosclerosis in Coronary arteries and the Pravastatin Limitation of Atherosclerosis in the Carotids trials. [45] A Markov model was used extrapolating the survival following the events observed in the trials based on data from the Framingham study. Patients (only men) were followed for 10 years. Results varied between 55 700 and 99 008 SEK/LYG. The same model, but using Belgian cost data, was applied by Muls and colleagues to assess the cost effectiveness in Belgium. [46] Their results varied between 103 769 and 190 426 SEK/LYG, the higher figures explained by a higher cost of the study drug and lower cost of other medical intervention. Tsevat and co-authors developed a Markov model based on the Cholesterol and Recurrent Events trial using US life tables to project mortality gains outside the trial. Depending on the assumption regarding mortality during the trial, the cost per QALY gained varied between 116 976 and 233 951 SEK/QALY. [47] Glasziou et al has studied the cost-effectiveness of pravastatin in patients with established heart disease but average cholesterol levels. [48] Costs occurring in the health care sector were collected during the Long-Term Intervention with Pravastatin in Ischaemic Disease trial and contrasted to the observed survival during the trial which was extrapolated using the mortality in the placebo arm. The resulting ICER was 59 452 SEK per LYG.

Three studies have evaluated the cost per event avoided in the Myocardial Ischaemia Reduction with Aggressive Cholesterol Lowering study. The studies estimated the 16-week cost of 80 mg atorvastatin compared to placebo. Only costs and effects during the

trial period were included. The three studies reported a cost per event avoided of 26 162 SEK in the UK, 44 103 SEK in the US and 15 136 SEK in Sweden. [49-51]

Scuffham et al studied the effects of fluvastatin in patients with a successful first PCI in the UK, based on clinical results from the Lescol Intervention Prevention Study. They used a Markov model to study the cost-effectiveness over 10 years using data on event rates and survival after events from the trial. The cost-effectiveness ratio was 47 854 SEK/QALY. [52]

Table 2. Economic evaluations in secondary prevention through cholesterol lowering.

Study	Intervention	Comparator	Country	Direct costs	Indirect costs	Outcome	ICER[1] (2004 SEK)
Jönsson et al	Simvastatin 20-40 mg	No treatment	Sweden	Yes	No	LYG	61 801
Johannesson et al	Simvastatin 20-40 mg	No treatment	Sweden	Yes	Yes	LYG	103 972[2]
Ashraf et al	Pravastatin 40 mg	No treatment	USA	Yes	No	LYG	55 700[3]
Muls et al	Pravastatin 40 mg	No treatment	Belgium	Yes	No	LYG	190 426[3]
Tsevat et al	Pravastatin 40 mg	No treatment	USA	Yes	No	QALY	233 951
Glasziou et al	Pravastatin 40 mg	No treatment	Australia	Yes	No	LYG	59 452
Buller et al	Atorvastatin 80 mg	No treatment	UK	Yes	No	Event avoided	26 162
Schwartz et al	Atorvastatin 80 mg	No treatment	USA	Yes	No	Event avoided	44 103
Olsson et al	Atorvastatin 80 mg	No treatment	Sweden	Yes	No	Event avoided	15 136
Scuffham et al	Fluvastatin 80 mg	No treatment	UK	Yes	No	QALY	47 854

[1]Incremental Cost Effectiveness Ratio
[2]This is the result from the subgroup showing the highest ICER, 70-year old women with 213 mg cholesterol per dl.
[3]This is the result from the subgroup showing the highest ICER, patients with one additional risk factor.

Interestingly, only one of the studies in table 2 included indirect costs and none cost in added years of life.

The use of clopidogrel has been investigated in a few different studies. Two studies have been performed based on the clinical findings of the CAPRIE-trial. This trial compared the use of clopidogrel (alone) to ASA in patients with myocardial infarction, stroke, or peripheral artery disease. Annemans and colleagues used a Markov model populated with data from the trial and the Saskatchewan database and reached the conclusion that clopidogrel was cost-effective in this indication based on the predicted cost-effectiveness ratio of 125 567 SEK/QALY. [53] A similar approach was used by Schleinitz and colleagues in a US setting, using US lifetable data to estimate survival following the events observed in CAPRIE. [54] Schleinitz et al reports the results depending on the diagnosis at inclusion in the study. The ICER for patients with peripheral artery disease was 249 805 SEK/QALY, for patients with a stroke it was 310 515 SEK/QALY while ASA was a dominant strategy in patients with MI.

Latour-Pérez et al has published findings based on an analysis of the CURE trial. [55] They used a Markov model with event data from the clinical trial and used data from the Framingham study to estimate survival after events. Costs relating to events were calculated based on assumed treatment practices. The study reported an ICER of 116 438 SEK/QALY for a population similar to that in the trial.

A more problematic study is the one published by Gaspoz and colleagues. [56] The study used a model to estimate the cost-effectiveness of ASA, clopidogrel or both in patients with cardiac arrest, myocardial infarction or angina. This is inappropriate, as this would represent a use of clopidogrel outside its indication. In the main scenario, the model then assumes treatment during 25 years with full compliance and no price offset at the expiry of the patent on clopidogrel. An ICER > 900 000 SEK/QALY was reported.

Janzon et al studied the cost-effectiveness of extended use of dalterpain in patients with unstable coronary artery disease managed with a non-invasive treatment strategy. [57] The analysis was performed alongside the FRISC-II trial. The cost per cardiovascular death avoided after one month was 32,129 SEK

Nyman and colleagues studied the use of gemfibrozil in patients with low levels of high-density lipoprotein cholesterol. [58] They used a Markov model with risks derived from hazard functions from the clinical trial. The resulting cost-effectiveness ratio was 55 285 SEK/QALY in the base case (a 65-year old patient).

Björholt and colleagues performed an economics evaluation including the Swedish patients in the HOPE study investigating the use of ACE-inhibitors in addition to standard treatment in patients at high cardiovascular risk. [59] The study was conducted alongside the clinical trial and survival in patients alive at the end of the trial was forecasted to estimate the total gain in life expectancy. Both direct and indirect cost were included and an ICER of 54 600 SEK per LYG was reported. The study also included an analysis including cost in added years of life, which gave an ICER of 208 300 SEK per LYG.

Ekman has studied the effect of adding bisoprolol to the treatment of patients with congestive hart failure in Sweden. [60] The study used the resource consumption during the trial to estimate the use of health care resources, giving an ICER of 14 164 SEK per LYG. When including cost in added years of life, the ICER from the societal perspective became 182 662 SEK.

Increased use of betablockers after MI was studied by Phillips and colleagues using the coronary heart disease model. [61] This is the same model that was used by Gaspoz to evaluate clopidogrel and ASA. They found that the cost-effectiveness of moving from current treatment practices to full use of betablockers was 37 144 SEK per QALY gained.

Table 3. Economic evaluations in secondary prevention through other means than cholesterol lowering.

Study	Intervention	Comparator	Country	Direct costs	Indirect costs	Outcome	ICER[1] (2004 SEK)
Clopidogrel							
Annemans et al	Clopidogrel	ASA	Belgium	Yes	No	QALY	125 567
Schleinitz et al	Copidogrel	ASA	USA	Yes	No	QALY	249 805
Latour-Pérez et al	Clopidogrel + ASA	ASA	Spain	Yes	No	QALY	116 438
Gaspoz et al	Clopidogrel + ASA	ASA	USA	Yes	No	QALY	>900 000
Other treatments							
Janzon et al	dalteparin	placebo	Sweden	Yes	No	Death avoided	32 129
Nyman et al	gemfibrozil	placebo	USA	Yes	No	QALY	55 285
Björholt et al	ACE-inhibitors	Standard treatment	Sweden	Yes	Yes	LYG	54 600
Ekman et al	Bisoprolol	Standard trreatment	Sweden	Yes	Yes	LYG	14 164
Phillips et al	Full use of betablockers	Current use	USA	Yes	No	QALY	37 144

[1]Incremental Cost Effectiveness Ratio

Only few studies used a societal perspective and include indirect costs in the analyses. The studies that did (Björholt et al and Ekman et al) also included cost in added years of life. All the studies except Janzon et al uses quality adjusted life years as the main outcome, which should be the aim in order to allow for cross-indication comparability. However, most of the underlying quality-of-life data is not very good but based on assumptions.

1.3.3 Diabetes mellitus

The costs of diabetes mellitus is an area that has received some attention in recent years. The CODE-2 study investigated the direct costs of type 2 diabetes in eight European countries. [62-64] There have also been many other studies based on both top-down and bottom-up approaches. [65-68]. The costs of diabetes are thus fairly well understood, and given the high costs associated with the disease and its cardiovascular complications in particular, it is surprising that so little attention has been paid to the economic aspects of the prevention of diabetes as such. A majority of the economic evaluations in diabetes have been focused on the cost-effectiveness of glycaemic control in the prevention of diabetes-related complications, and on control of hypertension and cholesterol levels to avoid cardiovascular disease. [40, 69-80] As patients with diabetes have an elevated risk of cardiovascular disease, risk reducing interventions such as antihypertensive treatments and cholesterol lowering have also been studied.

Only two studies have investigated the cost-effectiveness of developing type 2 diabetes previously. Both of these are based on the diabetes prevention program studying the use of metformin or lifestyle intervention to achieve this end. [13]

The diabetes prevention group analyzed the cost-effectiveness during the program by estimating the cost of identifying individuals with IGT, the cost of the program itself and medical costs outside the program. [81] Indirect costs were also included in the analysis. Utilities were estimated using the Quality of Well-being Index and the quality-adjusted survival during the trial was calculated. As there is a difference between the arms at the end of the trial, the cost per QALY calculated in this way is an overestimation. From the societal perspective, the ICER for the lifestyle intervention arm compared to placebo was 266 194 SEK per QALY gained. The corresponding figure for the metformin arm was 343 793. No comparison was made between lifestyle intervention and metformin, but based on the costs and QALYs reported, the ICER for lifestyle intervention (which was more costly but also more effective) compared to metformin would be 221 599 SEK per QALY. Since this figure is lower than the ICER for metformin compared to placebo, metformin would be an eliminated strategy due to extended dominance. This indicates that it would be possible to get the same or better health gains at the same or a lower cost as metformin by giving lifestyle intervention to part of the patients and no intervention to the rest.

Palmer et al analyzed the DPP in Australia, France, Germany, Switzerland and the United Kingdom. [82] They used a simple Markov model with states for IGT, type 2 diabetes mellitus and death. Probabilities were based on the DPP and local figures on mortality. In the base case, no treatment effect was assumed once the intervention was discontinued. The model predicted a gain in survival of 0.11 years for patients treated with metformin and 0.22 years with lifestyle intervention. Both interventions led to reductions in life-time costs in all countries except the UK where a slight increase in costs was observed. The cost-savings were larger with lifestyle intervention than with metformin. Only direct costs were included in the analysis. Should indirect costs be included, cost-savings are likely to become larger.

2 AIMS OF THE THESIS

The overall purpose of this project was to explore the use of various sources of epidemiological data in the creation of models for health economic evaluation in the fields of primary and secondary prevention of cardiovascular disease and diabetes mellitus. Specifically, this was done by:

- Investigating the cost-effectiveness of implementing a life-style intervention primary prevention program consisting of dietary advice, exercise or a combination of both (paper I).
- Investigating the cost-effectiveness of preventing the development of DM2 in patients with impaired glucose tolerance through an intensive life-style intervention program (paper II).
- Investigating the cost-effectiveness of adding clopidogrel to ASA in patients with unstable coronary artery disease based on the CURE trial (paper III).
- Investigating the cost effectiveness of a treatment strategy consisting of pretreatment with clopidogrel followed by 12 months treatment in combination with ASA in patients undergoing PCI based on the PCI-CURE trial (paper IV).

3 MATERIALS AND METHODS

3.1 EPIDEMIOLOGICAL DATA

3.1.1 The 60-year cohort

Recently, the baseline investigation of a population based screening program involving individuals living in the County of Stockholm and born between 1937-07-01 and 1938-06-30, i.e. individuals aged 60 at the time of the screening, has been concluded. In the program 5,460 men and women, or one third of the 60-year old population in the County of Stockholm, were invited to participate in medical examinations as well as to fill in extensive questionnaires on their perceived health, habits, socioeconomic situation and more. 78%, or 4,232 persons choose to participate in the program. The cohort will be followed for several years, tracking cardiovascular events and mortality as well as changes in the risk profiles.

3.1.2 The hospital discharge and cause of death registers

The hospital discharge register is a register covering all public in-patient care in Sweden from 1987 and onwards. The register is maintained by the Centre for Epidemiology at the National Board of Health and Welfare. The register contains information on age and gender of the patient, admission and discharge date, main and secondary diagnoses (according to ICD codes) and procedures undertaken. The county councils administer registration, which is mandatory. Nevertheless, there is some underreporting, estimated to below 2 % of hospitalisations.

The cause of death register contains the cause of death for all diseased residents in Sweden based on death certificates. The register contains some demographic information and the underlying cause of death (defined as the disease or injury that initiated the chain of diseases that finally resulted in death or the circumstances involving the accident or the act of violence that caused the lethal injury). The register is maintained by the Centre for Epidemiology at the National Board of Health and Welfare.

3.1.3 The RIKS-HIA register

The RIKS-HIA register is a register of all patients admitted for cardiac intensive care at hospitals participating in the register (in 2002, 74 out of 80 hospitals treating patients with acute coronary syndromes). The database contains some 100 variables on background factors and treatments received. The register is matched to the national registers on coronary angiography, coronary angioplasty, and bypass surgery as well as the hospital discharge register and the cause of death register.

3.2 CLINICAL TRIAL DATA

3.2.1 The Sollentuna study, a controlled randomized diet and exercise study

The Sollentuna study was performed in the County of Sollentuna, near Stockholm. 160 men aged 35-60 recruited from an ongoing cardiovascular prevention program were

randomized to dietary advice (group D), exercise (group E), dietary advice and exercise (group DE) or a control group. Inclusion criteria were no previous cardiovascular disease, diabetes or other severe illnesses; no regular use of drugs; total cholesterol between 5.2 and 7.8 mmol/l; fasting triglycerides <= 5.6 mmol/l; fasting blood glucose <= 6.7 mmol/l and diastolic blood pressure <= 100 mmHg. Patients underwent a first physical check-up during a visit to a physician. After randomization, they received advice on diet and/or exercise from the physician. Patients in the two groups receiving dietary advice also visited a dietitian giving further individual advice. The dietitian made a follow-up after 3 months to check compliance with the given advice. Patients in the exercise groups were asked to maintain a prepared activity log and were given the opportunity to join exercise groups. Patients were followed up at 6 and 18 months. [83-85]

3.2.2 The CURE and PCI-CURE trials

CURE (Clopidogrel in Unstable angina to prevent Recurrent ischaemic Events) was a phase III randomized, double blind parallel group clinical trial of clopidogrel versus placebo in patients with an acute coronary syndrome (unstable angina or myocardial infarction without ST segment elevation). [86] The primary objective of the clinical trial was to evaluate whether clopidogrel is superior to placebo in preventing ischaemic complications in patients with acute coronary syndrome (ACS) without ST segment elevation, i.e. unstable coronary artery disease, receiving acetyl salicylic acid (ASA) therapy. The secondary objective of the study was to evaluate the safety of clopidogrel. Patients were followed for a maximum of 12 months (median 9 months). The clinical trial showed that the primary end-points (cardiovascular death, myocardial infarction and stroke) are reduced by 21% in the clopidogrel group, with a 38 % increase in major bleedings but no significant difference in life-threatening bleeds.

The PCI-CURE study was a substudy investigating the outcomes in patients undergoing percutaneous coronary interventions (PCI). [87] Patients were pretreated with aspirin and study drug for a median of 10 days. After PCI, both patients in the active and placebo group were allowed to receive open-label thienopyridines (clopidogrel and ticlopidine) for a median of 4 weeks. After this period, patients in the active group received treatment for an additional 8 months (mean, 11 months maximum). 1 313 patients in the active group and 1 345 in the placebo had 30 days follow-up or more, making them eligible for the long term analysis. Adjusting for covariates that influence the likelihood of undergoing a PCI using propensity scores, long term-treatment (preceded by pre-treatment) with clopidogrel showed a relative risk of cardiovascular death and MI of 0.72.

3.2.3 The Diabetes Prevention Study

The Finnish Diabetes Prevention Study (DPS) randomized 522 men and women either to participate in the intervention program or to be part of a control group. Patients were on average 55.7 years old, with a body mass index (BMI) of 31 and a waist circumference of 102 cm. They had a fasting glucose level of 109 mg/dl (6.0 mmol/l), a total cholesterol level of 215 mg/dl (5,6 mmol/l) and a blood pressure of 140/86 mm Hg. The diet and exercise program included visits to the physician, seven visits to the

nutritionists during the first year and visits every three months thereafter and participation in individually tailored exercise groups along with encouragement of individual exercise. Dietary recommendations were based on food diaries. The goal of the program was to reduce weight by at least 5%, to reduce total intake of fat to less than 30% and the intake of saturated fat to less than 10% of the energy consumed, to increase the intake of fibre to at least 15 g per 1000 kcal and for subjects to perform moderate exercise at least 30 minutes per day.[15]

3.3 COST DATA

3.3.1 The Södertälje study

The Södertälje study investigated the cost of MI, angina pectoris, unstable angina, congestive heart failure and stroke in patients hospitalized at the department of medicine at Södertälje Hospital south of Stockholm. [88] 25 patients with each diagnosis were included.

The study was a retrospective study which compared research consumption one year prior to the clinical event to the consumption during the year following the event. The study included both direct and indirect costs. Direct costs included hospital costs, the cost of outpatient care and the cost of pharmaceuticals. Indirect costs were estimated using the human capital approach.

3.3.2 The CODE-2 study

The cost of diabetes mellitus – type 2 (CODE-2) was an international study aiming to investigate the direct health care cost of DM2 in Europe. [62] Eight countries were included: Belgium, France, Germany, Italy, the Netherlands, Spain, Sweden, and the UK. More than 7 000 patients were included in the study, of which 777 came from Sweden. Data from the Swedish patients were used in our analyses in paper IV.

The study was performed by administrating one questionnaire to the patient and one questionnaire to the treating physician. Information was collected about hospitalizations, ambulatory care visits and drug use, along with disease specific data. Unit costs were based on official price lists.

The study concluded that the cost of diabetes type 2 in Sweden was 7 billion SEK, or 6% of the total health care budget. The largest contributor to costs was inpatient care and the key cost driver was the presence of micro- and macrovascular complications.

3.4 MODELING APPROACH

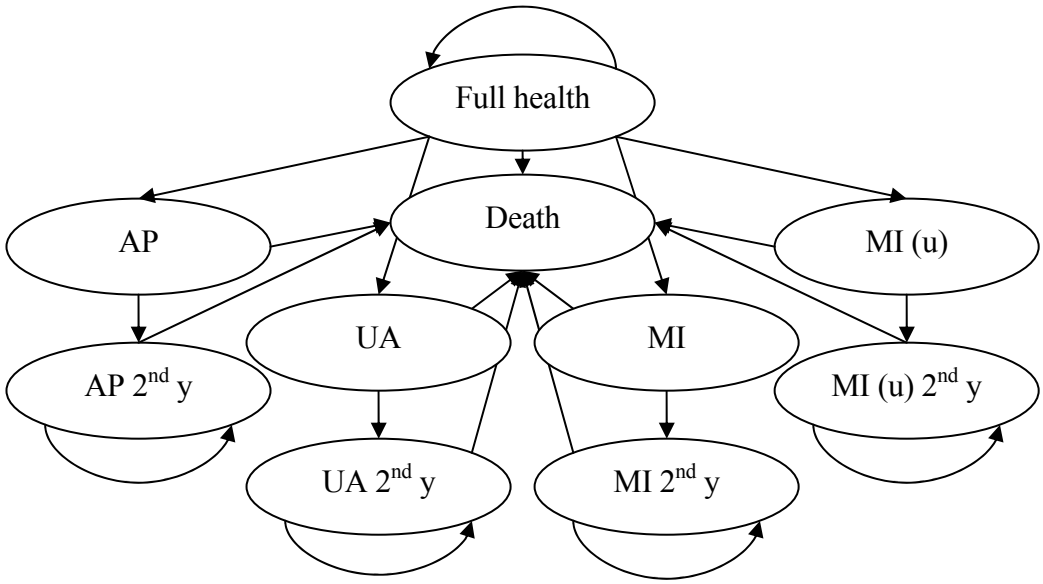
Since the risk of cardiovascular disease and diabetes mellitus and the consequences thereof span a long time with varying risk over time, the use of a decision tree to model these diseases is highly impractical. Furthermore, as the risk of cardiovascular disease is measured in terms of incidence and not time to heart disease from some specific reference point, it is vastly more intuitive to base the analysis on probabilities rather than time to event. This speaks for the use of Markov models to perform the analyses.

Although made up of slightly different disease states depending on the clinical data used to model the disease, the models have some structural elements in common. Patients start in a state indicating that they are at risk of the events we are trying to prevent. In paper I, this state represents full health, in paper II patients with IGT, in paper III patients hospitalized with ACS and in paper IV patients with ACS who has undergone a PCI and. In this state, patients have a yearly risk of suffering other events, or death from other causes. This risk is reduced while on treatment, either through the reduction of a relative risk from the clinical trials, or by a reduction in risk factors. Should patients suffer from an event, they move into a corresponding disease state. In all the models, cardiovascular diseases are divided into two states. One state captures costs and health effects during the first year after disease onset. Patients who survive the first year move into a health state capturing the costs and health effects during the second and following years. Patients remain in this state until they die.

The model structure used implies that patients can only suffer from one event, be it a stroke or a MI. This will lead to a slight overestimation of the cost-effectiveness ratios as patients suffering an event are more likely to suffer from additional events in the future (which is particularly true in when modeling first events in the primary prevention models). This conservative approach was chosen as there is rarely enough data to model additional events.

Figure 4 below shows the state transition diagram for the model used in paper I. Individuals start in the full health state and have a yearly risk of developing either angina pectoris, unstable angina, or a recognized or unrecognized (silent) myocardial infarction. Survivors move on to the corresponding second year state for the corresponding diagnosis. The risk of suffering an event is estimated using a risk function from the Framingham study. Intervention is modeled as a reduction in the risk factors included in the risk function for the duration of the intervention. Once the intervention is stopped, two scenarios were explored: in one, risk factors were assumed to move back to the baseline levels prior to intervention during one year. In the second scenario, the reduction in risk was assumed to be maintained.

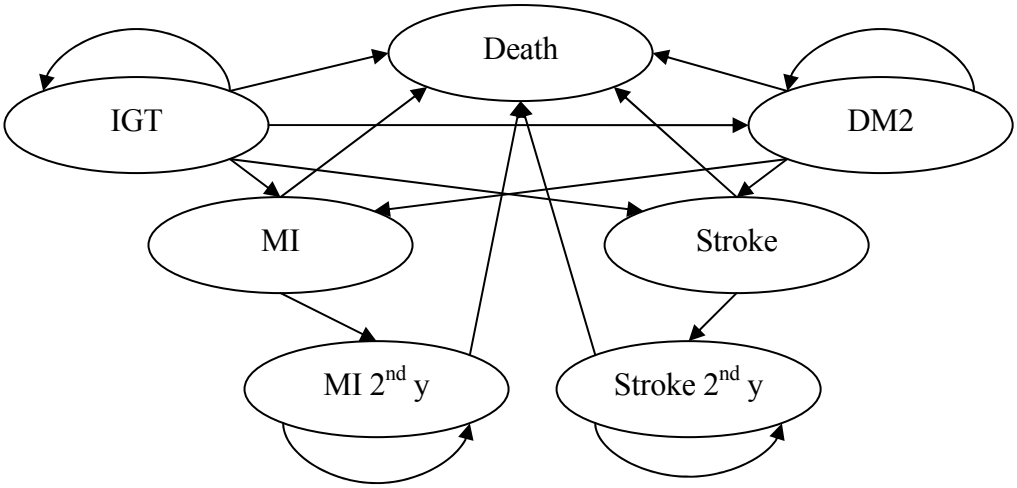
Figure 4. State transition diagram of the model used in paper I.



AP = angina pectoris, UAP = unstable angina, MI = myocardial infarction, MI (u) = myocardial infarction (unrecognised), y = year

Figure 5 shows the model of diabetes prevention used in paper II. Patients start in a state representing impaired glucose intolerance where they have a risk of developing manifest diabetes and of suffering a MI or a stroke. Once they develop diabetes, this condition is treated as irreversible and patients with diabetes have a higher risk of suffering from macrovascular complications. Patients who survive their first year with MI or stroke move on to the corresponding state for subsequent years. The risk of developing diabetes was estimated from the trial data as was the risk reduction in patients in the intervention program. The risk of developing MI and stroke was estimated using a risk function from the UKPDS study.

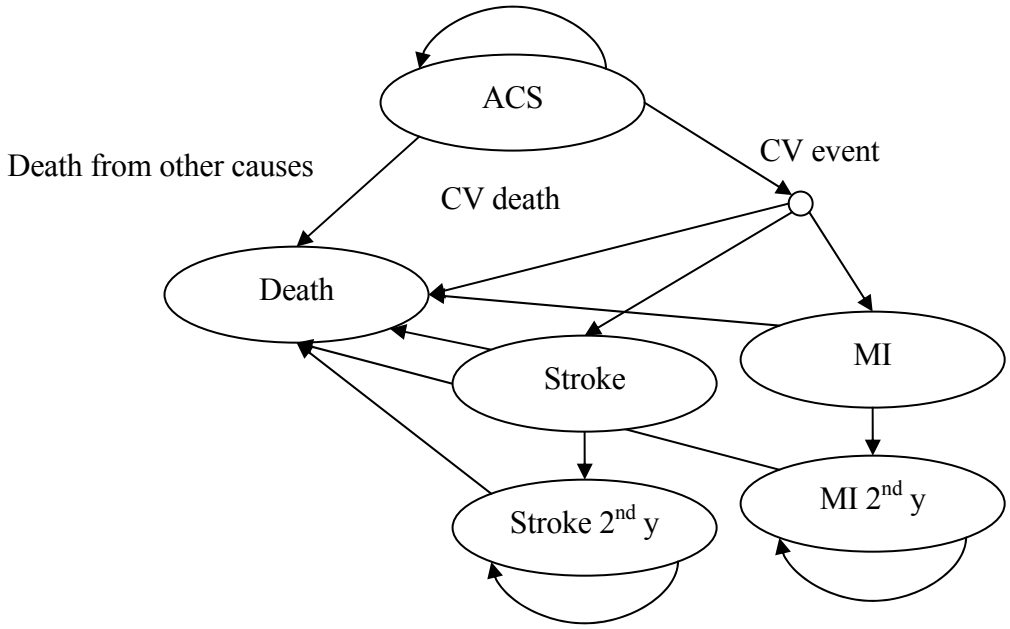
Figure 5. State transition of the model used in paper II.



IGT = impaired glucose tolerance, DM2 = diabetes mellitus type 2, MI = myocardial infarction, y = year

Figure 6 shows the model used in paper III. Patients start in a state where they are included when suffering an acute coronary syndrome. They have a yearly risk of suffering an event which can be either a stroke, a MI or death from cardiovascular causes. If they suffer an event (apart from cardiovascular death) they move into a one-year transitional state corresponding to the event. Survivors during that year move onto the corresponding 2nd-year state where they remain until death. The risk of suffering an event and mortality was estimated from the Swedish hospital discharge register using logistic regression and survival modeling techniques. In the model, patients are assumed to be treated during the first year, with a relative risk of events corresponding to the findings of the CURE trial. Once treatment is discontinued, no remaining effects are assumed in the model.

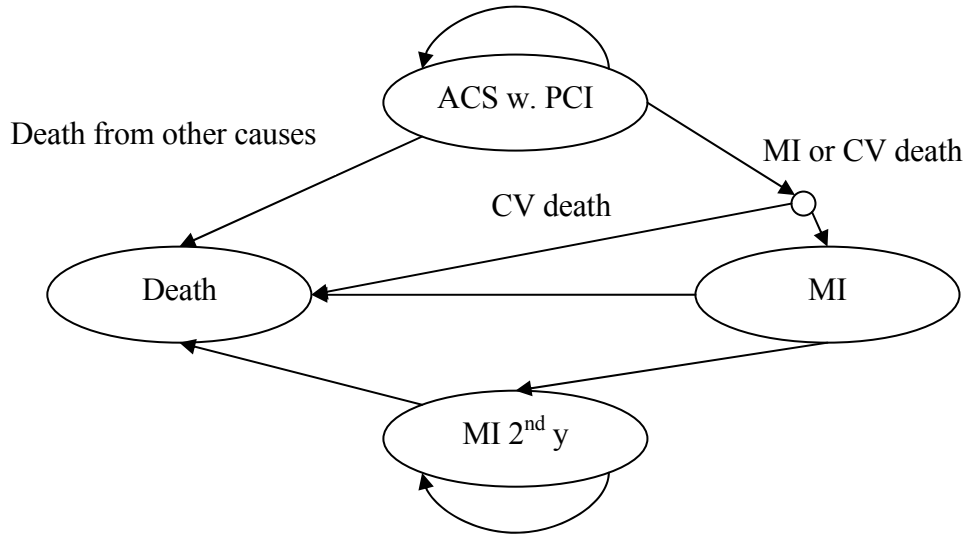
Figure 6. State transition diagram of the model used in paper III.



ACS = Acute coronary syndrome, CV = cardiovascular, MI = myocardial infarction, y = year

Figure 7 shows the model used in the analysis of the PCI-CURE trial. In structure, it is similar to the model used in paper III, but as stroke wasn't an endpoint in the trial, states corresponding to stroke were removed from the model. The model starts with a state for patients who have suffered from acute coronary syndromes and undergone a PCI. These patients have a yearly risk of suffering an event, defined as having an MI or dying from cardiovascular causes, and a yearly risk of dying from non/cardiovascular causes. Patients who suffer a MI move on to the MI state where they remain one year after which the survivors move on to the 2nd and following year state. The risk of events and mortality was estimated using data from patients extracted from the RIKS-HIA register. Patients are treated during one year where the risk reduction from the clinical trial is applied. No remaining effects are assumed (neither a remaining effect or treatment nor a rebound effect) after the first year of treatment.

Figure 7. State transition diagram of model used in paper IV.



ACS w. PCI = acute coronary syndrome with pecutaneous coronary intervention, MI = myocardial infarction, CV = cardiovascular, y = year

4 RESULTS

Cost-effectiveness of primary prevention of coronary heart disease through risk factor intervention in 60-year old men from the county of Stockholm – a stochastic model of exercise and dietary advice.

A Markov model was developed to investigate the long-term consequences of a lifestyle intervention program previously undertaken in Sollentuna. The intervention program consisted of four groups: dietary advice, exercise or a combination of both plus a control group. Patients were followed for 18 months, and all three interventions showed a significant reduction in known risk factors for cardiovascular disease (diastolic blood pressure and total cholesterol). The change in the occurrence of cardiovascular events due to the interventions was estimated using data from the Framingham study. Two scenarios were explored, one in which the effect of treatment gradually decreased during a period of two years, and one in which treatment effect was assumed to be maintained. The cost of intervention was based on the components included in the program, while the cost of events was based on published sources. The intervention was assumed to be applied to elective individuals in the 60-year old cohort.

Of the three interventions dietary advice was a dominant strategy, i.e. it has both better effects and lower costs compared to the other two. The results shown in table 4 below thus only show a comparison between dietary advice and no intervention.

Table 4. Incremental costs, survival and cost-effectiveness of dietary advice compared to no intervention.

	Incremental cost (SEK)	Life years gained (LYG)	ICER (SEK/LYG)[1]
Declining effects			
Direct costs	2,584	0.023	113,333
Direct + indirect costs	663	0.023	29,079
All costs	2,892	0.023	127,065
Remaining effects			
Direct costs	1,496	0.100	15,005
Direct + indirect costs	-1,384	0.100	Dominance
All costs	14,106	0.100	141,555

[1]Incremental Cost Effectiveness Ratio

When looking at the most conservative way of estimating the effects of the intervention after the trial, the cost-effectiveness ratios fall well below those generally considered cost-effective. The studied form of dietary advice should thus be considered money well spent. The difference in costs and effects between the three interventions was relatively small, indicating that exercise and a combination are also attractive alternatives in the absence of dietary advice alone.

Lifestyle intervention to prevent diabetes in men and women with impaired glucose tolerance is cost-effective.
The diabetes prevention study was a randomized intervention program that included visits to the physician, seven visits to the nutritionists during the first year and visits every three months thereafter and participation in individually tailored exercise groups along with encouragement of individual exercise. Dietary recommendations were based on food diaries. To evaluate the effect of implementing the DPS in a Swedish setting, we used a Markov model describing the conversion between IGT and DM2, along with states to simulate the risk of cardiovascular events. Microvascular complications were not incorporated as separate health states in the model. Instead, the cost of these complications were included in the cost for patients in the diabetes state. The incidence of DM2 in the population was based on the observed rate in DPS. The risk of developing macrovascular complications was based on risk functions from UKPDS. Mortality was based on estimates from the hospital discharge and causes of death registers. Costs were based on published sources.

We used individuals from the 60-year old cohort who fulfilled the inclusion criteria of DPS to get an estimate of the baseline risk factor profile of these patients in Sweden. We assumed that these patients would be treated for six years (the maximum follow-up period in DPS).

Table 5. Incremental costs, survival and cost-effectiveness of intensive lifestyle intervention.

	Incremental cost (SEK)	Life years gained (LYG)	ICER (SEK/LYG)[1]
Direct costs	-8 372	0.18	Dominance[2]
Direct + indirect costs	-16 973	0.18	Dominance[2]
All costs	4 286	0.18	21 645

[1]Incremental Cost Effectiveness Ratio
[2]Dominance indicates cost-savings and improved effectiveness.

The study indicates that the intervention program would be cost-saving when we consider only direct cost or a combination of direct and indirect costs. When costs in added years of life are included, a slight increase in cost is predicted due to the positive effect on survival. The resulting ICER in this case is extremely attractive.

Cost-effectiveness of clopidogrel in acute coronary syndromes in Sweden: a long term model based on the CURE trial.
We used a Markov model to extrapolate the effects of adding clopidogrel to ASA during one year as shown in the CURE trial. To estimate the risk of having an event in a Swedish population, we extracted patients with a diagnosis of unstable angina from the Swedish inpatient statistics and analyzed the outcomes in this group. The risk of subsequent events (defined as in the clinical trial: cardiovascular death, non-fatal MI and stroke) in the studied population was very similar to that of the placebo arm of the clinical trial. Treatment was assumed to last for one year, with no additional effects of treatment once it was discontinued. Costs were based on published sources. Two main scenarios were analyzed: one with the same mean age and gender distribution as in the clinical trial and one with age and gender as in the population extracted from the register. The results are presented in table 6.

Table 6. Incremental costs, survival and cost-effectiveness of clopidogrel in addition to ASA compared to ASA alone.

	Incremental cost (SEK)	Life years gained (LYG)	ICER (SEK/LYG)[1]
CURE population			
Direct costs	1,351	0.12	11,529
Direct + indirect costs	-456	0.12	Dominance
All costs	17,818	0.12	152,012
Register population			
Direct costs	1,259	0.15	8,522
Direct + indirect costs[2]	0	0.15	8,522
All costs	25,198	0.15	170,636

[1]Incremental Cost Effectiveness Ratio
[2] The register population was above 65 years and because of this no indirect costs were present.

The results indicate that the treatment strategy is cost-effective. Apart from study drug, the most influential cost-driver is costs in added years of life, as the predicted survival benefit is rather large.

The long-term cost-effectiveness of clopidogrel in addition to aspirin in patients undergoing percutaneous coronary intervention in Sweden.

To estimate the cost-effectiveness of clopidogrel in addition to ASA in patients undergoing PCI, a Markov model was constructed. The risk of events was based on patients from the RIKS-HIA register on coronary care. Patients were identified based on the inclusion criteria of the PCI-CURE trial and followed with regards to mortality and new MI (the endpoints in the trial). Patients were assumed to be pretreated with clopidogrel during a median time of 10 days prior to the PCI, and then treated for up to one year after the procedure. Costs were based on published sources. The results can be found in table 7.

Table 7. Incremental costs, survival and cost-effectiveness of clopidogrel in addition to ASA compared to ASA alone in patients undergoing PCI.

	Incremental cost (SEK)	Life years gained (LYG)	ICER (SEK/LYG)[1]
Direct costs	4 098	0.04	100 333
Direct + indirect costs	3 030	0.04	74 175
All costs	8 597	0.04	210 404

[1]Incremental Cost Effectiveness Ratio

The results show somewhat higher cost-effectiveness ratios compared to the results from the analysis of CURE. The largest contributing factor to this difference is that to avoid including the MI for which the patient was undergoing a PCI, we excluded all MIs occurring within seven days of admission to the intensive care unit. This leads to an underestimation of the risks used in the model and thus to higher cost-effectiveness ratio. In spite of this very conservative approach, cost-effectiveness ratios were still very attractive.

5 DISCUSSION

5.1 LIFE-STYLE INTERVENTION AS A PREVENTIVE MEASURE

The studies previously presented on life-style intervention of cardiovascular disease can be divided into those where the clinical effects are based on hypothetical interventions and those where it is based on clinical trial data or a meta-analysis of such data. The former are interesting to generate hypotheses, but to get reliable results it is important to have good underlying clinical data. This is important, as the cost-effectiveness of lifestyle interventions is determined not only by the cost of the intervention, but also by the demonstrated health effects of this program. This explains the different finding in our study compared to those of Salkeld and Johannesson. [32, 33] A program with no measurable health benefits compared to standard treatment can only be considered if it is associated with lower costs. The lesson from this is that the first and most important step is to establish that an intervention program works and has a clinical effect. Once this is established, it is time to assess whether or not it is economically justifiable.

The only previously published study based on significant effects (based on a meta analysis) indicated that exercise is cost-effective. [35] Our finding confirms this, but also indicates that dietary advice is cheaper and based on our clinical results, more effective. In the absence of dietary advice as a comparator, the cost-effectiveness ratios for exercise are favorable.

Palmer and colleagues found that intensive lifestyle intervention was cost-saving when using a simple Markov model based on data from the DPP. [82] Using a more detailed model, populated by completely different data (chiefly DPS and UKPDS) and a different set of costs we find the same thing in Sweden. Including all costs, i.e. also costs due to increased survival, our model predicts a very favorable cost-effectiveness ratio. This gives a very strong argument for implementing this type of program, particularly for the Swedish county councils who are the parties that will reap the benefits of the cost-savings.

A drawback of many studies on lifestyle intervention is their limited follow-up time. This is of course a question about quite different economics: research funding. This leads to two problems for economic evaluations. The first is the fact that the endpoints included in the studies are limited to surrogate endpoints as reduction in risk factor levels. This is generally considered to have slightly less value as evidence than trials with reduction in ‘hard’ endpoints such as mortality or reduction of cardiovascular events as outcome measures. It also forces us to model the effect from the intervention through the use of risk-equations instead of as a reduction in absolute risk. This adds uncertainty as there is uncertainty included when estimating the risk equation in the first place and the appropriate risk function needs to be used for the studied population.

The second issue with short duration of follow-up is that the maintenance of either the effect of the intervention or the persistence with which the intervention is this is assumed to be continued is unknown. In both our studies, we assumed that intervention would be discontinued and that there would be no remaining effects or a rapid progression back to the baseline levels for the risk factors. This is the most conservative

approach and could lead to an overestimation of the cost-effectiveness ratios if there is a remaining effect. Indeed, follow-up data from DPS indicated a lasting effect on the risk of developing type 2 diabetes 2 years after treatment was discontinued.

5.2 ANTITHROMBOTIC THERAPY

Paper II and paper III studies the use of the same intervention but in different groups of patients, and based on different underlying data sets. They give slightly different results: An ICER of 11,500 SEK per LYG in the CURE population and 100,000 SEK per LYG in the PCI-CURE population (including only direct costs). The explanation can be found in the underlying data. In the model used in paper II, we extracted data from the hospital discharge register. Apart from unstable angina patients, the CURE trial only included patients with NSTEMI and it was impossible to separate these from patients with ST-segment elevation in the register. For this reason, only patients with unstable angina were included when estimating the risks for the model. This may lead to a slight underestimation of mortality and thus an overestimation of the cost-effectiveness. Counteracting this is the fact that to get a long follow-up patients hospitalized in 1992 were included. Case-fatality has declined since then, and this may thus lead to an overestimation of mortality.

In paper III, the situation was different: A very good match could be made between patients in the RIKS-HIA register and the inclusion criteria of the trial. Unfortunately it was difficult to separate the MI for which the PCI was undertaken from possible subsequent events. For this reason, no events were counted during the first 7 days following the PCI. This led to an underestimation of the risk of an event and thus an overestimation of the cost-effectiveness ratio. Should an exact classification of events during the 7 days be possible, cost-effectiveness ratios would decline, as was seen in the sensitivity analysis that was performed as part of the study. If no events were excluded, the results indicated cost savings. The best estimate of cost-effectiveness is somewhere between these two estimates. In spite of the very conservative assumptions made, the study shows favorable cost-effectiveness ratios.

The study by Latour-Perez et al reports a higher cost-effectiveness ratio in their analysis of the CURE trial. [55] However, this study has some weaknesses: One is that the cost of events used in their model is only based on the cost of the diagnosis related group for the initial hospitalization for this event. This is a large underestimation of the cost of an event. They also report no difference in survival between the arms, which is puzzling since the same mortality rate is used following events in both arms and there is fewer events in the active treatment arm.

One much debated question that neither of our models can answer is how long to treat patients. Local recommendations in Sweden propose between 3 and 12 months treatment, all based on data from the same trial. Unfortunately, data from the trial cannot be used to estimate the risk reduction for different durations of treatment as comparisons between the arms at different time points would imply a comparison between two unbalanced groups. In order to answer this question, a trial where patients

are followed for different treatment durations and remain under observation once treatment is discontinued would be necessary.

5.3 THE USE OF EPIDEMIOLOGICAL DATA IN ECONOMIC EVALUATION

As illustrated in this thesis, epidemiological data can be used in several ways in economic evaluations:

1. As a source of baseline data describing the population targeted for intervention. The 60-year old cohort was used in this way in paper I and II.
2. As the foundation for estimating the risk of events in the target population and in subgroups. This is the way data from the hospital discharge register was used in paper II and RIKS-HIA was used in paper III.
3. As a way of measuring the potential effects of intervention where surrogate endpoints have been studied, as was the case of the Framingham data in paper I and UKPDS in paper II.

If we expand our definition of epidemiological data to also include clinical trials another item can be identified:

4. Establishing the effect of an intervention. This is how data from the Sollentuna study was used in paper I, DPS in paper II, the CURE trial in paper III, and the PCI-CURE trial in paper IV.

These uses put different demands on the underlying data with regards to representability, sample size and the information collected.

In the first example, representability is the key as a biased selection of the population leads to flawed results. A clear strength of our studies is the population based nature of the data materials used. If representability is a potential issue, the impact of this needs to be assessed. In the modeling setting this can be done through sensitivity analysis on the key parameters. If the impact on the result is large, it is questionable if the data set can be used in any meaningful way. The sample size is dependent on the number of parameters included that affect the results and the variations within these parameters. The exact figure is difficult to assess a priori, as it is dependent on the impact of each parameter on costs and effects. If the sample size is small, this will influence the uncertainty around the parameter estimates and thus lead to a greater variation in the output in a stochastic model. As decision making is primarily based on the mean costs and effects, this is of minor concern as long as the sample is representative. The information that should be collected from the sample can be determined in two ways: If a modeling approach with relevant parameters has already been determined, the corresponding parameters should be present or collected in the epidemiological data. If the point of the study is specifically to study a pre-defined dataset, a model needs to be created that incorporate the available data.

In the second and third example, the issue of representability is the same as in any epidemiological study. This is to say that representability is not important as long as

the findings are externally valid. The sample size is determined slightly differently in the two cases: In case three, the sample size is determined by the magnitude of the effect the parameters that need to be included in the risk equation. This is to say that if we wish to study a multifactorial intervention which affects blood pressure and lipid levels, we need to have a sufficient sample size to create a risk-equation that incorporates the effects on these two parameters. In the second case the objective is to assess the total risk-level in the population. This puts smaller demands on formal sample size calculations, but the larger the sample the more parameters can be included, which allows for subgroup analyses. However, if there is a need to perform analyses on a priori specified subgroups, sample size estimation need to be done as in case three. The data included in the dataset need of course to include the parameters which will be subject to subgroup analyses (in case 2) or that are affected by the intervention (in case 3). As in any epidemiological study, it is necessary to include confounding factors that may bias the estimates.

In the fourth case, representability need not be an issue. However, it is of importance to ensure that the clinical findings can be extrapolated to the studied risk group. If a convincing subgroup analysis was performed as part of the clinical trial, this can be used to validate this point. When working with economic evaluations, the clinical study is usually completed or long underway. This means that the economist has little impact on sample size and collected clinical parameters. Luckily, when a modeling approach is used to estimate cost-effectiveness, the data on clinical effects can be used directly from the trial which means that no particular sample size considerations need be taken for the economic evaluation. The same is true for the collected data.

5.4 DIRECTIONS FOR FUTURE RESEARCH

Based on the experience from the studies presented in this thesis some areas where more research is needed could be identified. Apart from studies of specific interventions which always will be necessary as new treatments options appear, some more general issues are presented here.

There are some limitations to the data sources used with regards to costs and outcomes which could be improved by future studies. There exists a quite extensive literature on quality of life in relation to cardiovascular disease. Unfortunately, it is uncommon to use quality of life instruments geared towards use in economic evaluation, i.e. instruments that can be converted to utilities and from that QALYs. Data on quality of life in patients with heart disease would allow for increased use of QALYs as the measure of effectiveness in future economic evaluations. This would have the advantage of allowing comparison of interventions across a wide range of disease areas, and is thought as the present gold standard. There are two ways that can be explored in order to achieve this: either conducting new studies utilizing instruments for which utility weights have been estimated (such as the EQ-5D, the HUI-MkIII or the 15D) or creating tariffs (by using time-trade off or standard gamble methodology) to convert the results from existing studies to utility values. The first approach seems to be the most straight-forward one.

Updated figures on the cost of cardiovascular disease would also be desired, as the present studies are somewhat old. The introduction of novel treatments or changes in treatment patterns is likely to change the overall cost associated with the disease. The sensitivity analyses undertaken as part of the studies presented here indicate that the findings are robust to variations in the cost, but in the analysis of other treatment strategies where the situation is less clear-cut, newer estimates based on larger samples could be important.

Although it would be better to rely on clinical trials measuring hard end-points to get better long-term estimates of the outcomes and circumventing the need for risk functions altogether, financial considerations will lead to and high use of surrogate endpoints. This is particularly true for studies without a strong financial backer (such as lifestyle interventions). This means that the question of the applicability of risk scores from other populations to the situation in Sweden would benefit from more attention, ideally by developing Swedish (or Scandinavian) risk functions or alternatively to perform a more extensive validation of the existing risk scores. Apart from the risk functions used in this thesis (from the Framingham study and the UKPDS) there are other functions that could be considered. Recently the development of a European risk score has been completed. [89] However, as the risk score is for prediction of fatal cardiovascular events only, this is of limited use in economic evaluations. The riskscore project, based on 48 000 individuals from different studies of hypertension suffers from the same problem. [90] The risk score from the prospective cardiovascular Munster study could probably be used in a Swedish setting. [91] A drawback of this study is that it only includes men.

Conversely, this thesis has illustrated the usefulness of Swedish epidemiological data in the construction of health economic models. To investigate the applicability of the Swedish data to other settings and the possibility to adjust the Swedish data to better match the situation in different countries would be very interesting, as it would allow for the use of the results derived from the Swedish register data in a more international setting.

6 CONCLUSION

This thesis has through practical applications demonstrated the use of epidemiological data in different health economic applications. The specific studies have indicated that:

- Dietary advice as implemented in the Sollentuna study is a cost-effective way of reducing the risk of cardiovascular disease. It is a dominating strategy compared to exercise or a combination of diet and exercise; however, in the absence of a program for dietary advice, exercise is also a cost-effective strategy.

- An intensive lifestyle intervention program directed towards patients with IGT at risk of developing DM2 is cost-saving for the health care payer, and highly cost-effective to society as a whole.

- Adding clopidogrel to ASA in patients with acute coronary syndromes (unstable angina or MI without ST-segment elevation) is a cost-effective strategy compared to ASA alone for a treatment period of 12 months. This is also true in patients with this diagnosis undergoing PCI.

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